CSA220380

1/4

INVENTARIO

mercio

ENCIA

Organizacion y Digitaliz... CSA Ltda

ad Industrial

s Creaciones

PCT

SOLICITUD

NTE DE INVENCIÓN

EXPEDIENTE No. 08-67245

TÍTULO COMPUESTO HETEROCILICO FUSIONADO

CLASIFICACIÓN INTERNACIONAL (007) 487/04; A61K 31/519

SOLICITANTE TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPON

APODERADO EMILIO FERRERO

C.C. 328.019 de Usa-quen

BOGOTÁ, D. C.,

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-067245- -00000-0000
Fecha: 2008-07-01 17:07:26 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 11189

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

2 SOLICITANTE (71)

Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**
sociedad constituida y existente bajo las leyes de Japón.

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

Domicilio: Osaka,
Japón

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

3 REPRESENTANTE O APODERADO

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

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

4 INVENTOR (ES) (72)

1. **Tomoyasu ISHIKAWA**
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2. **Kazuhiro MIWA**
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17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
Osaka 532-8686,
Japón

3. **Masaki SETO**
c/o Takeda Pharmaceutical Company Limited,
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
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Japón

4. **Hiroshi BANNO**
c/o Takeda Pharmaceutical Company Limited,
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5. **Youichi KAWAKITA**
c/o Takeda Pharmaceutical Company Limited,
10, Wadai,
Tsukuba-shi,
Ibaraki 300-4293,
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2006/324499 Fecha: 1 de diciembre de 2006
Publicación Internacional No. WO 2007/064045 A1 Fecha: 7 de junio de 2007

6 Título (54)

COMPUESTO HETEROCICLICO FUSIONADO

7 **Clasificación Internacional (51)** C07D 487/004

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	JP JP	2 de diciembre de 2005 7 de marzo de 2006	2005-349858 2006-060648

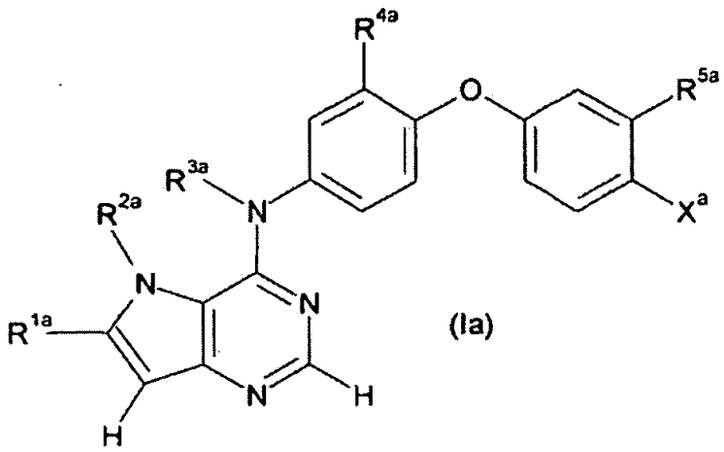
9 **Comprobante de pago No.:** 08-46,143 **Fecha:** 9 de junio de 2008

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 501.000.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



(Ia)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

NNJ

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2007/064045 A1

   Descripción:

   Páginas 620 en el idioma original

   Páginas 828 en español

   Reivindicaciones: Número (s) 33

   Figuras: Número (s)

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

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

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

179

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

14656-
0 Bues

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

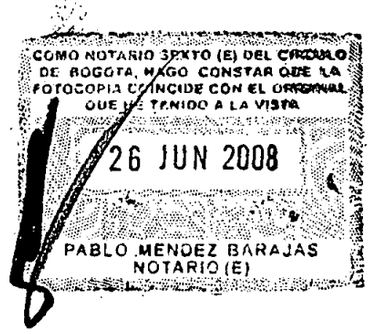
el presente nombramos a EMILIO FERRERO, tpa. 31929; NZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 55 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el grafo 1o del Artículo 543 del Código de Comercio, el primero como cipal y los demás como suplentes, en su orden, como mis (nuestros) esentantes en todos los asuntos de propiedad industrial con facultad recibir notificaciones y nombrar apoderados judiciales o ajudiciales. El primer representante suplente reemplazará al principal aso de ausencia o impedimento temporal o definitivo de aquél. La na regla se aplicará cuando el segundo representante suplente haya eemplazar al primero, o el tercero al segundo. En tales casos, el esentante principal, o el primero, o segundo suplente, en su caso, o os, declararán su intención de no ejercer la representación mediante aración autenticada por Notario Público en Colombia, o por Notario ro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si atare de impedimento, con el certificado respectivo. Si alguno de los brados faltare definitivamente, el siguiente tomará su lugar. Cuando re la ausencia o impedimento del representante principal, o de su iero o segundo suplentes, en su caso, podrán ejercer la esentación, en su orden, uno u otros según el caso, asumiéndola por olo hecho de ejercerla, cesando en ese momento el ejercicio de la esentación por el primero, segundo o tercer suplente en su caso.

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

más, confiero (conferimos) poder a los abogados arriba nombrados, obtener la protección de mi (nuestra) propiedad industrial y contra ompetencia desleal, a cuyo efecto autorizo (amos) a los dichos lerados para que me (nos) representen ante cualesquiera entidades o onas, ejerzan o no jurisdicción, especialmente ante las del orden inistrativo, contencioso-administrativo y judicial, así como los nales de arbitramento, en todo lo concerniente a los siguientes tos: a) Obtención de patentes de invención, modelos de utilidad, y ios industriales; el registro de marcas de fábrica, colectivas, nsivas, de servicio, lemas comerciales, nombres comerciales, ñas, nombres de dominio, variedades vegetales y denominaciones de n; su renovación, traspaso, cambio de nombre o domicilio, elación voluntaria; y el registro de licencias de uso de esos derechos: as acciones de competencia desleal, protección del consumidor, ciones u observaciones, cancelación administrativa y judicial, ad, medidas cautelares, concesión de licencias, la tutela, la cción de secretos industriales, y en general los juicios civiles, es, administrativos o contencioso-administrativos relacionados con derechos; acciones y procesos que promovamos o se nos

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, emblems, 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, licensing, 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 (E) DEL CIRCULO DE BOGOTA, DISTRITO CAPITAL, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE HE TENIDO A LA VISTA
27 JUN 2008
PABLO [illegible] RUIZ BARAJAS


COMO NOTARIO SEXTO (E) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
26 JUN 2008
PABLO MENDEZ BARAJAS
NOTARIO (E)

ev:n. Y para que en todos los asuntos arriba determinados, puedan ir este mandato, transigir, conciliar, admitir los hechos del o, desistir, cancelar, recibir, renunciar, y ratificar los actos de s 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 (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 JUN 2008

PABLO MEJIA BARAJAS
NOTARIO (E)

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

CODEX JURIS CIVILIS

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

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

313395

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

26 JUN 2008

PABLO MENDEZ BARAJAS
NOTARIO (E)

Certificado

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

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

8. **No. 04149**

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

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

MINISTERIO DE RELACIONES EXTERIORES · JAPÓN ·

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

LA CÁMARA DE COMERCIO E INDUSTRIA DE OSAKA
2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPÓN
FAX: (06) 6944-6248 TEL: 6944-~~6413~~ 6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

A quién pueda interesar:

CERTIFICADO DE MEMBRESÍA

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 JUN 2008
PABLO MEJIA BARAJAS

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

Número de Membresía: KT-01-00080

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

Diego Fernando Cadena

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

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES EXTERIORES

08 FEB -8 P 2:39

ucs

OFICINA DE LEGALIZACIONES BOGOTA D.C.

313391

Diego Vargas

ESTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

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

26 JUN 2008

PABLO MEN... CARAJAS

NOTA... (E)

1842 16

FICIO SISKI
ERA 4a N° 72-35
'A, 8 – COLOMBIA

CESION

ıtros) abajo firmado (s)

do(s) en

ınción:

mos) asi mismo que cedo(emos) y transfiero(erimos), sin
ı, a favor de la sociedad

a y existente de conformidad con las leyes de

da en

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

ASSIGNMENT

I (we), the undersigned
1. Tomoyasu ISHIKAWA
2. Kazuhiro MIWA
3. Masaki SETO
4. Hiroshi BANNO
5. Youichi KAWAKITA

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

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

state as well, that assign, without reservations or limitations in favour of
Takeda Pharmaceutical Company Limited
a corporation constituted and existing in conformity with the laws of
Japan
domiciled in 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 Japan
all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this
____ day of _____ 200___
en/in _____

Firma/Signature

Tomoyasu Ishikawa
. Tomoyasu ISHIKAWA

Kazuhiro Miwa
. Kazuhiro MIWA

Masaki Seto
. Masaki SETO

Hiroshi Banno
4. Hiroshi BANNO

Youichi Kawakita
5. Youichi KAWAKITA

© CAVELIER ABOGADOS

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Masaharu KEMMA

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

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

Certified

5. at **Osaka**

6. APR. – 7. 2008

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

8. No. 1710

9. Seal/stamp:

10. Signature:

Toshihiko TANAKI

For the Minister for Foreign Affairs

大阪法務局所属　公証人役場

認証登簿　平成２０年 第　121　号

嘱託人　三輪憲弘、瀬戸雅樹　は、本職の面前で添付書面に署名した。

また、嘱託人　石川智康、坂野浩、川北洋一　の　代理人　栗山 為重　は、本職に対し、石川智康、坂野浩、川北洋一　が添付書面の署名につき、自らしたものであることを承認している旨陳述した。

よって、これを認証する。

平成　２０　年　４　月　７　日

大阪市西区江戸堀１丁目１０番８号

公証人　見　満　正　治　役場において

大阪法務局所属

公 証 人　見満正治

18

REGISTER NUMBER 121 / 2008

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Kazuhiro MIWA and Masaki SETO.

And, I hereby certify that the signature of this document applied for has been approved by Tameshige KURIYAMA in my presence to be the true signature of Tomoyasu ISHIKAWA, Hiroshi BANNO and Youichi KAWAKITA.

Dated this 7 th day of April, 2008

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

Masaharu Kemma

Masaharu KEMMA
Notary attached
to The Osaka Legal Affairs Bureau

19

総 第 1326 号

証 明

大阪法務局所属公証人 見 満 正 治

平成 20年 4 月 7 日付

平成20 年 登簿 第 /2/ 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 20年4月7日
平成 年 月 日

大阪法務局長 髙 野 伸

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 08. 4. 7

Director of the Osaka Legal Affairs Bureau

1. (Firmado) Tomoyasu ISHIKAWA
2. (Firmado) Kazuhiro MIWA
3. (Firmado) Masaki SETO
4. ((Firmado) Hiroshi BANNO
5. (Firmado) Youichi KAWAKITA

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WWPPOSE01-374

REGISTRO NUMERO 121/2008

Yo, por el presente certifico que este documento fue suscrito ante mi y que las firmas que aparecen sobre el mismo son las firmas fieles y verdaderas de Kazuhiro MIWA y Masaki SETO.

Y, por el presente certifico que la firma de este documento solicitado ha sido aprobado por Tameshige KURIYAMA en mi presencia para incluir la firma fiel de Tomoyasu ISHIKAWA, Hiroshi BANNO y Youichi KAWAKITA.

Fechado Hoy dia 7 de Abril de 2008
10-8, Edobori 1-chome,
Nishi-ku, Japón

(Firmado) Masaharu KEMMA
Notario Adjunto
A la Oficina de Asuntos Legales de Osaka

APOSTILLE
(Convención de La Haya del 5 de Octubre de 1961)

1. País JAPON
   Este documento público
2. ha sido suscrito por Masaharu KEMMA
3. obrando en calidad de Notario Público de la Oficina de Asuntos Legales de Osaka
4. lleva el sello/estampilla de Masaharu KEMMA, Notario Público

TRADUCCION OFICIAL No. 08-1069
HILDA AGUILERA DE [illegible]
INTERPRETE OFICIAL
RES. No. 323 DEL MIN. DE JUSTICIA

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2007 (07.06.2007)

PCT

(10) International Publication Number
WO 2007/064045 A1

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C07D 487/04 (2006.01) *A61K 31/519* (2006.01)

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PCT/JP2006/324499

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1 December 2006 (01.12.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2005-349858 2 December 2005 (02.12.2005) JP
2006-060648 7 March 2006 (07.03.2006) 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

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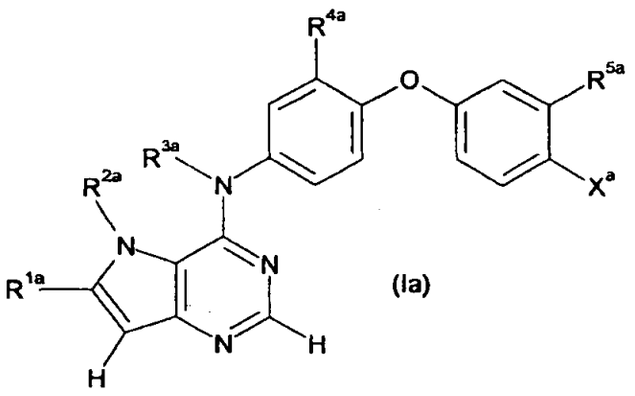
(54) Title: FUSED HETEROCYCLIC COMPOUND



(Ia)

(57) Abstract: The present invention provides a compound represented by the formula: wherein R^{1a} is a hydrogen atom, R^{2a} is a C_{1-6} alkyl group substituted by a group represented by-NR^{6a}-CO-$(CH_2)_n$-SO_2-optionally halogenated C_{1-4} alkyl wherein n is an integer of 1 to 4, R^{6a} is a hydrogen atom or a C_{1-4} alkyl group, and -$(CH_2)_n$- is optionally substituted by C_{1-4} alkyl, R^{3a} is a hydrogen atom or a C_{1-6} alkyl group, R^{4a} is a halogen atom or a C_{1-6} alkyl group, R^{5a} is a halogen atom or a C_{1-6} alkyl group, and X^a is a hydrogen atom or a halogen atom, or a salt thereof. The compound of the present invention has a superior tyrosine kinase inhibitory action, is highly safe, and is sufficiently satisfactory as a pharmaceutical product.

WO 2007/064045 A1

DESCRIPTION

FUSED HETEROCYCLIC COMPOUND

Technical Field

The present invention relates to a fused pyrimidine compound having a growth factor receptor tyrosine kinase inhibitory activity, which is useful for the prophylaxis or treatment of cancer, a production method thereof and use thereof.

Background of the Invention

The gene of cell growth factor and growth factor receptor is called a protooncogene and plays a key role in the pathology of human tumor. The epithelial cell growth factor receptor family (erbB) includes EGFR, HER2, HER3 and HER4, which are type I receptor type tyrosine kinases. These erbB family express in various cell groups, and are deeply involved in the control of the growth and differentiation of cells and the control of suppression of cell death (apoptosis suppression). For example, high expression of EGFR and HER2, and homeostatic activation of receptors are empirically known to transform cells.

It is also known that high expression and simultaneous expression of each of these receptors are poor prognostic factors in various cancer patients.

These receptors are bound with many peptide ligands such as EGF, TGFα and the like, and binding of the ligand promotes homo- or heterodimerization of the receptors. This induces increase of kinase activity from self-phosphorylation or transphosphorylation of the receptors, and causes activation of downstream signaling pathway (MAPK, Akt) via a protein bound with a particular phosphorylated tyrosine residue. This is the mechanism of the receptor activity of the above-mentioned cell growth, differentiation, cell death suppression and the like, which is considered to be

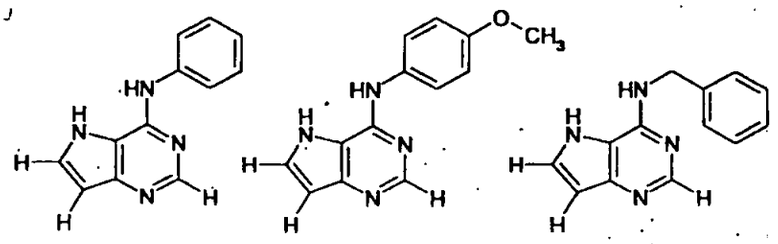
responsible for the high expression of receptor in cancer and malignant degeneration of cancer due to topical increase in the ligand concentration.

Many cancers are associated with the high expression of EGFR or HER2. For example, breast cancer (20-30%), ovarian cancer (20-40%), non-small cell lung cancer (30-60%), colorectal cancer (40-80%), prostate cancer (10-60%), bladder cancer (30-60%), kidney cancer (20-40%) and the like can be mentioned. Moreover, receptor expression and prognosis are correlated, and receptor expression is a poor prognostic factor in breast cancer, non-small cell lung cancer and the like.

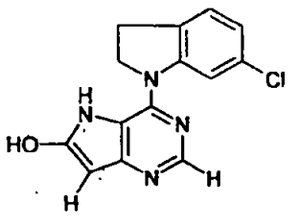
In recent years, clinical use of a humanized anti-HER2 antibody (Trastuzumab) against HER2 highly expressing breast cancer, clinical trial of anti-EGFR antibody and clinical trials of several low molecular weight receptor enzyme inhibitors have demonstrated a potential of these drugs against HER2 or EGFR for therapeutic drugs for cancer. While these drugs show a tumor growth inhibitory action in clinical and non-clinical trials, they are known to induce inhibition of receptor enzyme activity and suppression of downstream signaling pathway. Therefore, a compound inhibiting EGFR or HER2 kinase, or inhibiting activation of EGFR or HER2 kinase is effective as a therapeutic drug for cancer.

As a compound that inhibits receptor type tyrosine kinases represented by HER2/EGFR kinase, fused heterocyclic compounds (e.g., WO97/13771, WO98/02437, WO00/44728), quinazoline derivatives (e.g., WO02/02552, WO01/98277, WO03/049740, WO03/050108), thienopyrimidine derivatives (e.g., WO03/053446), aromatic azole derivatives (e.g., WO98/03648, WO01/77107, WO03/031442) and the like are known; however, there is no HER2 kinase inhibitory substance to the present that has been marketed as a therapeutic drug for cancer.

As to pyrrolo[3,2-d]pyrimidine derivatives, the following compounds are known as compounds having a cell growth inhibitory activity (Khim.-Farm. Zh., 1982, 16, 1338-1343; Collect. Czech. Chem. Commun., 2003, 68, 779-791).



As a compound having a receptor type tyrosine kinase inhibitory activity, the following pyrrolo[3,2-d]pyrimidine derivative is known (WO96/40142, WO98/23613).



Furthermore, as to pyrazolo[4,3-d]pyrimidine derivatives, 3,5,7-trisubstituted pyrazolo[4,3-d]pyrimidine derivatives are known as compounds having a CDK inhibitory action, a cell growth inhibitory action and/or an apoptosis inducing action (EP-A-1348707), and 3-isopropylpyrazolo[4,3-d]pyrimidine derivatives are known as compounds having a CDK1/cyclin B inhibitory activity (Bioorganic & Medicinal Chemistry Letters, 2003, 13, 2989-2992). Furthermore, synthesis of 3-methylpyrazolo[4,3-d]pyrimidine derivatives has been reported (The Journal of Organic Chemistry, 1956, 21, 833-836).

Disclosure of the Invention

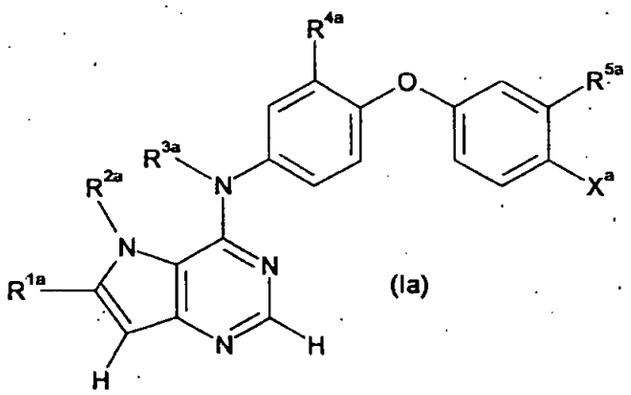
The present invention aims at providing a compound having a superior tyrosine kinase inhibitory action, which is low toxic and highly safe as a pharmaceutical

product.

The present inventors have conducted intensive studies in an attempt to solve the aforementioned problems and found that the compounds represented by the following formulas (Ia)-(Ih) and salts thereof have a superior tyrosine kinase inhibitory action. Further studies have resulted in the completion of the present invention.

Accordingly, the present invention relates to the following.

[1a] A compound represented by the formula:



wherein

R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6a}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl

wherein n is an integer of 1 to 4, R^{6a} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3a} is a hydrogen atom or a C_{1-6} alkyl group,

R^{4a} is a halogen atom or a C_{1-6} alkyl group,

R^{5a} is a halogen atom or a C_{1-6} alkyl group, and

X^a is a hydrogen atom or a halogen atom,

or a salt thereof,

provided that N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-

5-yl)ethyl]-2-(methylsulfonyl)acetamide is excluded.

[2a] The compound of the above-mentioned [1a], wherein X^a is a hydrogen atom.

[3a] The compound of the above-mentioned [2a], wherein R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-C_{1-4}$ alkyl wherein R^{6aa} is a hydrogen atom or a methyl group, R^{7a} and R^{8a} are the same or different and each is a hydrogen atom or a methyl group,

R^{3a} is a hydrogen atom,

R^{4a} is a chlorine atom or a methyl group, and

R^{5a} is a fluorine atom, a chlorine atom or a methyl group.

[4a] The compound of the above-mentioned [3a], wherein R^{7a} and R^{8a} are methyl groups.

[5a] A compound selected from the following:

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylsulfonyl)acetamide,

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N,2-dimethyl-2-(methylsulfonyl)propanamide,

N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

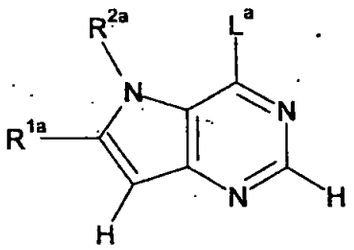
N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, and

N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,

or a salt thereof, or a hydrate thereof.

[6a] A prodrug of the compound of the above-mentioned [1a].

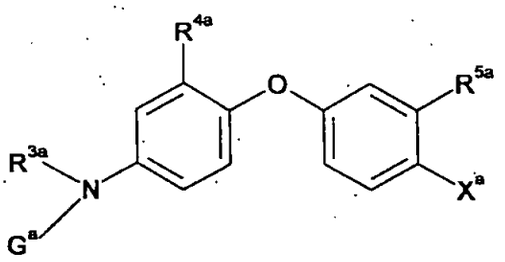
[7a] A production method of the compound of the above-mentioned [1a] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIa)

wherein L^a is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIa)

wherein G^a is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

[8a] A pharmaceutical agent comprising the compound of the above-mentioned [1a] or a salt thereof, or a prodrug thereof.

[9a] The pharmaceutical agent of the above-mentioned [8a], which is a tyrosine kinase inhibitor.

[10a] The pharmaceutical agent of the above-mentioned [8a], which is an agent for the prophylaxis or treatment of cancer.

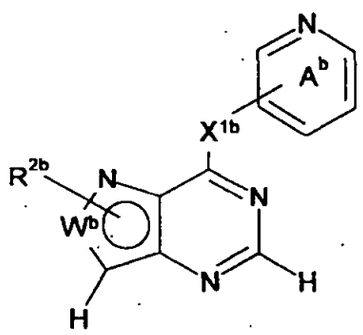
[11a] The pharmaceutical agent of the above-mentioned [10a], wherein the cancer is breast cancer, ovarian

cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[12a] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1a] or a salt thereof, or a prodrug thereof, to the mammal.

[13a] Use of the compound of the above-mentioned [1a] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[1b] A compound represented by the formula:



(Ib)

wherein

W^b is $C(R^{1b})$ or N,

ring A^b is an optionally substituted pyridine ring,

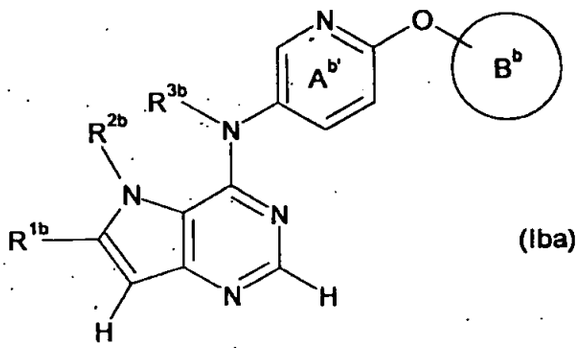
X^{1b} is $-NR^{3b}-Y^{1b}-$, -O-, -S-, -SO-, $-SO_2-$ or $-CHR^{3b}-$ wherein R^{3b} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3b} is optionally bonded to the carbon atom on the pyridine ring for ring A^b to form an optionally substituted ring structure, and Y^{1b} is a bond, or a C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene)-, each of which is optionally substituted, and

R^{1b} is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2b} is a hydrogen atom, or an optionally substituted

group bonded via a carbon atom or a sulfur atom, or R^{1b} and R^{2b}, or R^{2b} and R^{3b} are optionally bonded to form an optionally substituted ring structure,
or a salt thereof.

[2b] The compound of the above-mentioned [1b], which is a compound represented by the formula:



(Iba)

wherein ring $A^{b'}$ is an optionally further substituted pyridine ring, ring B^b is an optionally substituted C_{6-14} aryl group, and the other symbols are as defined above.

[3b] The compound of the above-mentioned [2b], wherein
R^{1b} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2b} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-C_{1-4}$ alkyl
wherein R^{6ba} is a hydrogen atom or a methyl group, n1 is an integer of 1 to 4, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,
(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$
wherein R^{6bb} is a hydrogen atom or a methyl group, n2 is an integer of 1 to 4, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl, and
(iv) hydroxy,
R^{3b} is a hydrogen atom,

ring $A^{b'}$ is a pyridine ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl, and

ring B^b is a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen.

[4b] The compound of the above-mentioned [2b], wherein ring $A^{b'}$ is a pyridine ring optionally substituted by halogen, and

ring B^b is a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen.

[5b] A compound selected from the following:

2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,

N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,

N-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide, and

N-(tert-butyl)-3-[(3-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}pyridin-2-yl)oxy]benzamide,

or a salt thereof.

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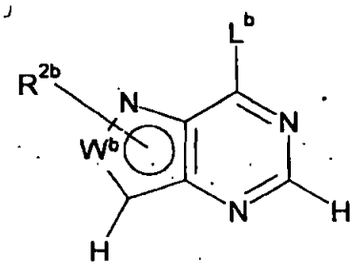
[6b] A prodrug of the compound of the above-mentioned [1b].

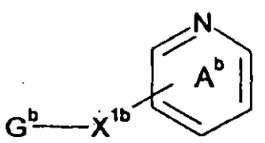
[7b] A production method of the compound of the above-mentioned [1b] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIb)

wherein L^b is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIb)

wherein G^b is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

[8b] A pharmaceutical agent comprising the compound of the above-mentioned [1b] or a salt thereof, or a prodrug thereof.

[9b] The pharmaceutical agent of the above-mentioned [8b], which is a tyrosine kinase inhibitor.

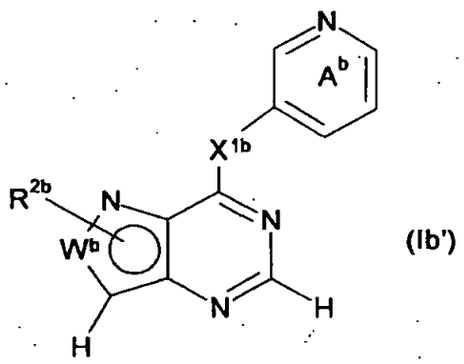
[10b] The pharmaceutical agent of the above-mentioned [8b], which is an agent for the prophylaxis or treatment of cancer.

[11b] The pharmaceutical agent of the above-mentioned [10b], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[12b] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1b] or a salt thereof, or a prodrug thereof, to the mammal.

[13b] Use of the compound of the above-mentioned [1b] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

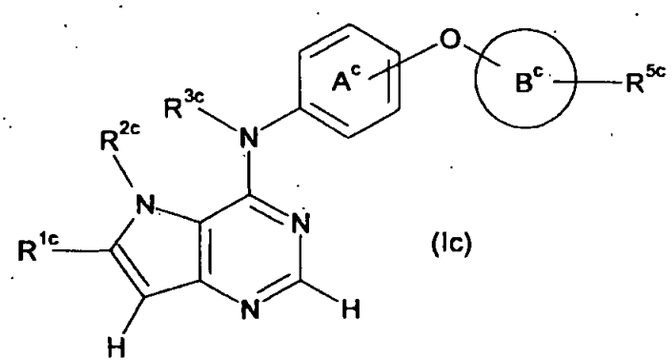
[14b] The compound of the above-mentioned [1b], which is a compound represented by the formula:



(Ib')

wherein each symbol is as defined above.

[1c] A compound represented by the formula:



(Ic)

wherein

R^{1c} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2c} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or

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R^{1c} and R^{2c}, or R^{2c} and R^{3c} are optionally bonded to form an optionally substituted ring structure,

R^{3c} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3c} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^c is an optionally substituted benzene ring,

R^{5c} is

(i) an optionally substituted amino group,

(ii) an optionally substituted carbamoyl group,

(iii) an optionally substituted ureido group,

(iv) an optionally substituted sulfamoyl group,

(v) an optionally substituted heterocyclic group,

(vi) an optionally substituted C_{2-6} alkoxy group

(vii) an optionally substituted aminomethyl group,

(viii) an optionally substituted carbamoylmethyl group,

(ix) an optionally substituted alkylsulfonyl group, or

(x) a cyano group, and

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group,

each of which is optionally further substituted besides R^{5c},

or a salt thereof,

provided that

N-(tert-butyl)-4-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide hydrochloride,

4-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2,2-dimethylpropyl)benzamide,

3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzonitrile,

3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzonitrile,

3-[2-chloro-4-(6,7-dihydro-9H-pyrimido[4',5':4,5]pyrrolo[2,1-c][1,4]oxazin-4-

ylamino)phenoxy]benzonitrile hydrochloride, and
(2E)-N-[(2E)-3-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-6-yl)prop-2-en-1-yl]-4-(dimethylamino)but-2-enamide
are excluded.

[2c] The compound of the above-mentioned [1c], wherein R^{1c} is a hydrogen atom.

[3c] A compound selected from the following:
2-{2-[4-({3-chloro-4-[3-(1,3-thiazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,
N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide,
3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2-hydroxy-1,1-dimethylethyl)benzamide,
N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,
N-(3-{2-chloro-4-[(6-cyano-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide,
N-(tert-butyl)-5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluorobenzamide,
N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,
N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]acetamide,

N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

N-{2-[4-({3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide,

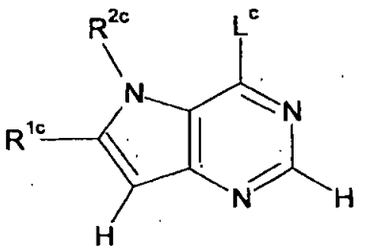
2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol, and

N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

or a salt thereof.

[4c] A prodrug of the compound of the above-mentioned [1c].

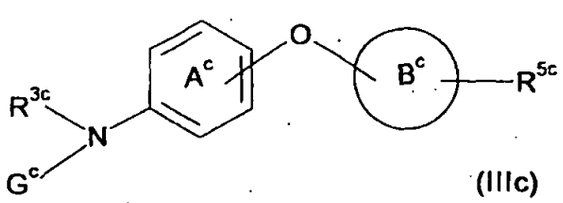
[5c] A production method of the compound of the above-mentioned [1c] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIc)

wherein L^c is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIc)

wherein G^c is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

[6c] A pharmaceutical agent comprising the compound of the above-mentioned [1c] or a salt thereof, or a prodrug thereof.

[7c] The pharmaceutical agent of the above-mentioned [6c], which is a tyrosine kinase inhibitor.

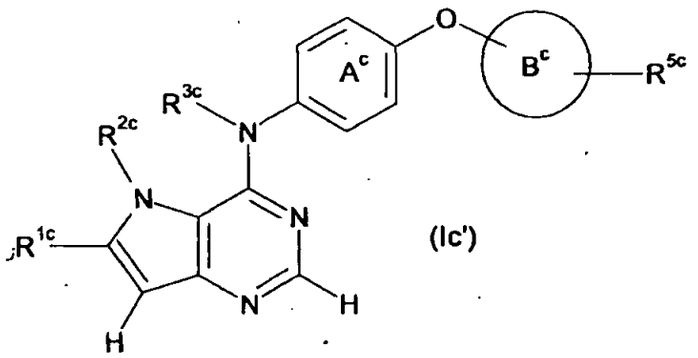
[8c] The pharmaceutical agent of the above-mentioned [6c], which is an agent for the prophylaxis or treatment of cancer.

[9c] The pharmaceutical agent of the above-mentioned [8c], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[10c] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1c] or a salt thereof, or a prodrug thereof, to the mammal.

[11c] Use of the compound of the above-mentioned [1c] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

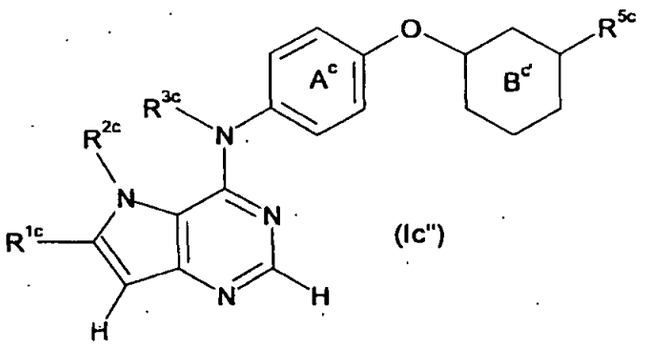
[12c] The compound of the above-mentioned [1c], which is a compound represented by the formula:



(Ic')

wherein each symbol is as defined above.

[13c] The compound of the above-mentioned [1c], which is a compound represented by the formula:



(Ic")

wherein ring $B^{c'}$ is a phenyl group or a cyclohexyl group, each of which is optionally further substituted besides R^{5c}, and the other symbols are as defined above.

[14c] The compound of the above-mentioned [1c], wherein R^{2c} is a C_{1-6} alkyl group optionally substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom

or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl.

[15c] The compound of the above-mentioned [1c], wherein

R^{1c} is a hydrogen atom or a cyano group,

R^{2c} is a C_{1-6} alkyl group optionally substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

(ii) a mono-C_{1-6} alkyl-amino group,

(iii) a di-C_{1-6} alkyl-amino group,

(iv) an optionally halogenated C_{1-6} alkanoyl-amino group,

(v) a hydroxy-C_{1-6} alkanoyl-amino group,

(vi) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vii) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(viii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(ix) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,

(x) a C_{3-7} cycloalkyl-carbonyl-amino group,

(xi) a C_{1-6} alkoxy-carbonyl-amino group,
(xii) a carbamoyl group,
(xiii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,
(xiv) a hydroxy-C_{1-6} alkyl-carbamoyl group,
(xv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,
(xvi) a C_{6-14} aryl-C_{1-6} alkyl-carbamoyl group,
(xvii) a C_{2-6} alkynyl-carbamoyl group,
(xviii) a piperidyl-C_{1-6} alkyl-carbamoyl group,
(xix) a morpholinyl-C_{1-6} alkyl-carbamoyl group,
(xx) a C_{3-7} cycloalkyl-carbamoyl group optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,
(xxi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,
(xxii) a ureido group,
(xxiii) a C_{1-6} alkyl-ureido group,
(xxiv) a C_{3-7} cycloalkyl-ureido group,
(xxv) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
(xxvi) a sulfamoyl group optionally substituted by C_{1-6} alkyl,
(xxvii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,
(xxviii) a C_{2-6} alkoxy group optionally substituted by substituent(s) selected from the group consisting of C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl,
(xxix) a carbamoylmethyl group optionally substituted by C_{1-6} alkyl,

(xxx) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,

(xxxi) a C_{1-6} alkylsulfonyl group optionally having C_{3-7} cycloalkyl or halogen, or

(xxxii) a cyano group, and

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[16c] The compound of the above-mentioned [1c] or [12c], wherein

R^{5c} is an amino group optionally substituted by substituent(s) selected from the group consisting of

(i) C_{1-6} alkyl,

(ii) optionally halogenated C_{1-6} alkanoyl,

(iii) hydroxy-C_{1-6} alkanoyl,

(iv) C_{1-6} alkanoyl having hydroxy and halogen,

(v) C_{3-7} cycloalkyl-C_{1-6} alkanoyl,

(vi) C_{1-6} alkanoyl having C_{3-7} cycloalkyl and halogen,

(vii) C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl,

(viii) C_{3-7} cycloalkyl-carbonyl, and

(ix) C_{1-6} alkoxy-carbonyl,

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

R^{1c} is a hydrogen atom,

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[17c] The compound of the above-mentioned [1c] or [12c], wherein

R^{5c} is a carbamoyl group optionally substituted by substituent(s) selected from the group consisting of

(i) optionally halogenated C_{1-6} alkyl,

(ii) hydroxy-C_{1-6} alkyl,

(iii) C_{1-6} alkoxy-C_{1-6} alkyl,

(iv) C_{6-14} aryl-C_{1-6} alkyl,

(v) C_{2-6} alkynyl,

(vi) piperidyl-C_{1-6} alkyl,

(vii) morpholinyl-C_{1-6} alkyl, and

(viii) C_{3-7} cycloalkyl optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

R^{1c} is a hydrogen atom,

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) -O-C_{1-4} alkyl,
(vii) -S-C_{1-4} alkyl,
(viii) -SO_2-C_{1-4} alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and -$(CH_2)_n$- is optionally substituted by C_{1-4} alkyl,
R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[18c] The compound of the above-mentioned [1c] or [12c], wherein
R^{5c} is a ureido group optionally substituted by substituent(s) selected from the group consisting of
(i) C_{1-6} alkyl,
(ii) C_{3-7} cycloalkyl, and
(iii) 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
R^{1c} is a hydrogen atom,
R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) -NR^{6c}-CO-$(CH_2)_n$-SO_2-optionally halogenated C_{1-4} alkyl,
(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,
(iii) -O-$(CH_2)_n$-OH,
(iv) hydroxy,
(v) -NR^{6c}-CO-C_{1-4} alkyl,
(vi) -O-C_{1-4} alkyl,
(vii) -S-C_{1-4} alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[19c] The compound of the above-mentioned [1c] or [12c], wherein

R^{5c} is a sulfamoyl group optionally substituted by C_{1-6} alkyl,

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

R^{1c} is a hydrogen atom,

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of

halogen and methyl.

[20c] The compound of the above-mentioned [1c] or [12c], wherein

R^{5c} is a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

R^{1c} is a hydrogen atom,

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[21c] The compound of any one of the above-mentioned [16c] to [20c], wherein

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl

wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

(iii) $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino.

[22c] The compound of the above-mentioned [1c] or [12c], wherein

R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6ca}-CO-(CH_2)_{n1}-SO_2-$optionally halogenated C_{1-4} alkyl

wherein n1 is an integer of 1 to 4, R^{6ca} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,

R^{1c} is a hydrogen atom,

R^{3c} is a hydrogen atom,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having C_{1-6} alkylsulfonyl, or (b) mono- or di- substituted by C_{1-6} alkyl,

(ii) a carbamoyl group optionally substituted by C_{1-6} alkyl,

(iii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by optionally halogenated C_{1-6} alkyl,

(iv) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,

(v) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,

(vi) a C_{1-6} alkylsulfonyl group optionally substituted by C_{3-7} cycloalkyl, or

(vii) a cyano group, and

ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[23c] The compound of the above-mentioned [22c], wherein R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group.

[24c] The compound of the above-mentioned [1c] or [12c], wherein

R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6cb}-CO-(CH_2)_{n2}-OH$ wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

R^{1c} is a hydrogen atom,

R^{3c} is a hydrogen atom,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having hydroxy, or (b) mono- or di-substituted by C_{1-6} alkyl,

(ii) a carbamoyl group optionally substituted by C_{1-6} alkyl,

(iii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by optionally halogenated C_{1-6} alkyl,

(iv) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,

(v) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,

(vi) a C_{1-6} alkylsulfonyl group optionally substituted by C_{3-7} cycloalkyl, or

(vii) a cyano group, and

ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[25c] The compound of the above-mentioned [24c], wherein R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NH-CO-CH_2-CR^{9c}R^{10c}-OH$

wherein R^{9c} and R^{10c} are the same or different and each is a C_{1-4} alkyl group.

[26c] The compound of the above-mentioned [1c] or [12c], wherein

R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,

R^{1c} is a hydrogen atom,

R^{3c} is a hydrogen atom,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{3-7} cycloalkyl-carbonyl-amino group,

(ix) a C_{1-6} alkoxy-carbonyl-amino group,

(x) a carbamoyl group,

(xi) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xii) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xiii) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{3-7} cycloalkyl-carbamoyl group,

(xv) a ureido group,

(xvi) a C_{1-6} alkyl-ureido group,

(xvii) a C_{3-7} cycloalkyl-ureido group,

(xviii) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,

(xix) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,

(xx) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by

optionally halogenated C_{1-6} alkyl or C_{1-6} alkoxy-carbonyl,
(xxi) an optionally halogenated C_{2-6} alkoxy group,
(xxii) a C_{1-6} alkylsulfonyl group, or
(xxiii) a cyano group, and
ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[27c] The compound of the above-mentioned [1c] or [12c], wherein
R^{2c} is a C_{1-6} alkyl group substituted by hydroxy,
R^{1c} is a hydrogen atom,
R^{3c} is a hydrogen atom,
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
R^{5c} is
(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having hydroxy, or (b) mono- or di-substituted by C_{1-6} alkyl,
(ii) a carbamoyl group optionally substituted by optionally halogenated C_{1-6} alkyl,
(iii) a C_{3-7} cycloalkyl-carbamoyl group optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,
(iv) a C_{6-14} aryl-C_{1-6} alkyl-carbamoyl group,
(v) a hydroxy-C_{1-6} alkyl-carbamoyl group,
(vi) a morpholinyl-C_{1-6} alkyl-carbamoyl group,
(vii) a C_{2-6} alkynyl-carbamoyl group,
(viii) a carbamoylmethyl group optionally substituted by C_{1-6} alkyl,
(ix) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,
(x) an aminomethyl group optionally substituted by C_{1-6} alkoxy-carbonyl, or
(xi) a C_{1-6} alkylsulfonyl group optionally substituted by

C_{3-7} cycloalkyl, and

ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[28c] The compound of the above-mentioned [1c] or [12c], wherein

R^{1c} is a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2c} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6c}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,
(ix) a C_{3-7} cycloalkyl-carbonyl-amino group,
(x) a C_{1-6} alkoxy-carbonyl-amino group,
(xi) a carbamoyl group,
(xii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,
(xiii) a hydroxy-C_{1-6} alkyl-carbamoyl group,
(xiv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,
(xv) a C_{3-7} cycloalkyl-carbamoyl group,
(xvi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,
(xvii) a ureido group,
(xviii) a C_{1-6} alkyl-ureido group,
(xix) a C_{3-7} cycloalkyl-ureido group,
(xx) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
(xxi) a sulfamoyl group optionally substituted by C_{1-6} alkyl, or
(xxii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl, and

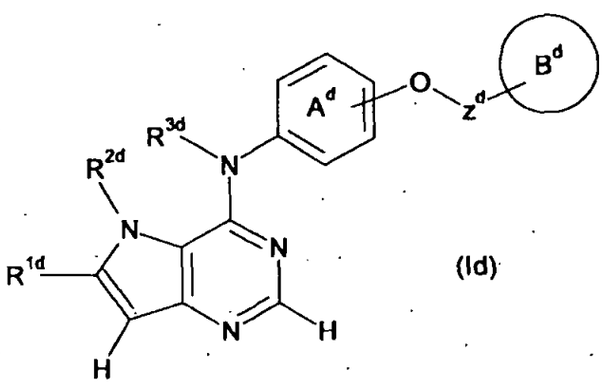
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

[29c] The compound of any one of the above-mentioned [14c] to [20c] and [28c], wherein ring B^c is a phenyl group or a cyclohexyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s)

selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen, and is substituted by R^{5c} at the meta-position of the phenyl group or the β-position of the cyclohexyl group.

[30c] The compound of any one of the above-mentioned [22c] to [27c], wherein ring B^c is a phenyl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen, which phenyl is substituted by R^{5c} at the meta-position of the phenyl group.

[1d] A compound represented by the formula:



(Id)

wherein

R^{1d} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2d} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or,

R^{1d} and R^{2d}, or R^{2d} and R^{3d} are optionally bonded to form an optionally substituted ring structure,

R^{3d} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3d} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^d is an optionally substituted benzene ring,

Z^d is an optionally substituted C_{1-3} alkylene,

ring B^d is an optionally substituted heterocyclic group, or a salt thereof,

provided that

ethyl 5-[(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl]-2-furoate,

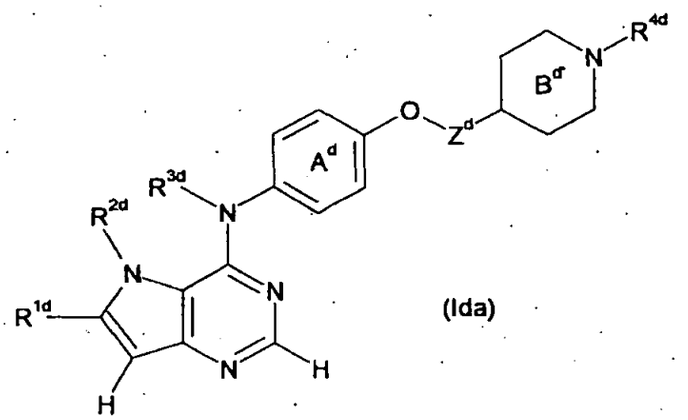
5-[(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl]-2-furancarboxylic acid,

2-[2-(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol, and

N-[2-(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

are excluded.

[2d] The compound of the above-mentioned [1d], which is a compound represented by the formula:



(Ida)

wherein R^{4d} is an acyl group or an optionally substituted ureido group, ring $B^{d'}$ is a piperidyl group optionally further substituted besides R^{4d}, and the other symbols are as defined above.

[3d] A compound selected from the following:

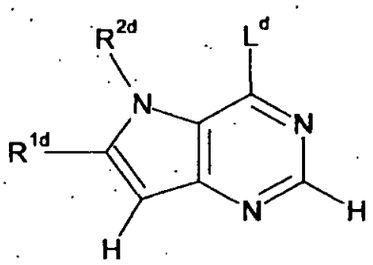
tert-butyl 4-{[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]methyl}piperidine-1-carboxylate, and

tert-butyl 4-[(2-chloro-4-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)methyl]piperidine-1-carboxylate, or a salt thereof.

[4d] A prodrug of the compound of the above-mentioned [1d].

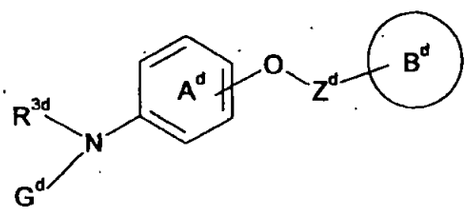
[5d] A production method of the compound of the above-mentioned [1d] or a salt thereof, which comprises reacting a compound represented by the formula:



(IId)

wherein L^d is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIId)

wherein G^d is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

[6d] A pharmaceutical agent comprising the compound of the above-mentioned [1d] or a salt thereof, or a prodrug thereof.

[7d] The pharmaceutical agent of the above-mentioned [6d], which is a tyrosine kinase inhibitor.

[8d] The pharmaceutical agent of the above-mentioned [6d], which is an agent for the prophylaxis or treatment of cancer.

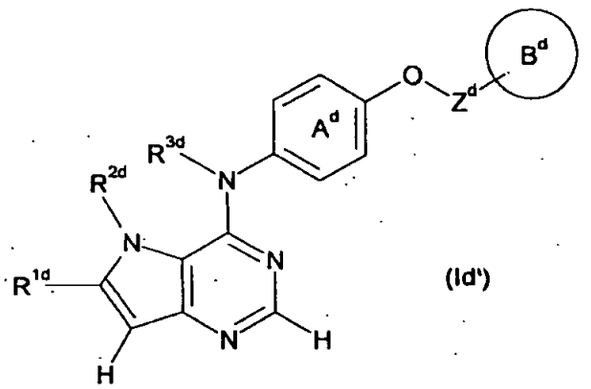
[9d] The pharmaceutical agent of the above-mentioned

[8d], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[10d] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1d] or a salt thereof, or a prodrug thereof, to the mammal.

[11d] Use of the compound of the above-mentioned [1d] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[12d] The compound of the above-mentioned [1d], which is a compound represented by the formula:



(Id')

wherein each symbol is as defined above.

[13d] The compound of the above-mentioned [2d], wherein R^{1d} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2d} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6d}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6d}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6d} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3d} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^d is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

Z^d is methylene,

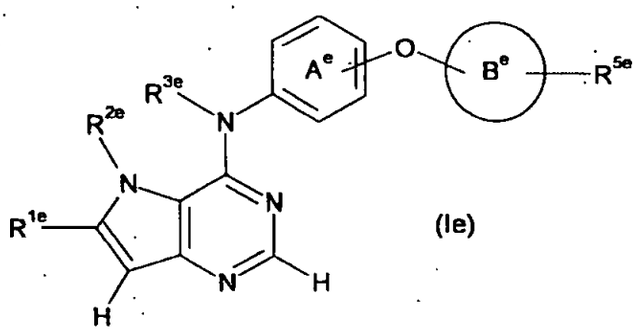
ring B^d is a piperidyl group, and

R^{4d} is a C_{1-6} alkoxy-carbonyl group, a C_{5-8} cycloalkyl-carbonyl group, a C_{1-6} alkyl-ureido group or a C_{5-8} cycloalkyl-ureido group.

[14d] The compound of the above-mentioned [2d], wherein R^{3d} is a hydrogen atom, and

ring A^d is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[1e] A compound represented by the formula:



(Ie)

wherein

R^{1e} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2e} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or,

R^{1e} and R^{2e}, or R^{2e} and R^{3e} are optionally bonded to form an optionally substituted ring structure,

R^{3e} is a hydrogen atom or an optionally substituted

aliphatic hydrocarbon group, or R^{3e} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^e is an optionally substituted benzene ring,

R^{5e} is

(i) a linear alkyl group substituted by optionally substituted heterocyclic group,

(ii) a linear alkyl group substituted by optionally substituted imino,

(iii) a linear alkyl group substituted by optionally substituted aryl, which is optionally further halogenated or hydroxylated,

(iv) an optionally substituted branched alkyl group,

(v) an optionally substituted alkenyl group,

(vi) a hydroxy group substituted by optionally substituted aryl,

(vii) a hydroxy group substituted by C_{1-6} alkyl,

(viii) a hydroxy group substituted by halogenated C_{2-6} alkyl,

(ix) a halogenated C_{2-6} alkyl group,

(x) an optionally substituted cycloalkyl group, or

(xi) a C_{1-6} alkyl-carbonyl group optionally substituted by optionally substituted aryl, and

ring B^e is a C_{6-14} aryl group optionally further substituted besides R^{5e},

or a salt thereof,

provided that

2-(2-{4-[(3-chloro-4-{4-[3-(1H-imidazol-1-yl)propyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol dihydrochloride,

2-(2-{4-[(3-chloro-4-{4-[4-(1H-1,2,3-triazol-1-yl)butyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol, and

1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-

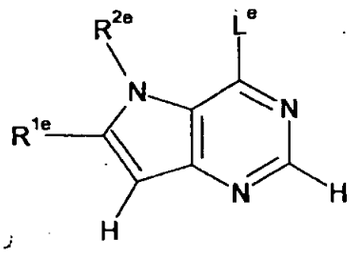
yl}amino)phenoxy]phenyl}ethanone
are excluded.

[2e] The compound of the above-mentioned [1e], wherein the "linear alkyl group substituted by optionally substituted heterocyclic group" for R^{5e} is
(i) a methyl group substituted by optionally substituted heterocyclic group, or
(ii) a linear alkyl group substituted by substituted heterocyclic group.

[3e] A compound selected from the following:
2-[4-({3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol,
(1Z)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one O-ethyloxime,
1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-ol,
1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one,
N-(2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide, and
N-{2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
or a salt thereof.

[4e] A prodrug of the compound of the above-mentioned [1e].

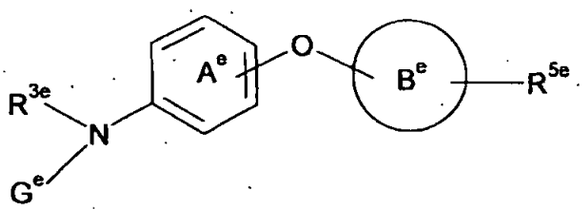
[5e] A production method of the compound of the above-mentioned [1e] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIe)

wherein L^e is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIe)

wherein G^e is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

[6e] A pharmaceutical agent comprising the compound of the above-mentioned [1e] or a salt thereof, or a prodrug thereof.

[7e] The pharmaceutical agent of the above-mentioned [6e], which is a tyrosine kinase inhibitor.

[8e] The pharmaceutical agent of the above-mentioned [6e], which is an agent for the prophylaxis or treatment of cancer.

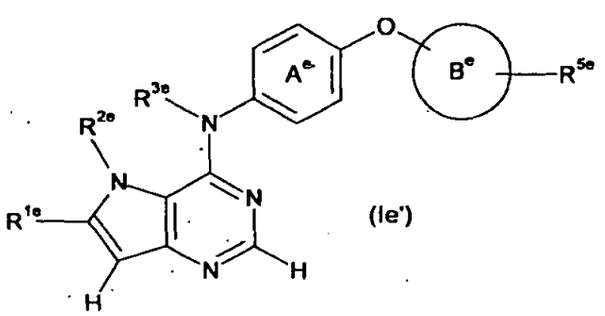
[9e] The pharmaceutical agent of the above-mentioned [8e], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[10e] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1e] or a salt thereof, or a prodrug thereof, to the

mammal.

[11e] Use of the compound of the above-mentioned [1e] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[12e] The compound of the above-mentioned [1e], which is a compound represented by the formula:



(Ie')

wherein each symbol is as defined above.

[13e] The compound of the above-mentioned [1e], wherein

R^{1e} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2e} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6e}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6e}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6e} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3e} is a hydrogen atom,

ring A^e is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5e} is

(i) a 5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero

atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl,

(ii) a linear C_{1-6} alkyl group substituted by hydroxyimino or C_{1-6} alkoxyimino,

(iii) a linear C_{1-6} alkyl group substituted by C_{6-14} aryl, which is optionally further halogenated or hydroxylated,

(iv) an optionally halogenated branched C_{3-6} alkyl group,

(v) a C_{2-6} alkenyl group,

(vi) a hydroxy group substituted by C_{6-14} aryl,

(vii) a hydroxy group substituted by C_{1-6} alkyl,

(viii) a hydroxy group substituted by halogenated C_{2-6} alkyl,

(ix) a halogenated C_{2-6} alkyl group,

(x) a C_{3-7} cycloalkyl group optionally substituted by cyano or carbamoyl, or

(xi) a C_{1-6} alkyl-carbonyl group optionally substituted by phenyl, and

ring B^e is a C_{6-14} aryl group optionally further substituted, besides R^{5e}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

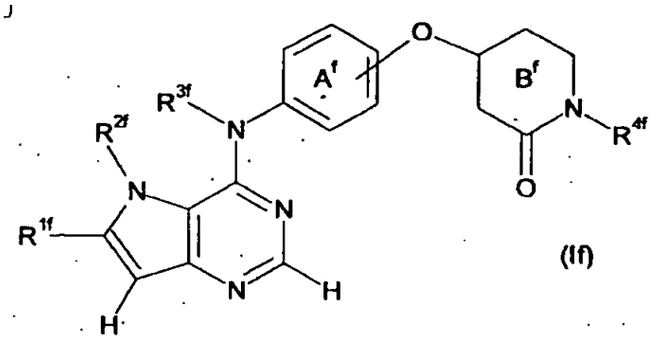
[14e] The compound of the above-mentioned [13e], wherein the "5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl" for R^{5e} is

(i) a 5- to 8-membered heterocyclyl-methyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl, or

(ii) a 5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero

atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and having C_{1-6} alkyl.

[1f] A compound represented by the formula:



(If)

wherein

R^{1f} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2f} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or,

R^{1f} and R^{2f}, or R^{2f} and R^{3f} are optionally bonded to form an optionally substituted ring structure,

R^{3f} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3f} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^f is an optionally substituted benzene ring,

ring B^f is a piperidyl group optionally further substituted besides R^{4f}, and

R^{4f} is (i) an optionally substituted C_{1-6} alkyl group, or (ii) an optionally substituted C_{5-8} cycloalkyl group,

or a salt thereof.

[2f] The compound of the above-mentioned [1f], wherein

R^{1f} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2f} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6f}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6f} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3f} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^f is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

ring B^f is a piperidyl group, and

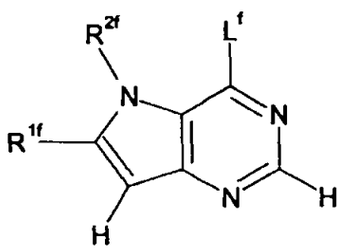
R^{4f} is (i) an optionally substituted C_{1-6} alkyl group, or (ii) an optionally substituted C_{5-8} cycloalkyl group.

[3f] The compound of the above-mentioned [1f], wherein R^{3f} is a hydrogen atom, and

ring A^f is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

[4f] A prodrug of the compound of the above-mentioned [1f].

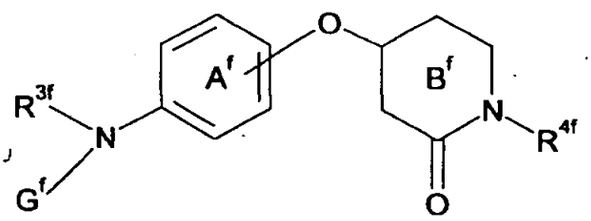
[5f] A production method of the compound of the above-mentioned [1f] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIIf)

wherein L^f is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIf)

wherein G^f is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

[6f] A pharmaceutical agent comprising the compound of the above-mentioned [1f] or a salt thereof, or a prodrug thereof.

[7f] The pharmaceutical agent of the above-mentioned [6f], which is a tyrosine kinase inhibitor.

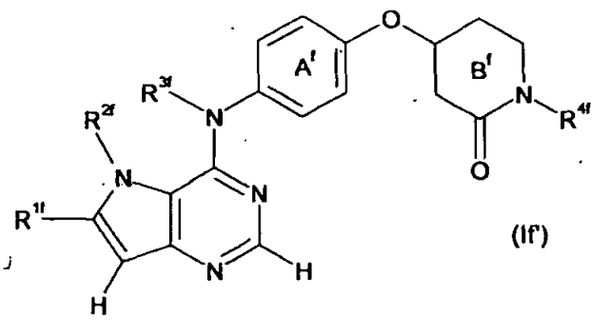
[8f] The pharmaceutical agent of the above-mentioned [6f], which is an agent for the prophylaxis or treatment of cancer.

[9f] The pharmaceutical agent of the above-mentioned [8f], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[10f] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1f] or a salt thereof, or a prodrug thereof, to the mammal.

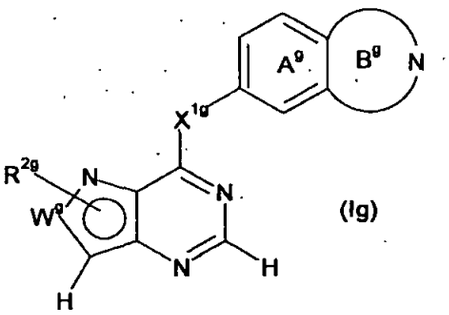
[11f] Use of the compound of the above-mentioned [1f] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[12f] The compound of the above-mentioned [1f], which is a compound represented by the formula:



wherein each symbol is as defined above.

[1g] A compound represented by the formula:



wherein

W^g is $C(R^{1g})$ or N,

ring A^g is an optionally substituted benzene ring,

ring B^g is an optionally substituted nitrogen-containing heterocycle,

X^{1g} is $-NR^{3g}-Y^{1g}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^{3g}-$ wherein R^{3g} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3g} is optionally bonded to the carbon atom on the benzene ring for ring A^g to form an optionally substituted ring structure, and Y^{1g} is a bond, or a C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene$)-$, each of which is optionally substituted, and

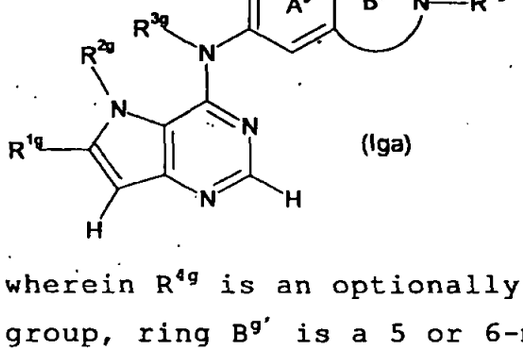
R^{1g} is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2g} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1g} and R^{2g}, or R^{2g} and R^{3g} are optionally bonded to form an optionally substituted ring structure,

or a salt thereof.

[2g] The compound of the above-mentioned [1g], which is a compound represented by the formula:



(Iga)

wherein R^{4g} is an optionally substituted hydrocarbon group, ring $B^{g'}$ is a 5 or 6-membered nitrogen-containing heterocycle optionally further substituted besides R^{4g}, and the other symbols are as defined above.

[3g] The compound of the above-mentioned [2g], wherein

R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2g} is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,

R^{4g} is (i) an optionally substituted C_{6-14} aryl-C_{1-8} alkyl group, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, (iii) a C_{1-8} alkyl group, or (iv) an optionally substituted C_{6-14} aryl group.

[4g] The compound of the above-mentioned [2g], wherein

R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2g} is

(i) a hydrogen atom,

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

(iii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

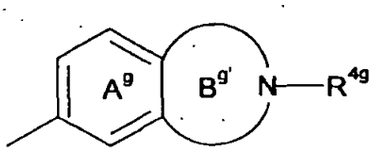
(c) $-NR^{5g}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(d) hydroxy, and

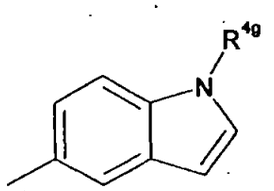
(e) amino

wherein n is an integer of 1 to 4, R^{5g} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

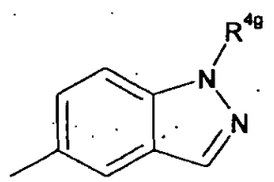
R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,



is the formula



or



, and

R^{4g} is (i) a C_{6-14} aryl-C_{1-8} alkyl group optionally substituted by substituent(s) selected from the group consisting of halogen, C_{1-6} alkyl-carbamoyl and halo C_{1-6} alkoxy, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, or (iii) an optionally substituted C_{6-14} aryl group.

[5g] A compound selected from the following:

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide,

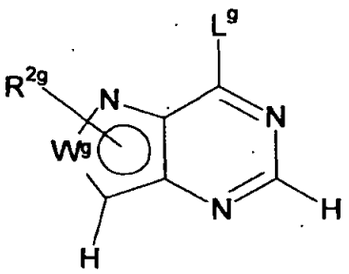
N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide,

N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indazol-1-yl)methyl]benzamide, and
N-(tert-butyl)-6-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]pyridine-2-carboxamide,
or a salt thereof.

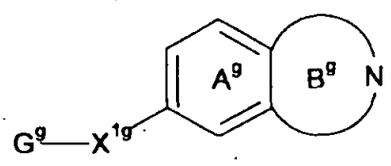
[6g] A prodrug of the compound of the above-mentioned [1g].

[7g] A production method of the compound of the above-mentioned [1g] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIg)

wherein L^g is a leaving group, and the other symbols are as defined above,
or a salt thereof and a compound represented by the formula:



(IIIg)

wherein G^g is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

[8g] A pharmaceutical agent comprising the compound of the above-mentioned [1g] or a salt thereof, or a prodrug thereof.

[9g] The pharmaceutical agent of the above-mentioned [8g], which is a tyrosine kinase inhibitor.

[10g] The pharmaceutical agent of the above-mentioned [8g], which is an agent for the prophylaxis or treatment

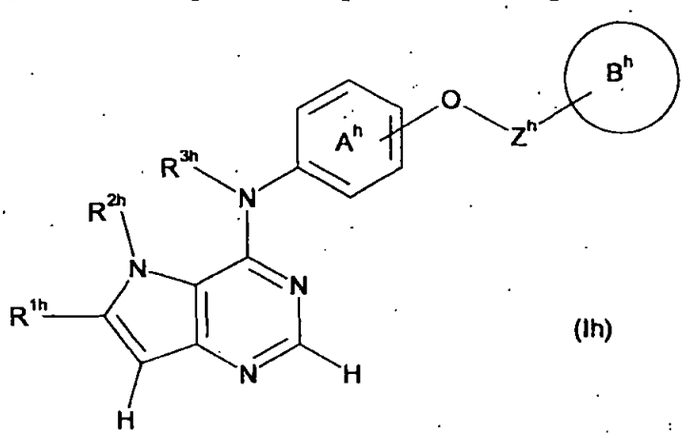
of cancer.

[11g] The pharmaceutical agent of the above-mentioned [10g], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[12g] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1g] or a salt thereof, or a prodrug thereof, to the mammal.

[13g] Use of the compound of the above-mentioned [1g] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[1h] A compound represented by the formula:



(Ih)

wherein

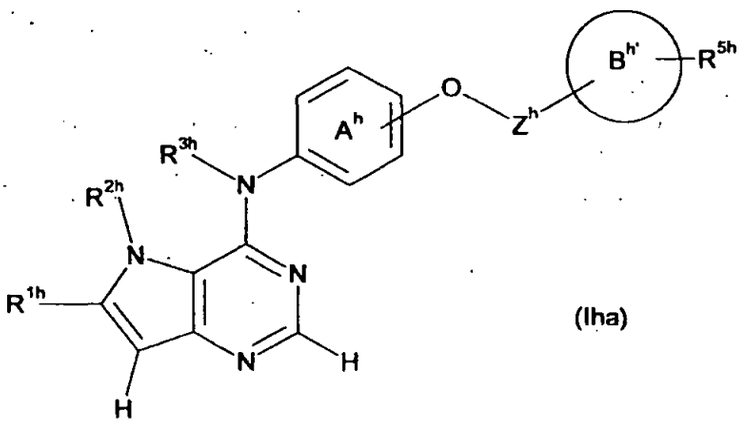
R^{1h} is a halogen atom or a halogenated C_{1-6} alkyl group,

R^{2h} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or R^{1h} and R^{2h}, or R^{2h} and R^{3h} are bonded to form an optionally substituted ring structure,

R^{3h} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3h} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

Z^h is a bond or an optionally substituted C_{1-3} alkylene, ring A^h is an optionally substituted benzene ring, and ring B^h is (i) an optionally substituted C_{6-14} aryl group, (ii) an optionally substituted heterocyclic group, or (iii) an optionally substituted C_{5-8} cycloalkyl group, or a salt thereof.

[2h] The compound of the above-mentioned [1h], which is a compound represented by the formula:



(IIa)

wherein

R^{5h} is

(i) an optionally substituted amino group,

(ii) an optionally substituted carbamoyl group,

(iii) an optionally substituted ureido group,

(iv) an optionally substituted sulfamoyl group,

(v) an optionally substituted heterocyclic group,

(vi) an optionally substituted hydrocarbon group,

(vii) a halogen atom, or

(viii) an optionally substituted carboxyl group, and

ring $B^{h'}$ is (i) a C_{6-14} aryl group, (ii) a heterocyclic group, or (iii) a C_{5-8} cycloalkyl group, each of which is optionally further substituted besides R^{5h}, and the other symbols are as defined above.

[3h] A compound selected from the following:

N-(3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide,

6-chloro-N-{3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-4-amine,

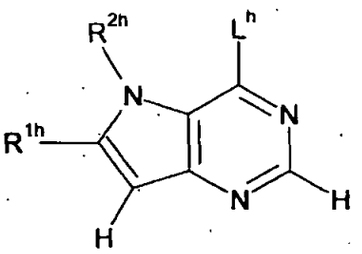
N-[3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide, and

N-(tert-butyl)-3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,

or a salt thereof.

[4h] A prodrug of the compound of the above-mentioned [1h].

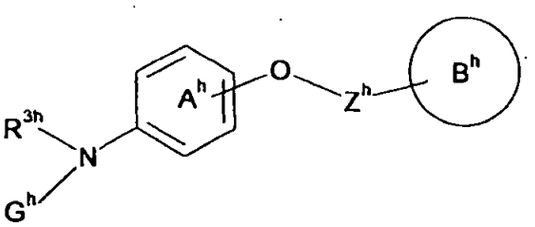
[5h] A production method of the compound of the above-mentioned [1h] or a salt thereof, which comprises reacting a compound represented by the formula:



(IIh)

wherein L^h is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIh)

wherein G^h is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

[6h] A pharmaceutical agent comprising the compound of the above-mentioned [1h] or a salt thereof, or a prodrug

thereof.

[7h] The pharmaceutical agent of the above-mentioned [6h], which is a tyrosine kinase inhibitor.

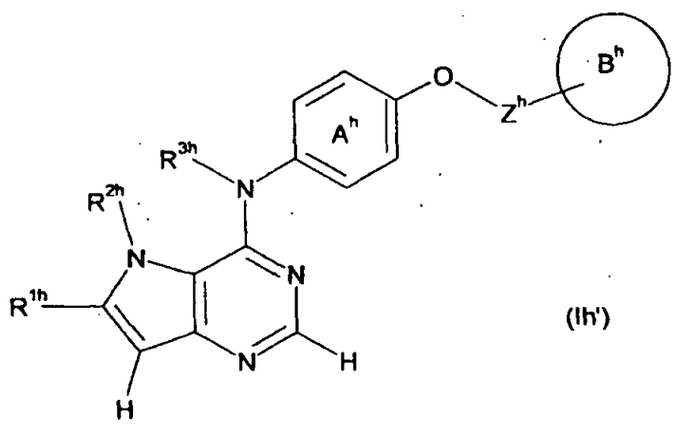
[8h] The pharmaceutical agent of the above-mentioned [6h], which is an agent for the prophylaxis or treatment of cancer.

[9h] The pharmaceutical agent of the above-mentioned [8h], wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

[10h] A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1h] or a salt thereof, or a prodrug thereof, to the mammal.

[11h] Use of the compound of the above-mentioned [1h] or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

[12h] The compound of the above-mentioned [1h], which is a compound represented by the formula:



(Ih')

wherein each symbol is as defined above.

[13h] The compound of the above-mentioned [2h], wherein R^{1h} is a halogen atom or an optionally halogenated C_{1-6} alkyl group,

R^{2h} is

(i) a hydrogen atom,

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

(iii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{6h}-CO-(CH_2)_n-OH$,

(c) $-NR^{6h}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6h} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3h} is a hydrogen atom or a C_{1-6} alkyl group,

Z^h is a bond or methylene,

ring A^h is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5h} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,

(ix) a C_{3-7} cycloalkyl-carbonyl-amino group,

(x) a C_{1-6} alkoxy-carbonyl-amino group,

(xi) a carbamoyl group,

(xii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xiii) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,
(xv) a C_{3-7} cycloalkyl-carbamoyl group,
(xvi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,
(xvii) a ureido group,
(xviii) a C_{1-6} alkyl-ureido group,
(xix) a C_{3-7} cycloalkyl-ureido group,
(xx) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
(xxi) a sulfamoyl group optionally substituted by C_{1-6} alkyl,
(xxii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,
(xxiii) an optionally halogenated C_{1-6} alkyl group,
(xxiv) a C_{1-6} alkoxy-carbonyl group,
(xxv) a halogen atom, or
(xxvi) a carboxyl group, and
ring $B^{h'}$ is a phenyl group, a pyridyl group or a piperidyl group, each of which is optionally further substituted besides R^{5h}.

Each symbol used in the present specification is described in detail in the following.

In the present specification, unless otherwise specified, as the "halogen atom" (and "halogen" in substituent), fluorine atom, chlorine atom, bromine atom and iodine atom can be mentioned.

In the present specification, unless otherwise specified, as the "alkyl group", a straight chain or branched alkyl group having 1 to 10 (e.g., 1 to 10, 1 to 8, 1 to 6, 2 to 6, 1 to 4) carbon atoms, 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.

In the present specification, unless otherwise specified, as the "C_{1-10} alkyl group", 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.

In the present specification, unless otherwise specified, as the "C_{1-8} alkyl group", 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 and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-6} alkyl group", 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 and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{2-6} alkyl group", for example, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl,

3,3-dimethylbutyl, 2-ethylbutyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-4} alkyl group", for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "alkenyl group", an alkenyl group having 2 to 10 (e.g., 2 to 10, 2 to 8, 2 to 6, 2 to 4) carbon atoms, 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.

In the present specification, unless otherwise specified, 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.

In the present specification, unless otherwise specified, as the "C_{2-8} 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.

In the present specification, unless otherwise specified, as the "C_{2-6} 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 and the like

can be mentioned.

In the present specification, unless otherwise specified, as the "C_{2-4} alkenyl group", for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "alkynyl group", an alkynyl group having 2 to 10 (e.g., 2 to 10, 2 to 8, 2 to 6, 2 to 4) carbon atoms, 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.

In the present specification, unless otherwise specified, 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.

In the present specification, unless otherwise specified, as the "C_{2-8} 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.

In the present specification, unless otherwise specified, as the "C_{2-6} 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 and the like can be mentioned.

In the present specification, unless otherwise

specified, as the "C_{2-4} alkynyl group", for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "cycloalkyl group", a cycloalkyl group having 3 to 10 (e.g., 3 to 10, 3 to 8, 3 to 7, 3 to 6, 5 to 8) carbon atoms, 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, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

In the present specification, unless otherwise specified, 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, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{3-8} 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 and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{3-7} cycloalkyl group", for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{5-8} cycloalkyl group", for example, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "cycloalkenyl group", a cycloalkenyl group having 3 to 10 carbon atoms, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like can be mentioned.

In the present specification, unless otherwise specified, 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.

In the present specification, unless otherwise specified, as the "cycloalkadienyl group", a cycloalkadienyl group having 4 to 10 carbon atoms, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like can be mentioned.

In the present specification, unless otherwise specified, 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.

In the present specification, unless otherwise specified, the term "aryl group" encompasses a monocyclic aryl group and a fused polycyclic aryl group. As the "aryl group", an aryl group having 6 to 18 (e.g., 6 to 18, 6 to 14, 6 to 10) carbon atoms, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{6-18} aryl group", for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{6-14} aryl group", for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthyl, biphenylyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{6-10} aryl group", for example, phenyl, naphthyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "aralkyl group", an aralkyl group having 7 to 16 carbon atoms, for example, benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{7-16} aralkyl group", for example, benzyl, phenethyl, phenylpropyl, naphthylmethyl, biphenylylmethyl and the like can be mentioned.

In the present specification, unless otherwise specified, as the "alkanoyl group", an alkanoyl group having 1 to 7 (e.g., 1 to 7, 1 to 6) carbon atoms, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl) and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-6} alkanoyl group", for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, valeryl, pivaloyl) and the like can be mentioned.

In the present specification, unless otherwise specified, as the "alkoxy group", an alkoxy group having 1 to 6 (e.g., 1 to 6, 2 to 6, 1 to 4) carbon atoms, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-6} alkoxy group", for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy and the like can be mentioned.

In the present specification, unless otherwise

specified, as the "C_{2-6} alkoxy group", for example, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-pentyloxy, n-hexyloxy and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-4} alkoxy group", for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and the like can be mentioned.

In the present specification, unless otherwise specified, as the "alkylene", an alkylene having 1 to 4 (e.g., 1 to 4, 1 to 3) carbon atoms, for example, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2-$ and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-4} alkylene", for example, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2-$ and the like can be mentioned.

In the present specification, unless otherwise specified, as the "C_{1-3} alkylene", for example, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$ and the like can be mentioned.

In the present specification, unless otherwise specified, as the "hydrocarbon group" of the "optionally substituted hydrocarbon group", for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkenyl group, a cycloalkadienyl group, an aryl group, an aralkyl group, an arylalkenyl group, a cycloalkyl-alkyl group and the like can be mentioned. Of these, 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_{7-16} aralkyl group, a C_{8-13} arylalkenyl group, a C_{3-10} cycloalkyl-C_{1-6} alkyl group and the like are preferable.

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group are each optionally condensed with a benzene ring, and as such a fused ring group, for example, indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like can be mentioned. In addition, as the above-mentioned hydrocarbon group, a crosslinked hydrocarbon group such as norbornanyl, adamantyl and the like, and the like can also 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, cyclopropylmethyl, cyclohexylmethyl and the like can be mentioned.

The above-mentioned C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group, which are exemplarily recited as the "hydrocarbon group", each optionally has 1 to 3 substituents at substitutable positions.

As such substituents, for example,

(1) a C_{3-10} cycloalkyl group (e.g., cyclopropyl, cyclohexyl) optionally substituted by 1 to 3 substituents selected from the group consisting of
halogen;
hydroxy;
carboxyl;
sulfo;
cyano;
azido;
nitro;
nitroso;
optionally halogenated C_{1-4} alkyl;
optionally halogenated C_{2-4} alkenyl;
optionally halogenated C_{2-4} alkynyl;
C_{3-7} cycloalkyl;
C_{6-14} aryl;

C_{7-16} aralkyl;
formyl;
optionally halogenated C_{1-6} alkyl-carbonyl;
optionally halogenated C_{1-6} alkoxy-carbonyl;
optionally halogenated C_{1-6} alkylsulfonyl;
carbamoyl;
carbamoyl mono- or di-substituted by optionally halogenated C_{1-6} alkyl;
mono- or di-C_{6-14} aryl-carbamoyl;
thiocarbamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;
ureido optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;
mono- or di-C_{6-14} aryl-ureido;
sulfamoyl optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl;
optionally halogenated C_{1-6} alkoxy;
optionally halogenated C_{2-6} alkenyloxy;
C_{3-10} cycloalkyloxy;
C_{7-16} aralkyloxy;
C_{6-14} aryloxy;
C_{1-6} alkyl-carbonyloxy;
C_{3-10} cycloalkyl-C_{1-6} alkoxy;
C_{1-6} alkylsulfonyloxy;
mercapto;
optionally halogenated C_{1-6} alkylthio;
C_{7-16} aralkylthio;
C_{6-14} arylthio;
C_{1-6} alkylsulfinyl;
oxo;
C_{1-3} alkylenedioxy (e.g., methylenedioxy, ethylenedioxy);
hydroxyimino optionally substituted by C_{1-6} alkyl;
and the like (Substituent Group S);

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

Substituent Group S;

(3) a heterocyclic group optionally substituted by 1 to 3 substituents selected from Substituent Group S;

(4) an amino group optionally substituted by 1 or 2 substituents selected from the group consisting of C_{1-6} alkyl optionally substituted by substituent(s) selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkoxy and the like;

optionally halogenated C_{2-4} alkenyl;

optionally halogenated C_{2-4} alkynyl;

C_{3-7} cycloalkyl;

C_{6-14} aryl;

C_{7-16} aralkyl;

4 to 7-membered (preferably 5 or 6-membered) heterocyclic group (e.g., non-aromatic heterocyclic group such as morpholinyl and the like) containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom;

formyl;

C_{1-6} alkyl-carbonyl optionally substituted by substituent(s) selected from the group consisting of halogen, hydroxy, C_{3-7} cycloalkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkoxy and the like;

C_{1-6} alkoxy-carbonyl;

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

C_{7-16} aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);

C_{3-7} cycloalkyl-carbonyl;

C_{1-6} alkyl-carbamoyl (e.g., methylaminocarbonyl, ethylaminocarbonyl);

C_{6-14} aryl-carbamoyl (e.g., phenylaminocarbonyl, 1-naphthylaminocarbonyl, 2-naphthylaminocarbonyl);

C_{7-16} aralkyl-carbamoyl (e.g., benzylaminocarbonyl);

C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl);

C_{6-14} arylsulfonyl (e.g., benzenesulfonyl, toluenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl);

C_{7-16} aralkylsulfonyl (e.g., benzylsulfonyl);

and the like (Substituent Group T);

(5) an amidino group;

(6) an optionally formylated or halogenated C_{1-6} alkyl-carbonyl group;

(7) an optionally halogenated C_{1-6} alkoxy-carbonyl group;

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

(9) a carbamoyl group optionally substituted by 1 or 2 substituents selected from Substituent Group T;

(10) a thiocarbamoyl group optionally mono- or di-substituted by optionally halogenated C_{1-6} alkyl group;

(11) a ureido group optionally substituted by 1 or 2 substituents selected from Substituent Group T;

(12) a sulfamoyl group optionally substituted by 1 or 2 substituents selected from Substituent Group T;

(13) a carboxyl group;

(14) a hydroxy group;

(15) a C_{1-6} alkoxy group optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, carboxyl, C_{1-6} alkoxy and C_{1-6} alkoxy-carbonyl;

(16) an optionally halogenated C_{2-6} alkenyloxy group (e.g., ethenyloxy);

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

(18) a C_{7-16} aralkyloxy group (e.g., benzyloxy);

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

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

(21) a mercapto group;

(22) an optionally halogenated C_{1-6} alkylthio group

(e.g., methylthio, ethylthio);

(23) a C_{7-16} aralkylthio group (e.g., benzylthio);

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

(25) a sulfo group;

(26) a cyano group;

(27) an azido group;

(28) a nitro group;

(29) a nitroso group;

(30) a halogen atom;

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

(32) an oxo group;

(33) a C_{3-10} cycloalkyl-C_{1-6} alkoxy group (e.g., cyclopropylmethoxy);

(34) a C_{1-3} alkylenedioxy group (e.g., methylenedioxy, ethylenedioxy);

(35) a hydroxyimino group optionally substituted by C_{1-6} alkyl;

and the like (Substituent Group U) can be mentioned. When the number of the substituents is not less than 2, respective substituents may be the same or different.

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-16} aralkyl group, C_{8-13} arylalkenyl group and C_{3-10} cycloalkyl-C_{1-6} alkyl group, which are exemplarily recited as the "hydrocarbon group", each optionally have 1 to 3 substituents at substitutable positions.

As such substituents, for example,

(1) a substituent selected from Substituent Group U;

(2) a C_{1-10} alkyl group optionally substituted by 1 to 3 substituents selected from Substituent Group U;

(3) a C_{2-10} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from Substituent Group U;

(4) a C_{7-16} aralkyl group (e.g., benzyl) optionally

substituted by 1 to 3 substituents selected from Substituent Group U;
and the like (Substituent Group V) can be mentioned. When the number of the substituents is not less than 2, respective substituents may be the same or different.

In the present specification, unless otherwise specified, as the "heterocyclic group" of the "optionally substituted heterocyclic group", an aromatic heterocyclic group and a non-aromatic heterocyclic group can be mentioned.

As the aromatic heterocyclic group, for example, a 4 to 7-membered (preferably 5 or 6-membered) monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom and a fused aromatic heterocyclic group can be mentioned. As the fused aromatic heterocyclic group, for example, a group derived from a fused ring wherein a ring corresponding to such 4- to 7-membered monocyclic aromatic heterocyclic group, and 1 or 2 rings selected from the group consisting of a 5- or 6-membered ring containing 1 or 2 nitrogen atoms, a 5-membered ring containing one sulfur atom, a benzene ring and the like are condensed, 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 (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl) and the like;

fused aromatic heterocyclic groups such as quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 6-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl, 6-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzisoxazolyl (e.g., 7-benzisoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl), benzotriazolyl (e.g., 1H-1,2,3-benzotriazol-5-yl), indolyl (e.g., indol-1-yl, indol-2-yl, indol-3-yl, indol-5-yl), indazolyl (e.g., 1H-indazol-3-yl), pyrrolopyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl, 1H-pyrrolo[2,3-b]pyrazin-6-yl), imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, 2H-imidazo[1,2-a]pyridin-3-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), pyrazolopyridinyl (e.g., 1H-pyrazolo[4,3-c]pyridin-3-yl), pyrazolothienyl (e.g., 2H-pyrazolo[3,4-b]thiophen-2-yl), pyrazolotriazinyl (e.g., pyrazolo[5,1-c][1,2,4]triazin-3-yl) and the like;

and the like can be mentioned.

As the non-aromatic heterocyclic group, for example, a 4 to 7-membered (preferably 5 or 6-membered) monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom and a fused non-aromatic heterocyclic group can be mentioned. As the fused non-aromatic heterocyclic group, for example, a group derived from a fused ring wherein a ring corresponding to such 4- to 7-membered monocyclic non-aromatic heterocyclic group, and 1 or 2 rings selected from the group consisting of a 5- or 6-membered ring containing 1 or 2 nitrogen atoms, a 5-membered ring containing one sulfur atom, a benzene ring and the like are condensed, and the like can be mentioned.

As preferable examples of the non-aromatic heterocyclic group,
monocyclic non-aromatic heterocyclic groups such as oxetanyl (e.g., 2-oxetanyl, 3-oxetanyl), pyrrolidinyl (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl), piperidinyl (e.g., piperidino, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl, 2-piperazinyl, 3-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-2-yl), thiazolidinyl (e.g., thiazolidin-2-yl), imidazolidinyl (e.g., imidazolidin-2-yl, imidazolidin-3-yl), oxazolinyl (e.g., oxazolin-2-yl), thiazolinyl (e.g., thiazolin-2-yl), imidazolinyl (e.g., imidazolin-2-yl, imidazolin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), 2-thioxo-1,3-oxazolidin-5-yl, pyranyl (e.g., 4-pyranyl), tetrahydropyranyl (e.g., 2-

tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl), thiopyranyl (e.g., 4-thiopyranyl), tetrahydrothiopyranyl (e.g., 2-tetrahydrothiopyranyl, 3-tetrahydrothiopyranyl, 4-tetrahydrothiopyranyl), 1-oxidotetrahydrothiopyranyl (e.g., 1-oxidotetrahydrothiopyran-4-yl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyran-4-yl), tetrahydrofuryl (e.g., tetrahydrofuran-3-yl, tetrahydrofuran-2-yl), pyrazolidinyl (e.g., pyrazolidin-1-yl, pyrazolidin-3-yl), pyrazolinyl (e.g., pyrazolin-1-yl), tetrahydropyrimidinyl (e.g., tetrahydropyrimidin-1-yl), dihydrotriazolyl (e.g., 2,3-dihydro-1H-1,2,3-triazol-1-yl), tetrahydrotriazolyl (e.g., 2,3,4,5-tetrahydro-1H-1,2,3-triazol-1-yl) and the like;

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

and the like can be mentioned.

The "heterocyclic group" of the "optionally substituted heterocyclic group" optionally has 1 to 3 substituents at substitutable positions. As such substituents, for example, substituents selected from

Substituent Group V can be mentioned. When the number of the substituents is not less than 2, respective substituents may be the same or different.

In the present specification, unless otherwise specified, as the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group", a linear or branched aliphatic hydrocarbon group having 1 to 10 carbon atoms (preferably, 1 to 8 carbon atoms) can be mentioned. As the "aliphatic hydrocarbon group", for example, a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group and a C_{3-10} cycloalkyl group can be mentioned (each group is as defined above).

The "aliphatic hydrocarbon group" is optionally substituted by substituent(s) selected from Substituent Group V, particularly, 1 to 3 substituents selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino. When the number of the substituents is not less than 2, respective substituents may be the same or different.

In the present specification, unless otherwise specified, as the "acyl group", for example, $-COR^{Y1}$, $-CO-OR^{Y1}$, $-SO_2R^{Y1}$, $-SOR^{Y1}$, $-PO(OR^{Y1})(OR^{Y2})$ (wherein R^{Y1} and R^{Y2} are the same or different and each is a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group), and the like can be mentioned.

In the present specification, unless otherwise specified, the "amino group" of the "optionally substituted amino group", the "carbamoyl group" of the "optionally substituted carbamoyl group", the "ureido group" of the "optionally substituted ureido group" and the "sulfamoyl group" of the "optionally substituted

sulfamoyl group" optionally have 1 or 2 substituents at substitutable position(s). As such substituents, for example, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an acyl group and the like can be mentioned. Of these, 1 or 2 substituents selected from Substituent Group T are preferable. When the number of the substituents is not less than 2, respective substituents may be the same or different.

When the nitrogen atom constituting the above-mentioned amino group, carbamoyl group, ureido group or sulfamoyl group is substituted by two substituents, these substituents may in combination form, together with the adjacent nitrogen atom, a nitrogen-containing heterocycle. As the "nitrogen-containing heterocycle", for example, a 3 to 8-membered nitrogen-containing heterocycle containing, as a ring-constituting atom besides carbon atoms, at least one nitrogen atom and optionally further containing one or two heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom can be mentioned. As preferable examples of the nitrogen-containing heterocycle, a 5 or 6-membered cyclic amine optionally containing an oxygen atom (e.g., 1-pyrrolidine, piperidine, 1-piperazine, morpholine) can be mentioned.

In the present specification, unless otherwise specified, the "imino group" of the "optionally substituted imino group" optionally has 1 or 2 substituents at substitutable position(s). As such substituents, for example, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an acyl group and the like can be mentioned. Of these, substituents selected from Substituent Group T are preferable. When the number of the substituents is not less than 2, respective

substituents may be the same or different.

In the present specification, unless otherwise specified, as the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom", a group represented by the formula: $-X^x-R^x$, an amino group and a hydroxy group can be mentioned.

In the above-mentioned formula, X^x is a bond, $-NR^Y-$ (wherein R^Y is a hydrogen atom or a C_{1-6} alkyl group), or $-O-$.

In the above-mentioned formula, R^x is a cyano group, or a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclylcarbonyl group or a heterocyclyl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

In the above-mentioned formula, the "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "carbamoyl group", "C_{1-8} alkyl-carbonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group", "heterocyclic group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclylcarbonyl group" and "heterocyclyl-C_{1-4} alkyl-carbonyl group" for R^x are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from, for example, the following group (Substituent Group X)

(a) a halogen atom,

(b) an oxo group,

(c) an optionally halogenated C_{1-4} alkyl group,

(d) $-(CH_2)_m-Q^x$ group,

(e) $-(CH_2)_m-Z^{1x}$-optionally halogenated C_{1-4} alkyl group,

(f) $-(CH_2)_m-Z^{1x}-C_{3-8}$ cycloalkyl group,

(g) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Q^x$ group,

(h) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}$-optionally halogenated C_{1-4} alkyl group,

(i) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-C_{3-8}$ cycloalkyl group,

(j) $-(CH_2)_m-Z^{1x}$-optionally substituted heterocyclic group (preferably, the heterocyclic group is a 5- to 8-membered heterocyclic group containing 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and optionally oxidized sulfur atom),

(k) $-(CH_2)_m-Z^{2x}-C_{1-4}$ alkoxy group, and

(l) $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-(CH_2)_n-Z^{1x}-C_{1-4}$ alkyl group.

R^Y is preferably a hydrogen atom or methyl, particularly preferably a hydrogen atom.

In the above-mentioned formula,

m is an integer of 0 to 4,

n is an integer of 1 to 4,

Q^x is hydroxy, carboxy, cyano, nitro, $-NR^{1x}R^{2x}$, $-CONR^{1x}R^{2x}$ or $-SO_2NR^{1x}R^{2x}$,

Z^{1x} is $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-SO_2-$ or $-NR^{3x}-C(=NH)-NH-$,

Z^{2x} is $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{3x}-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-C(=NH)-NH-$, $-NR^{3x}-SO_2-$ or $-SO_2-NR^{3x}-$.

In the above-mentioned formula, $-(CH_2)_m-$ and $-(CH_2)_n-$ are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from, for example, the group consisting of halogen, optionally halogenated C_{1-4} alkyl and hydroxy, and when m or n is not less than 2, a subset $-CH_2CH_2-$ of $-(CH_2)_m-$ or $-(CH_2)_n-$ is optionally replaced by $-CH=CH-$ or

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-C≡C-.

In the above-mentioned formula, R^{1x} and R^{2x} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl, or R^{1x} and R^{2x} are optionally bonded to form a ring together with the nitrogen atom. In the above-mentioned formula, R^{3x} is a hydrogen atom or a C_{1-4} alkyl, and R^{4x} is a C_{1-4} alkyl.

When R^{1x} and R^{2x} are bonded to form a ring together with the nitrogen atom, as the nitrogen-containing heterocycle, for example, 3 to 8-membered (preferably 5 or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocyclic groups such as azetidine, pyrrolidine, piperidine, homopiperidine, heptamethylenimine, morpholine, thiomorpholine, piperazine, homopiperazine and the like can be mentioned.

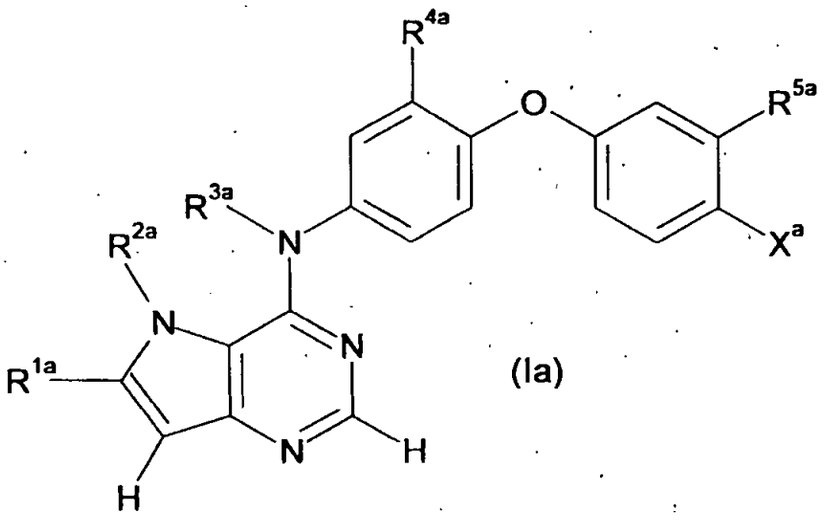
In the present specification, unless otherwise specified, as the "optionally substituted group bonded via a carbon atom or a sulfur atom", a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a carbamoyl group, a C_{1-8} alkyl-carbonyl group, a C_{1-8} alkylthio group, a C_{1-8} alkylsulfonyl group, a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a C_{6-18} aryl-C_{1-4} alkyl group, a C_{6-18} aryl-carbonyl group, a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, a C_{6-18} arylthio group, a C_{6-18} arylsulfonyl group, a heterocyclic group, a heterocyclyl-C_{1-4} alkyl group, a heterocyclylcarbonyl group, a heterocyclyl-C_{1-4} alkyl-carbonyl group, a heterocyclylthio group and a heterocyclyl-C_{1-4} alkylthio group, each of which is optionally substituted, and the like can be mentioned.

The "C_{1-8} alkyl group", "C_{2-8} alkenyl group", "C_{2-8} alkynyl group", "carbamoyl group", "C_{1-8} alkyl-carbonyl group", "C_{1-8} alkylthio group", "C_{1-8} alkylsulfonyl group", "C_{3-8} cycloalkyl group", "C_{6-18} aryl group", "C_{6-18} aryl-C_{1-4} alkyl group", "C_{6-18} aryl-carbonyl group", "C_{6-18}

aryl-C_{1-4} alkyl-carbonyl group", "C_{6-18} arylthio group", "C_{6-18} arylsulfonyl group", "heterocyclic group", "heterocyclyl-C_{1-4} alkyl group", "heterocyclylcarbonyl group", "heterocyclyl-C_{1-4} alkyl-carbonyl group", "heterocyclylthio group" and "heterocyclyl-C_{1-4} alkylthio group" are optionally substituted by one or more (preferably 1 to 5, more preferably 1 to 3) substituents selected from, for example, Substituent Group X.

[compound (Ia)]

The present invention provides a compound represented by the formula (Ia) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ia)").



(Ia)

wherein each symbol is as defined above.

R^{2a} is preferably a C_{1-6} alkyl group (particularly, an ethyl group) substituted by a group represented by the formula "$-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-C_{1-4}$ alkyl".

In the formula, R^{6aa} is a hydrogen atom or a methyl group, and R^{7a} and R^{8a} are the same or different and each is a hydrogen atom or a methyl group. R^{7a} and R^{8a} are preferably methyl groups.

R^{3a} is preferably a hydrogen atom.

As the "halogen atom" for R^{4a}, a chlorine atom is

preferable. As the "C_{1-6} alkyl group" for R^{4a}, a methyl group is preferable. R^{4a} is preferably a chlorine atom or a methyl group.

As the "halogen atom" for R^{5a}, a fluorine atom and a chlorine atom are preferable. As the "C_{1-6} alkyl group" for R^{5a}, a methyl group is preferable. R^{5a} is preferably a fluorine atom, a chlorine atom or a methyl group.

As the "halogen atom" for X^a, a fluorine atom is preferable. X^a is preferably a hydrogen atom or a fluorine atom, more preferably a hydrogen atom.

As preferable embodiment of compound (Ia), compound (Ia) wherein

R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group (particularly, an ethyl group) substituted by a group represented by $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-C_{1-4}$ alkyl

wherein R^{6aa} is a hydrogen atom or a methyl group, R^{7a} and R^{8a} are the same or different and each is a hydrogen atom or a methyl group,

R^{3a} is a hydrogen atom,

R^{4a} is a chlorine atom or a methyl group,

R^{5a} is a fluorine atom, a chlorine atom or a methyl group, and

X^a is a hydrogen atom or fluorine atom (preferably, a hydrogen atom),

can be mentioned.

As more preferable embodiment of compound (Ia), compound (Ia) wherein

R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group (particularly, an ethyl group) substituted by a group represented by $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-C_{1-4}$ alkyl

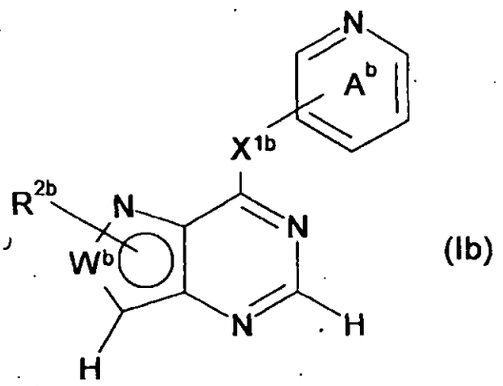
wherein R^{6aa} is a hydrogen atom or a methyl group, R^{7a} and

R^{8a} are methyl groups,
R^{3a} is a hydrogen atom,
R^{4a} is a chlorine atom or a methyl group,
R^{5a} is a fluorine atom, a chlorine atom or a methyl group, and
X^a is a hydrogen atom or fluorine atom (preferably, a hydrogen atom),
can be mentioned.

As compound (Ia), particularly preferably,
N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,
N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylsulfonyl)acetamide,
N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N,2-dimethyl-2-(methylsulfonyl)propanamide,
N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,
N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, and
N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,
and salts and hydrates thereof can be mentioned.

[compound (Ib)]

The present invention provides also a compound represented by the formula (Ib) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ib)").



(Ib)

wherein each symbol is as defined above.

In the above-mentioned formula (Ib), the "pyridine ring" of the "optionally substituted pyridine ring" for ring A^b is optionally substituted by, for example, a group represented by the formula: $-Y^{2b}-B^{b'}$. Y^{2b} is a bond, -O-, -O-(C_{1-3} alkylene)-, $-NR^{2b}-$ (wherein R^{2b} is a hydrogen atom or a C_{1-6} alkyl group), or -S-, and $B^{b'}$ is a C_{6-18} aryl group (preferably, a C_{6-14} aryl group, more preferably a phenyl group), a heterocyclic group (preferably, a 5 or 6-membered heterocyclic group, more preferably a pyridyl group or a piperidyl group), a C_{3-8} cycloalkyl group (preferably, a cyclohexyl group), a carbamoyl group, a ureido group, a C_{6-18} aryl-carbonyl group or a C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted.

Y^{2b} is preferably a bond, -O- or $-OCH_2-$, more preferably -O- or $-OCH_2-$, particularly preferably -O-.

The "C_{6-18} aryl group", "heterocyclic group", "C_{3-8} cycloalkyl group", "carbamoyl group", "ureido group", "C_{6-18} aryl-carbonyl group" and "C_{6-18} aryl-C_{1-4} alkyl-carbonyl group" of the "C_{6-18} aryl group, heterocyclic group, C_{3-8} cycloalkyl group, carbamoyl group, ureido group, C_{6-18} aryl-carbonyl group or C_{6-18} aryl-C_{1-4} alkyl-carbonyl group, each of which is optionally substituted" for $B^{b'}$ each optionally have 1 to 5, the same or different substituents at any substitutable positions.

As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen are preferable.

$B^{b'}$ is preferably an optionally substituted C_{6-14} aryl group, more preferably a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen (preferably a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl), particularly preferably a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen (preferably, a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl).

The "pyridine ring" of the "optionally substituted pyridine ring" for ring A^b optionally further has, besides the group represented by the formula: $-Y^{2b}-B^{b'}$, 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, halogen and methyl are preferable.

Ring A^b is preferably a pyridine ring optionally further substituted, besides the group represented by the formula: $-Y^{2b}-B^{b'}$, by substituent(s) selected from the group consisting of halogen and methyl, more preferably

a pyridine ring optionally further substituted, besides the group represented by the formula: $-Y^{2b}-B^{b'}$, by halogen.

As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3b}, a C_{1-6} alkyl group is preferable.

The "C_{1-4} alkylene" and "-O-(C_{1-4} alkylene)-" of the "C_{1-4} alkylene or -O-(C_{1-4} alkylene)-, each of which is optionally substituted" for Y^{1b} are optionally substituted by 1 to 3 substituent selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino.

X^{1b} is preferably $-NR^{3b}-$. In the formula, R^{3b} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

W^b is preferably $C(R^{1b})$.

As the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1b}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1b} is preferably a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2b}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-C_{1-4}$ alkyl

wherein R^{6ba} is a hydrogen atom or a methyl group, n1 is an integer of 1 to 4, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

wherein R^{6bb} is a hydrogen atom or a methyl group, n2 is an integer of 1 to 4, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

(iii) $-O-(CH_2)_{n3}-OH$

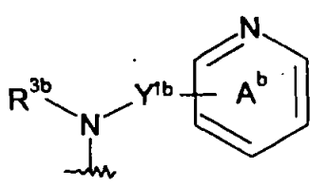
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl, and

(iv) hydroxy

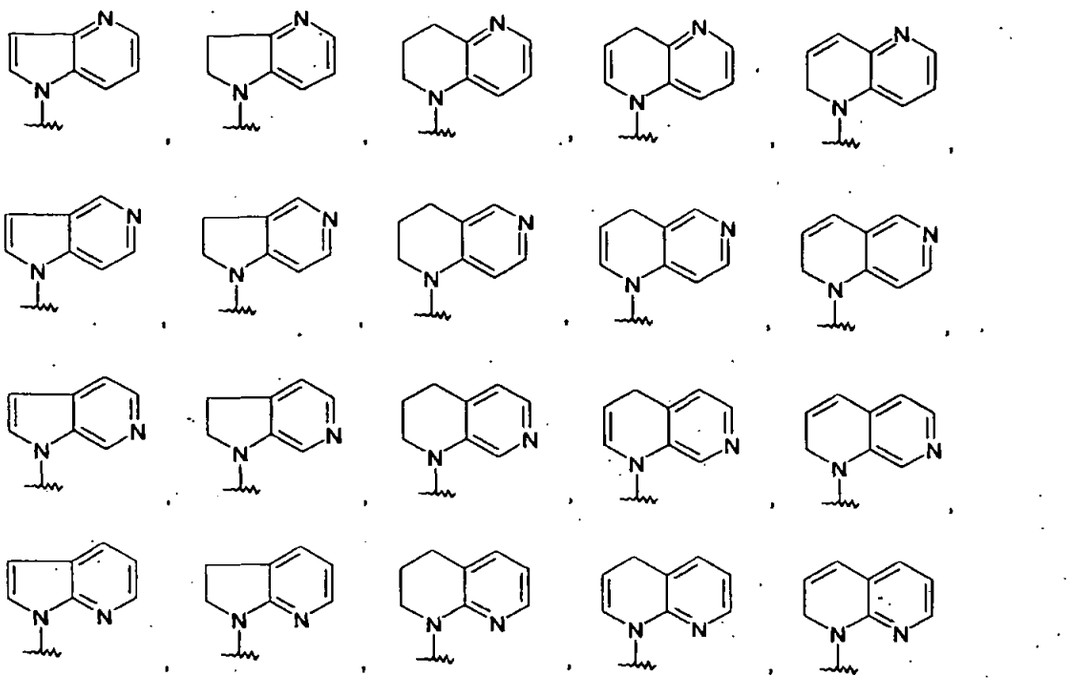
can be used.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{3b} bonded to the carbon atom on the pyridine ring for ring A^b, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

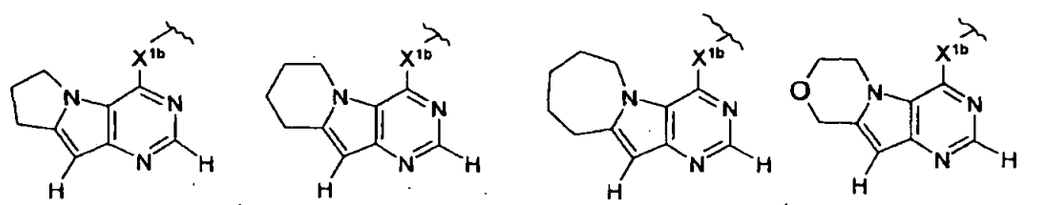


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1b} and R^{2b} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{1b} and R^{2b} bonded to each other, for example,

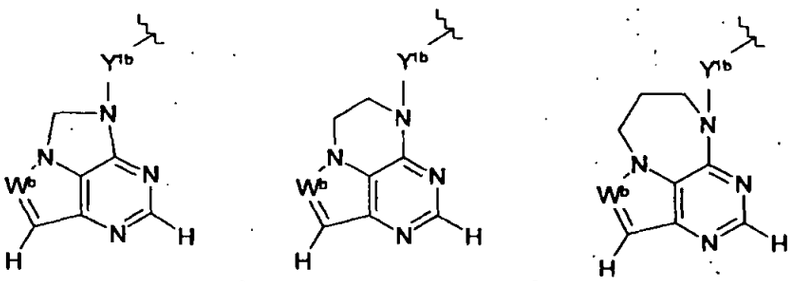


wherein each symbol is as defined above,

and the like can be mentioned.

R^{2b} and R^{3b} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2b} and R^{3b} bonded to each other, for example,

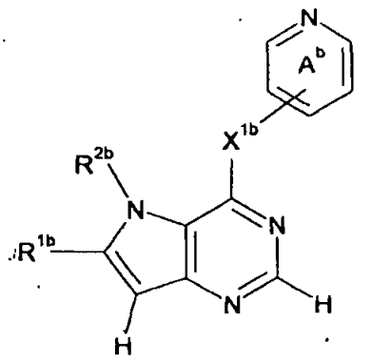


wherein each symbol is as defined above,

and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1b} and R^{2b}, or R^{2b} and R^{3b} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

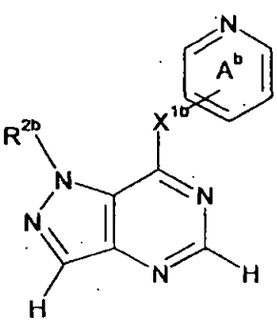
When W^b is $C(R^{1b})$, compound (Ib) is represented by the following formula (IbA):



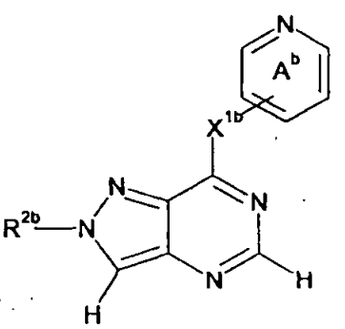
(IbA)

wherein each symbol is as defined above.

When W^b is N, compound (Ib) is represented by the following formula (IbB) or (IbC):



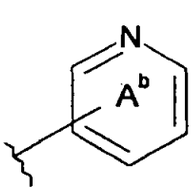
(IbB)



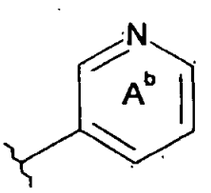
(IbC)

wherein each symbol is as defined above.

In the above-mentioned formulas, the partial structural formula

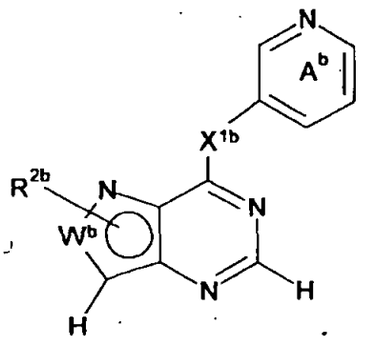


is preferably



wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (Ib') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ib')") can be mentioned:

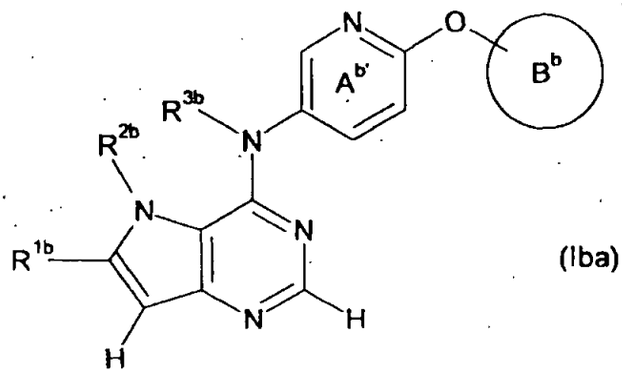


(Ib')

wherein each symbol is as defined above.

[compound (Iba)]

As preferable embodiment of compound (Ib), a compound represented by the following formula (Iba) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Iba)") can be mentioned:



(Iba)

wherein ring $A^{b'}$ is an optionally further substituted pyridine ring, ring B^b is an optionally substituted C_{6-14} aryl group, and the other symbols are as defined above.

In the above-mentioned formula (Iba), the "pyridine ring" of the "optionally further substituted pyridine ring" for ring $A^{b'}$ optionally further has, besides the group represented by the formula: $-O-B^b$, 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, halogen and methyl are preferable.

Ring A^b is preferably a pyridine ring optionally further substituted, besides the group represented by the formula: $-O-B^b$, by substituent(s) selected from the group consisting of halogen and methyl, more preferably a pyridine ring optionally further substituted, besides the group represented by the formula: $-O-B^b$, by halogen.

The "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for ring B^b optionally has 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen are preferable.

Ring B^b is preferably a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen (preferably a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl), more preferably a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen (preferably, a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl).

As more preferable embodiment of compound (Ib), compound (Iba) wherein, the above-mentioned formula (Iba),

R^{1b} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2b} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-C_{1-4}$ alkyl

wherein R^{6ba} is a hydrogen atom or a methyl group, n1 is an integer of 1 to 4, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

wherein R^{6bb} is a hydrogen atom or a methyl group, n2 is an integer of 1 to 4, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

(iii) $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl, and

(iv) hydroxy,

R^{3b} is a hydrogen atom,

ring $A^{b'}$ is a pyridine ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl, and

ring B^b is a phenyl group optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen,

can be mentioned.

As another more preferable embodiment of compound (Ib), compound (Iba) wherein, the above-mentioned formula (Iba),

ring $A^{b'}$ is a pyridine ring optionally substituted by halogen, and

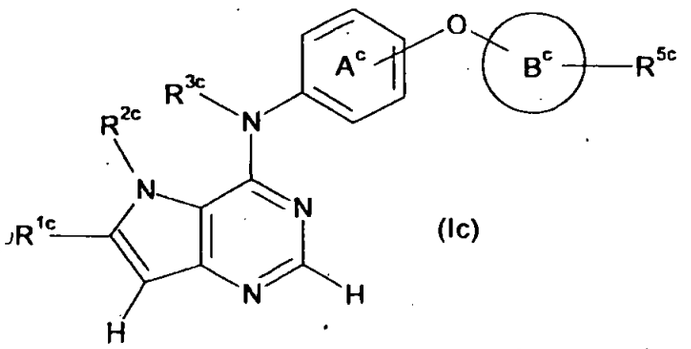
ring B^b is a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl

and halogen,
can be mentioned.

As compound (Ib), particularly preferably,
2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,
N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,
N-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide, and
N-(tert-butyl)-3-[(3-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}pyridin-2-yl)oxy]benzamide,
and salts thereof can be mentioned.

[compound (Ic)]

The present invention provides also a compound represented by the formula (Ic) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ic)").



(Ic)

wherein each symbol is as defined above.

In the above-mentioned formula (Ic), as the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1c}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1c} is preferably a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom or a cyano group, particularly preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2c}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,
can be used, and more preferably, substituent(s) selected from the group consisting of
(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl
wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,
(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$
wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino
can be used.

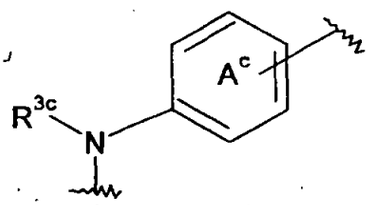
As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3c}, a C_{1-6} alkyl group is preferable.

R^{3c} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

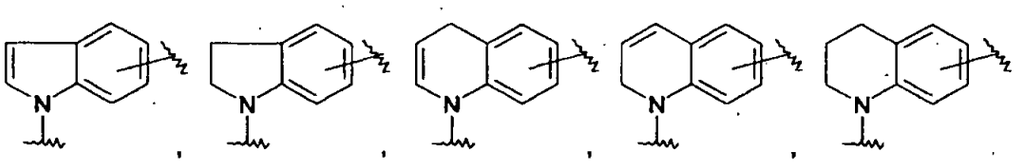
As the "ring structure" of the "optionally substituted ring structure" formed by R^{3c} bonded to the carbon atom on the adjacent benzene ring, a saturated or

unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

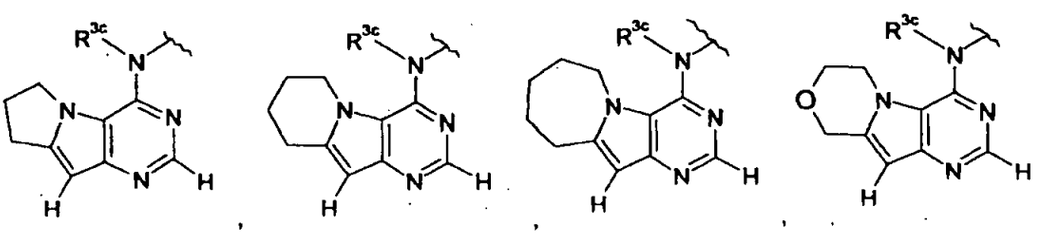


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1c} and R^{2c} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{1c} and R^{2c} bonded to each other, for example,

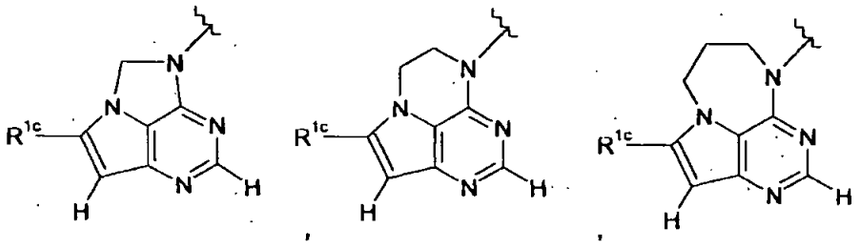


wherein each symbol is as defined above,

and the like can be mentioned.

R^{2c} and R^{3c} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2c} and R^{3c} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1c} and R^{2c}, or R^{2c} and R^{3c} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

The "benzene ring" of the "optionally substituted benzene ring" for ring A^c optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, halogen and methyl are preferable.

Ring A^c is preferably a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

As the "optionally substituted amino group" for R^{5c}, an amino group, a mono- or di-C_{1-6} alkyl-amino group, an

optionally halogenated C_{1-6} alkanoyl-amino group, a hydroxy-C_{1-6} alkanoyl-amino group, a C_{1-6} alkanoyl-amino group having hydroxy and halogen, a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group, a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen, a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group, a C_{3-7} cycloalkyl-carbonyl-amino group and a C_{1-6} alkoxy-carbonyl-amino group are preferable.

As the "optionally substituted carbamoyl group" for R^{5c}, a carbamoyl group, an optionally halogenated C_{1-6} alkyl-carbamoyl group, a hydroxy-C_{1-6} alkyl-carbamoyl group, a C_{1-6} alkyoxy-C_{1-6} alkyl-carbamoyl group, a C_{6-14} aryl-C_{1-6} alkyl-carbamoyl group, a C_{2-6} alkynyl-carbamoyl group, a piperidyl-C_{1-6} alkyl-carbamoyl group, a morpholinyl-C_{1-6} alkyl-carbamoyl group, a C_{3-7} cycloalkyl-carbamoyl group optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl, and a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom are preferable.

As the "optionally substituted ureido group" for R^{5c}, a ureido group, a C_{1-6} alkyl-ureido group, a C_{3-7} cycloalkyl-ureido group, and a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom are preferable.

As the "optionally substituted sulfamoyl group" for R^{5c}, a sulfamoyl group optionally substituted by C_{1-6} alkyl is preferable.

As the "optionally substituted heterocyclic group" for R^{5c}, a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group

consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl is preferable.

As the "optionally substituted C_{2-6} alkoxy group" for R^{5c}, a C_{2-6} alkoxy group optionally substituted by substituent(s) selected from the group consisting of C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl is preferable.

As the "optionally substituted aminomethyl group" for R^{5c}, an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl is preferable.

As the "optionally substituted carbamoylmethyl group" for R^{5c}, a carbamoylmethyl group optionally substituted by C_{1-6} alkyl is preferable.

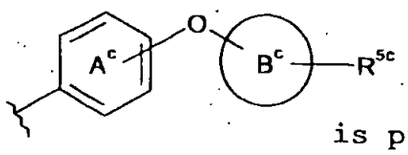
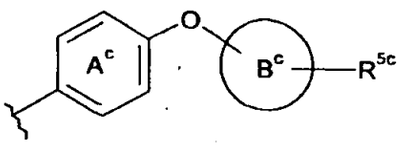
As the "optionally substituted alkylsulfonyl group" for R^{5c}, a C_{1-6} alkylsulfonyl group optionally having C_{3-7} cycloalkyl or halogen is preferable.

As the "C_{6-14} aryl group" of the "optionally further substituted C_{6-14} aryl group" for ring B^c, a phenyl group is preferable.

As the "C_{5-8} cycloalkyl group" of the "optionally further substituted C_{5-8} cycloalkyl group" for ring B^c, a cyclohexyl group is preferable.

The "C_{6-14} aryl group" of the "optionally further substituted C_{6-14} aryl group" for ring B^c and the "C_{5-8} cycloalkyl group" of the "optionally further substituted C_{5-8} cycloalkyl group" for ring B^c, each optionally have, besides R^{5c}, 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, optionally halogenated C_{1-6} alkyl and halogen are preferable.

In the above-mentioned formula, the partial structural formula

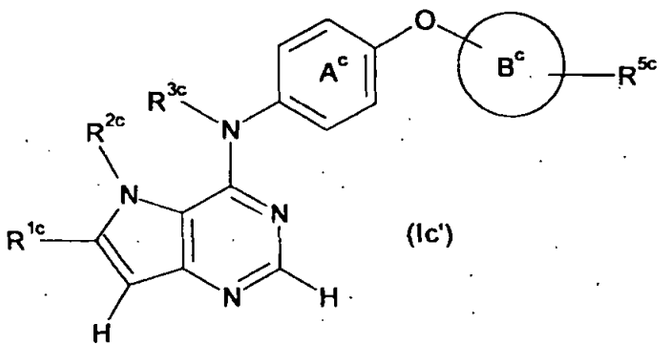



is preferably

wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (Ic') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ic')"), and a compound represented by the following formula (Ic'') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ic'')") can be mentioned:

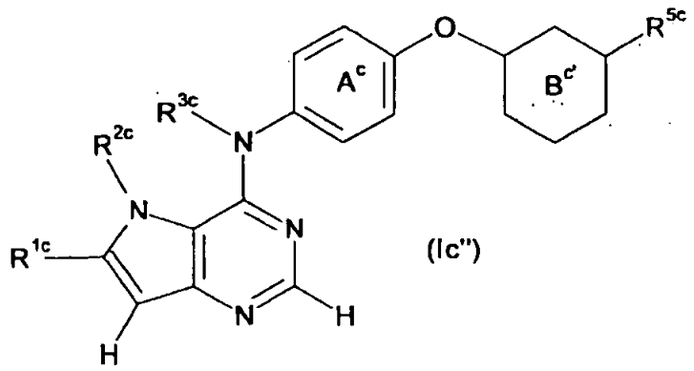
[compound (Ic')]



(Ic')

wherein each symbol is as defined above.

[compound (Ic'')]



(Ic")

wherein ring $B^{c'}$ is a phenyl group or a cyclohexyl group, each of which is optionally further substituted besides R^{5c}, and the other symbols are as defined above.

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As preferable embodiment of compound (Ic), compound (Ic) wherein

R^{2c} is a C_{1-6} alkyl group optionally substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OR$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

can be mentioned.

As another preferable embodiment of compound (Ic), compound (Ic) wherein

R^{1c} is a hydrogen atom or a cyano group,

R^{2c} is a C_{1-6} alkyl group optionally substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally

substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

(ii) a mono-C_{1-6} alkyl-amino group,

(iii) a di-C_{1-6} alkyl-amino group,

(iv) an optionally halogenated C_{1-6} alkanoyl-amino group,

(v) a hydroxy-C_{1-6} alkanoyl-amino group,

(vi) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vii) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(viii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(ix) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,

(x) a C_{3-7} cycloalkyl-carbonyl-amino group,

(xi) a C_{1-6} alkoxy-carbonyl-amino group,

(xii) a carbamoyl group,

(xiii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xiv) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,

(xvi) a C_{6-14} aryl-C_{1-6} alkyl-carbamoyl group,

(xvii) a C_{2-6} alkynyl-carbamoyl group,

(xviii) a piperidyl-C_{1-6} alkyl-carbamoyl group,

(xix) a morpholinyl-C_{1-6} alkyl-carbamoyl group,

(xx) a C_{3-7} cycloalkyl-carbamoyl group optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,

(xxi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,

(xxii) a ureido group,

(xxiii) a C_{1-6} alkyl-ureido group,

(xxiv) a C_{3-7} cycloalkyl-ureido group,

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(xxv) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,

(xxvi) a sulfamoyl group optionally substituted by C_{1-6} alkyl,

(xxvii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,

(xxviii) a C_{2-6} alkoxy group optionally substituted by substituent(s) selected from the group consisting of C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy and C_{1-6} alkyl-carbamoyl,

(xxix) a carbamoylmethyl group optionally substituted by C_{1-6} alkyl,

(xxx) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,

(xxxi) a C_{1-6} alkylsulfonyl group optionally having C_{3-7} cycloalkyl or halogen, or

(xxxii) a cyano group, and

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

can be mentioned.

As another preferable embodiment of compound (Ic), compound (Ic) wherein

R^{5c} is an amino group optionally substituted by substituent(s) selected from the group consisting of

(i) C_{1-6} alkyl,

(ii) optionally halogenated C_{1-6} alkanoyl,

(iii) hydroxy-C_{1-6} alkanoyl,
(iv) C_{1-6} alkanoyl having hydroxy and halogen,
(v) C_{3-7} cycloalkyl-C_{1-6} alkanoyl,
(vi) C_{1-6} alkanoyl having C_{3-7} cycloalkyl and halogen,
(vii) C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl,
(viii) C_{3-7} cycloalkyl-carbonyl, and
(ix) C_{1-6} alkoxy-carbonyl,
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
R^{1c} is a hydrogen atom,
R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,
(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,
(iii) $-O-(CH_2)_n-OH$,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,
R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl

wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

(iii) $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino.

As another preferable embodiment of compound (Ic), compound (Ic) wherein

R^{5c} is a carbamoyl group optionally substituted by substituent(s) selected from the group consisting of

(i) optionally halogenated C_{1-6} alkyl,

(ii) hydroxy-C_{1-6} alkyl,

(iii) C_{1-6} alkoxy-C_{1-6} alkyl,

(iv) C_{6-14} aryl-C_{1-6} alkyl,

(v) C_{2-6} alkynyl,

(vi) piperidyl-C_{1-6} alkyl,

(vii) morpholinyl-C_{1-6} alkyl, and

(viii) C_{3-7} cycloalkyl optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

R^{1c} is a hydrogen atom,

R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

(vi) $-O-C_{1-4}$ alkyl,

(vii) $-S-C_{1-4}$ alkyl,

(viii) $-SO_2-C_{1-4}$ alkyl, and

(ix) amino

wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl

wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,

(iii) $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,

(iv) hydroxy,

(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,

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(vi) -O-C_{1-4} alkyl,
(vii) -S-C_{1-4} alkyl,
(viii) -SO_2-C_{1-4} alkyl, and
(ix) amino.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{5c} is a ureido group optionally substituted by substituent(s) selected from the group consisting of
(i) C_{1-6} alkyl,
(ii) C_{3-7} cycloalkyl, and
(iii) 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
R^{1c} is a hydrogen atom,
R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) -NR^{6c}-CO-$(CH_2)_n$-SO_2-optionally halogenated C_{1-4} alkyl,
(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,
(iii) -O-$(CH_2)_n$-OH,
(iv) hydroxy,
(v) -NR^{6c}-CO-C_{1-4} alkyl,
(vi) -O-C_{1-4} alkyl,
(vii) -S-C_{1-4} alkyl,
(viii) -SO_2-C_{1-4} alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and -$(CH_2)_n$- is optionally substituted by C_{1-4} alkyl,
R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl
wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,
(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$
wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{5c} is a sulfamoyl group optionally substituted by C_{1-6} alkyl,
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
R^{1c} is a hydrogen atom,
R^{2c} is a C_{1-6} alkyl group substituted by substituent(s)

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selected from the group consisting of
(i) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,
(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,
(iii) $-O-(CH_2)_n-OH$,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,
R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl
wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,
(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$
wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,

(vii) -S-C_{1-4} alkyl,
(viii) -SO_2-C_{1-4} alkyl, and
(ix) amino.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{5c} is a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,
ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
R^{1c} is a hydrogen atom,
R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) -NR^{6c}-CO-$(CH_2)_n$-SO_2-optionally halogenated C_{1-4} alkyl,
(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,
(iii) -O-$(CH_2)_n$-OH,
(iv) hydroxy,
(v) -NR^{6c}-CO-C_{1-4} alkyl,
(vi) -O-C_{1-4} alkyl,
(vii) -S-C_{1-4} alkyl,
(viii) -SO_2-C_{1-4} alkyl, and
(ix) amino
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and -$(CH_2)_n$- is optionally substituted by C_{1-4} alkyl,
R^{3c} is a hydrogen atom or a C_{1-6} alkyl group, and
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of

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halogen and methyl,
can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl
wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group,
(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$
wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,
(iv) hydroxy,
(v) $-NR^{6c}-CO-C_{1-4}$ alkyl,
(vi) $-O-C_{1-4}$ alkyl,
(vii) $-S-C_{1-4}$ alkyl,
(viii) $-SO_2-C_{1-4}$ alkyl, and
(ix) amino.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6ca}-CO-(CH_2)_{n1}-SO_2-$optionally halogenated C_{1-4} alkyl
wherein n1 is an integer of 1 to 4, R^{6ca} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,
R^{1c} is a hydrogen atom,
R^{3c} is a hydrogen atom,
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of

halogen and methyl,

R^{5c} is

(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having C_{1-6} alkylsulfonyl, or (b) mono- or di- substituted by C_{1-6} alkyl,

(ii) a carbamoyl group optionally substituted by C_{1-6} alkyl,

(iii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by optionally halogenated C_{1-6} alkyl,

(iv) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,

(v) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,

(vi) a C_{1-6} alkylsulfonyl group optionally substituted by C_{3-7} cycloalkyl, or

(vii) a cyano group, and

ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NH-CO-CR^{7c}R^{8c}-SO_2-C_{1-4}$ alkyl wherein R^{7c} and R^{8c} are the same or different and each is a hydrogen atom or a C_{1-4} alkyl group.

As another preferable embodiment of compound (Ic), compound (Ic) wherein

R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

wherein n2 is an integer of 1 to 4, R^{6cb} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
R^{1c} is a hydrogen atom,
R^{3c} is a hydrogen atom,
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
R^{5c} is
(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having hydroxy, or (b) mono- or di-substituted by C_{1-6} alkyl,
(ii) a carbamoyl group optionally substituted by C_{1-6} alkyl,
(iii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by optionally halogenated C_{1-6} alkyl,
(iv) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,
(v) an aminomethyl group optionally substituted by C_{1-6} alkyl-carbonyl,
(vi) a C_{1-6} alkylsulfonyl group optionally substituted by C_{3-7} cycloalkyl, or
(vii) a cyano group, and
ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
can be mentioned.

In the above-mentioned embodiment, more preferably, R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-NH-CO-CH_2-CR^{9c}R^{10c}-OH$

wherein R^{9c} and R^{10c} are the same or different and each is a C_{1-4} alkyl group.

As another preferable embodiment of compound (Ic), compound (Ic) wherein

R^{2c} is a C_{1-6} alkyl group substituted by a group represented by $-O-(CH_2)_{n3}-OH$

wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl,

R^{1c} is a hydrogen atom,

R^{3c} is a hydrogen atom,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{3-7} cycloalkyl-carbonyl-amino group,

(ix) a C_{1-6} alkoxy-carbonyl-amino group,

(x) a carbamoyl group,

(xi) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xii) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xiii) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{3-7} cycloalkyl-carbamoyl group,

(xv) a ureido group,

(xvi) a C_{1-6} alkyl-ureido group,

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(xvii) a C_{3-7} cycloalkyl-ureido group,
(xviii) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,
(xix) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,
(xx) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by optionally halogenated C_{1-6} alkyl or C_{1-6} alkoxy-carbonyl,
(xxi) an optionally halogenated C_{2-6} alkoxy group,
(xxii) a C_{1-6} alkylsulfonyl group, or
(xxiii) a cyano group, and
ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
can be mentioned.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{2c} is a C_{1-6} alkyl group substituted by hydroxy,
R^{1c} is a hydrogen atom,
R^{3c} is a hydrogen atom,
ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,
R^{5c} is
(i) an amino group optionally (a) mono-substituted by C_{1-6} alkanoyl optionally having hydroxy, or (b) mono- or di-substituted by C_{1-6} alkyl,
(ii) a carbamoyl group optionally substituted by optionally halogenated C_{1-6} alkyl,

(iii) a C_{3-7} cycloalkyl-carbamoyl group optionally substituted by C_{1-6} alkyl or C_{2-6} alkynyl,
(iv) a C_{6-14} aryl-C_{1-6} alkyl-carbamoyl group,
(v) a hydroxy-C_{1-6} alkyl-carbamoyl group,
(vi) a morpholinyl-C_{1-6} alkyl-carbamoyl group,
(vii) a C_{2-6} alkynyl-carbamoyl group,
(viii) a carbamoylmethyl group optionally substituted by C_{1-6} alkyl,
(ix) a C_{2-6} alkoxy group optionally substituted by C_{3-7} cycloalkyl, halogen, C_{1-6} alkoxy or C_{1-6} alkyl-carbamoyl,
(x) an aminomethyl group optionally substituted by C_{1-6} alkoxy-carbonyl, or
(xi) a C_{1-6} alkylsulfonyl group optionally substituted by C_{3-7} cycloalkyl, and
ring B^c is a C_{6-14} aryl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,
can be mentioned.

As another preferable embodiment of compound (Ic), compound (Ic) wherein
R^{1c} is a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2c} is
(i) a C_{1-6} alkyl group, or
(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(a) $-NR^{6c}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,
(b) $-NR^{6c}-CO-(CH_2)_n-OH$,
(c) $-O-(CH_2)_n-OH$, and
(d) hydroxy
wherein n is an integer of 1 to 4, R^{6c} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3c} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^c is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5c} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,

(ix) a C_{3-7} cycloalkyl-carbonyl-amino group,

(x) a C_{1-6} alkoxy-carbonyl-amino group,

(xi) a carbamoyl group,

(xii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xiii) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,

(xv) a C_{3-7} cycloalkyl-carbamoyl group,

(xvi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,

(xvii) a ureido group,

(xviii) a C_{1-6} alkyl-ureido group,

(xix) a C_{3-7} cycloalkyl-ureido group,

(xx) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,

(xxi) a sulfamoyl group optionally substituted by C_{1-6} alkyl, or

(xxii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl, and

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

can be mentioned.

Of the above-mentioned preferable embodiments of compound (Ic), a compound corresponding compound (Ic'') is particularly preferable. That is,

(i) a compound wherein ring B^c is a phenyl group or a cyclohexyl group, each of which is optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen, and is substituted by R^{5c} at the meta-position of the phenyl group or the β-position of the cyclohexyl group, and

(ii) a compound wherein ring B^c is a phenyl group optionally further substituted, besides R^{5c}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen, which phenyl is substituted by R^{5c} at the meta-position of the phenyl group,

are particularly preferable.

As compound (Ic), particularly preferably,

2-{2-[4-({3-chloro-4-[3-(1,3-thiazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,

N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide,

3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2-hydroxy-1,1-dimethylethyl)benzamide,

N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,

N-(3-{2-chloro-4-[(6-cyano-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide,

N-(tert-butyl)-5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluorobenzamide,

N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,

N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]acetamide,

N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

N-{2-[4-({3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,

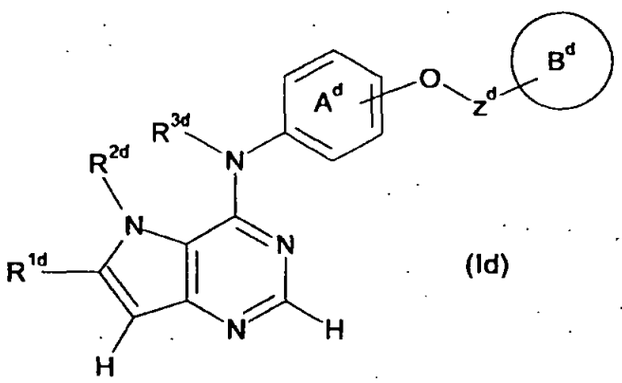
2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide,

2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethanol, and
N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,
and salts thereof can be mentioned.

[compound (Id)]

The present invention also provides a compound represented by the formula (Id) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Id)").



(Id)

wherein each symbol is as defined above.

In the above-mentioned formula (Id), as the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1d}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1d} is preferably a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2d}, an optionally

substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(a) $-NR^{6d}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6d}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6d} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

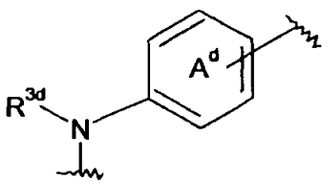
can be used.

As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3d}, a C_{1-6} alkyl group is preferable.

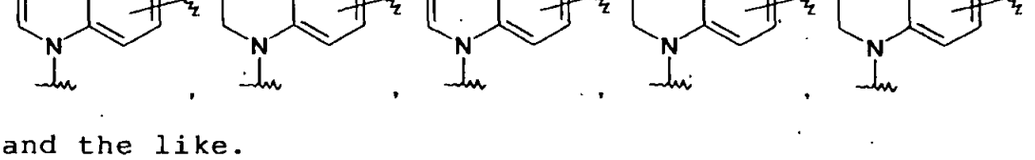
R^{3d} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{3d} bonded to the carbon atom on the adjacent benzene ring, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

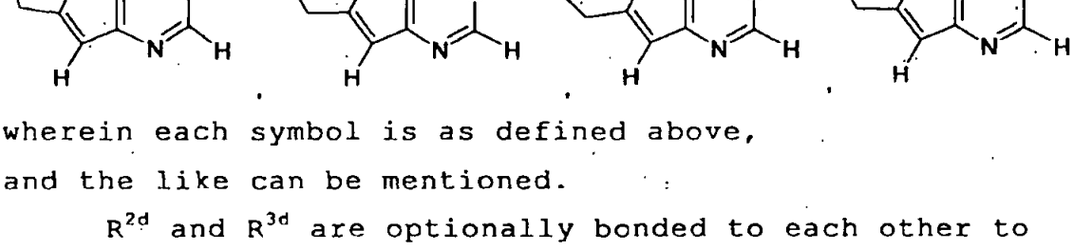


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1d} and R^{2d} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

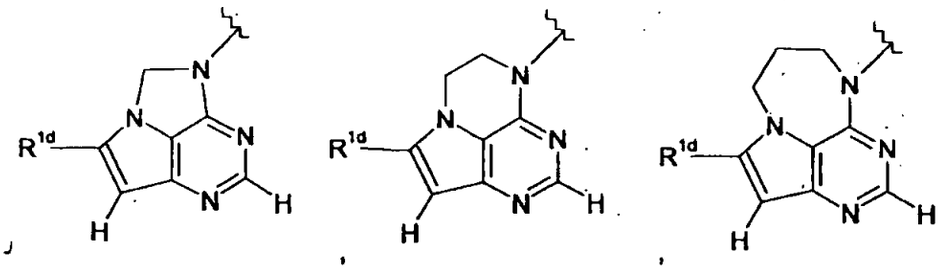
As the "ring structure" of the "optionally substituted ring structure" formed by R^{1d} and R^{2d} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

R^{2d} and R^{3d} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2d} and R^{3d} bonded to each other, for example,



wherein each symbol is as defined above,

and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1d} and R^{2d}, or R^{2d} and R^{3d} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

The "benzene ring" of the "optionally substituted benzene ring" for ring A^d optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, halogen and methyl are preferable.

Ring A^d is preferably a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl, more preferably a benzene ring optionally substituted by halogen.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for ring B^d, a 5 or 6-membered monocyclic heterocyclic group is preferable, and a piperidyl group is more preferable.

The "heterocyclic group" of the "optionally substituted heterocyclic group" for ring B^d optionally has 1 to 5, the same or different substituents at any substitutable positions. As the substituents, acyl and substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, acyl and optionally

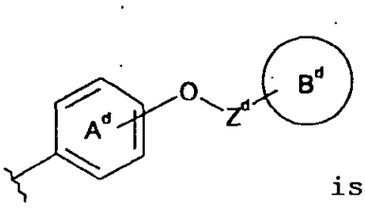
substituted ureido are preferable, and C_{1-6} alkoxy-carbonyl, C_{5-8} cycloalkyl-carbonyl, C_{1-6} alkyl-ureido and C_{5-8} cycloalkyl-ureido are more preferable.

Ring B^d is preferably a heterocyclic group (preferably, a 5 or 6-membered monocyclic heterocyclic group, more preferably, a piperidyl group) optionally substituted by acyl or optionally substituted ureido, more preferably a heterocyclic group (preferably, a 5 or 6-membered monocyclic heterocyclic group, more preferably, a piperidyl group) optionally substituted by C_{1-6} alkoxy-carbonyl, C_{5-8} cycloalkyl-carbonyl, C_{1-6} alkyl-ureido or C_{5-8} cycloalkyl-ureido.

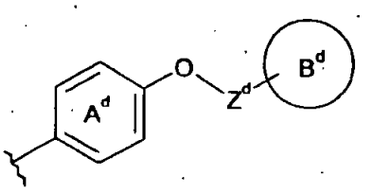
As the "C_{1-3} alkylene" of the "optionally substituted C_{1-3} alkylene" for Z^d, methylene is preferable.

The "C_{1-3} alkylene" of the "optionally substituted C_{1-3} alkylene" for Z^d is optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino.

In the above-mentioned formula, the partial structural formula



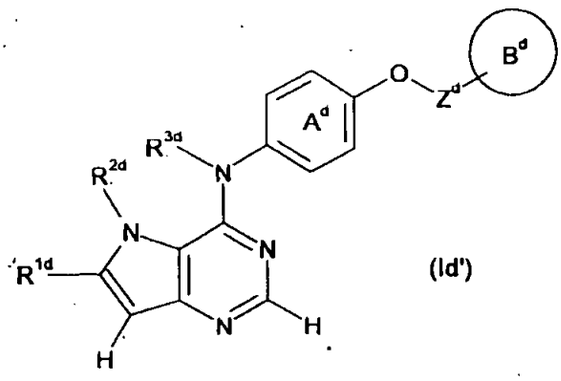
is preferably



wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (Id') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Id')") can be mentioned:

[compound (Id')]

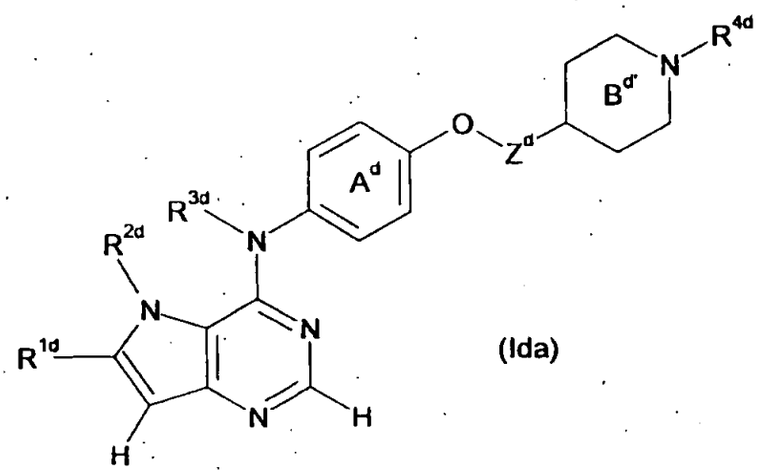


(Id')

wherein each symbol is as defined above.

As preferable embodiment of compound (Id), a compound represented by the following formula (Ida) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ida)") can be mentioned:

[compound (Ida)]



(Ida)

wherein R^{4d} is an acyl group or an optionally substituted ureido group, ring $B^{d'}$ is a piperidyl group optionally further substituted besides R^{4d}, and the other symbols are as defined above.

In the above-mentioned formula (Ida), as the "acyl group" for R^{4d}, a C_{1-6} alkoxy-carbonyl group and a C_{5-8} cycloalkyl-carbonyl group are preferable.

In the above-mentioned formula (Ida), as the "optionally substituted ureido group" for R^{4d}, a C_{1-6}

alkyl-ureido group and a C_{5-8} cycloalkyl-ureido group are preferable.

The "piperidyl group" of the "optionally further substituted piperidyl group" for ring $B^{d'}$ optionally has, besides R^{4d}, 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

As more preferable embodiment of compound (Id), compound (Ida) wherein, in the above-mentioned formula (Ida),

R^{1d} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2d} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6d}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6d}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6d} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3d} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^d is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

Z^d is methylene,

ring $B^{d'}$ is a piperidyl group, and

R^{4d} is a C_{1-6} alkoxy-carbonyl group, a C_{5-8} cycloalkyl-carbonyl group, a C_{1-6} alkyl-ureido group or a C_{5-8} cycloalkyl-ureido group,

can be mentioned.

As another more preferable embodiment of compound (Id), compound (Ida) wherein, the above-mentioned formula (Ida),

R^{3d} is a hydrogen atom, and

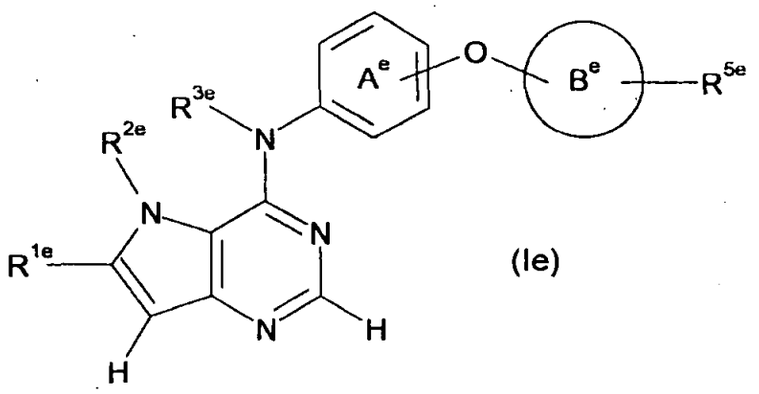
ring A^d is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

can be mentioned.

As compound (Id), particularly preferably, tert-butyl 4-{[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]methyl}piperidine-1-carboxylate, and tert-butyl 4-[(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)methyl]piperidine-1-carboxylate, and salts thereof can be mentioned.

[compound (Ie)]

The present invention provides also a compound represented by the formula (Ie) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ie)").



(Ie)

wherein each symbol is as defined above.

In the above-mentioned formula (Ie), as the

"optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1e}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1e} is preferably a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom or a cyano group, particularly preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2e}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(a) $-NR^{6e}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6e}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6e} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

can be used.

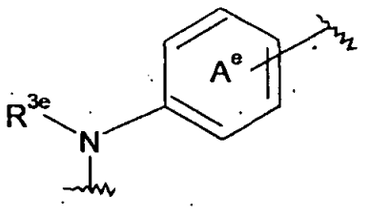
As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3e}, a C_{1-6} alkyl group is preferable.

R^{3e} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

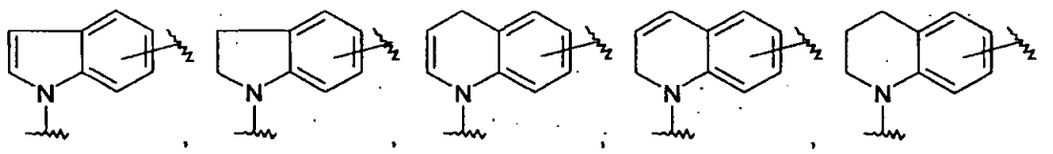
As the "ring structure" of the "optionally

substituted ring structure" formed by R^{3e} bonded to the carbon atom on the adjacent benzene ring, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

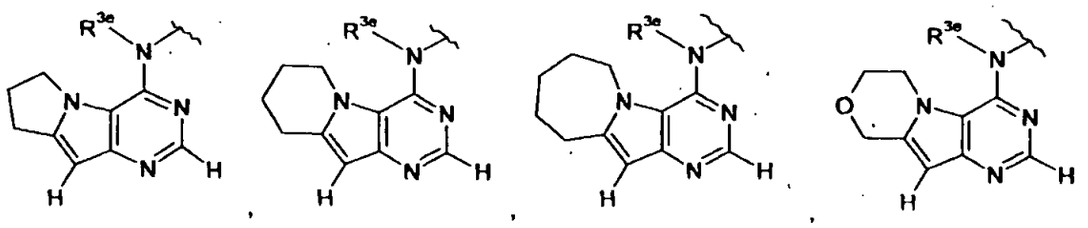


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1e} and R^{2e} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

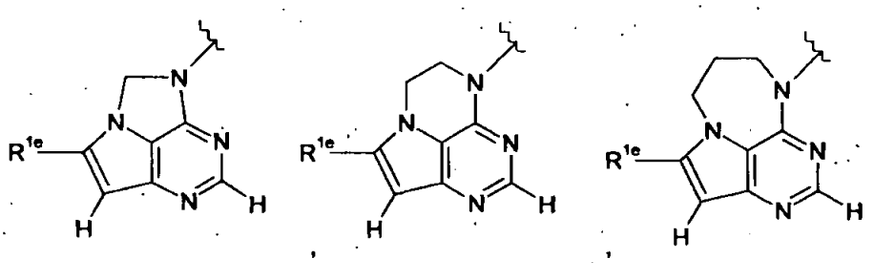
As the "ring structure" of the "optionally substituted ring structure" formed by R^{1e} and R^{2e} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

R^{2e} and R^{3e} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2e} and R^{3e} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1e} and R^{2e}, or R^{2e} and R^{3e} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

The "benzene ring" of the "optionally substituted benzene ring" for ring A^e optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be

mentioned. Of these, halogen and methyl are preferable.

Ring A^e is preferably a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

As the linear alkyl group at R^{5e}, a linear alkyl group having 1 to 10 (preferably 1 to 8, more preferably 1 to 6) carbon atoms can be mentioned. Specifically, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl can be mentioned.

As the branched alkyl group at R^{5e}, a branched alkyl group having 3 to 10 (preferably 3 to 8, more preferably 3 to 6) carbon atoms can be mentioned. Specifically, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, 1-ethylpropyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like can be mentioned.

As the substituent for the "aryl" of the "linear alkyl group substituted by optionally substituted aryl, which is optionally further halogenated or hydroxylated", "hydroxy group substituted by optionally substituted aryl" and "C_{1-6} alkyl-carbonyl group optionally substituted by optionally substituted aryl" for R^{5e}, substituents similar to the above-mentioned Substituent Group V can be mentioned.

As the substituent of "optionally substituted branched alkyl group", "optionally substituted alkenyl group" and "optionally substituted cycloalkyl group" for R^{5e}, substituents similar to the above-mentioned Substituent Group U can be mentioned.

As the "linear alkyl group substituted by optionally substituted heterocyclic group" for R^{5e}, a 5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having

C_{1-6} alkyl is preferable.

As the "linear alkyl group substituted by optionally substituted imino" for R^{5e}, a linear C_{1-6} alkyl group substituted by hydroxyimino or C_{1-6} alkoxyimino is preferable.

As the "linear alkyl group substituted by optionally substituted aryl, which is optionally further halogenated or hydroxylated" for R^{5e}, a linear C_{1-6} alkyl group substituted by C_{6-14} aryl, which is optionally further halogenated or hydroxylated is preferable.

As the "optionally substituted branched alkyl group" for R^{5e}, an optionally halogenated branched C_{3-6} alkyl group is preferable.

As the "optionally substituted alkenyl group" for R^{5e}, a C_{2-6} alkenyl group is preferable.

As the "hydroxy group substituted by optionally substituted aryl" for R^{5e}, a hydroxy group substituted by C_{6-14} aryl is preferable.

As the "halogenated C_{2-6} alkyl" of the "hydroxy group substituted by halogenated C_{2-6} alkyl" for R^{5e} and "halogenated C_{2-6} alkyl group" for R^{5e}, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl and the like, each of which is halogenated, can be mentioned. Of these, halogenated ethyl is preferable.

As the "optionally substituted cycloalkyl group" for R^{5e}, a C_{3-7} cycloalkyl group optionally substituted by cyano or carbamoyl is preferable.

As the "C_{1-6} alkyl-carbonyl group optionally substituted by optionally substituted aryl" for R^{5e}, C_{1-6} alkyl-carbonyl group optionally substituted by phenyl is preferable.

As the "linear alkyl group substituted by optionally substituted heterocyclic group" for R^{5e}, (i) a methyl group substituted by optionally substituted

heterocyclic group, and

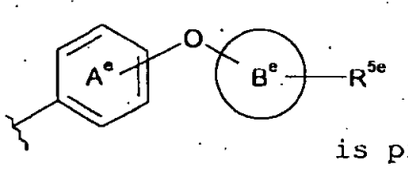
(ii) a linear alkyl group substituted by substituted heterocyclic group

are preferable.

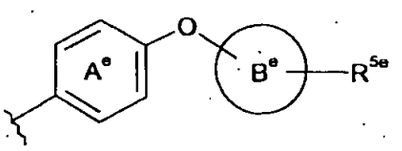
The "C_{6-14} aryl group" of the "optionally further substituted C_{6-14} aryl group" for ring B^e optionally has, besides R^{5c}, 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, optionally halogenated C_{1-6} alkyl and halogen are preferable.

Ring B^e is preferably a C_{6-14} aryl group (preferably, a phenyl group) optionally further substituted, besides R^{5e}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen.

In the above-mentioned formula, the partial structural formula



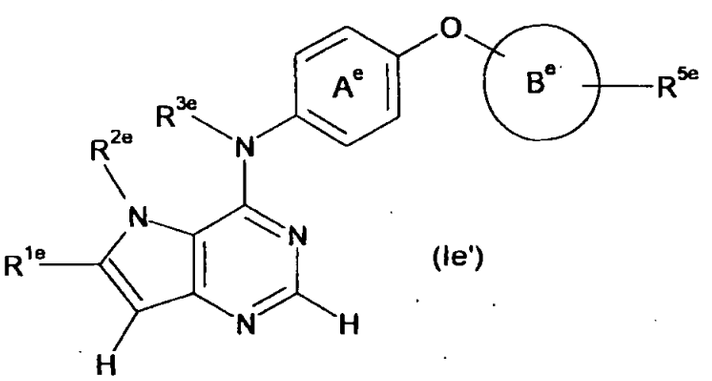
is preferably



wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (Ie') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ie')") can be mentioned:

[compound (Ie')]



(Ie')

wherein each symbol is as defined above.

As preferable embodiment of compound (Ie), compound (Ie) wherein

R^{1e} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2e} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6e}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6e}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6e} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3e} is a hydrogen atom,

ring A^e is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5e} is

(i) a 5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl,

(ii) a linear C_{1-6} alkyl group substituted by hydroxyimino or C_{1-6} alkoxyimino,

(iii) a linear C_{1-6} alkyl group substituted by C_{6-14} aryl, which is optionally further halogenated or hydroxylated,

(iv) an optionally halogenated branched C_{3-6} alkyl group,

(v) a C_{2-6} alkenyl group,

(vi) a hydroxy group substituted by C_{6-14} aryl,

(vii) a hydroxy group substituted by C_{1-6} alkyl,

(viii) a hydroxy group substituted by halogenated C_{2-6} alkyl,

(ix) a halogenated C_{2-6} alkyl group,

(x) a C_{3-7} cycloalkyl group optionally substituted by cyano or carbamoyl, or

(xi) a C_{1-6} alkyl-carbonyl group optionally substituted by phenyl, and

ring B^e is a C_{6-14} aryl group optionally further substituted, besides R^{5e}, by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and halogen,

can be mentioned.

In the above-mentioned preferable embodiment of compound (Ie), a compound wherein

the "5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl" for R^{5e} is

(i) a 5- to 8-membered heterocyclyl-methyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and optionally having C_{1-6} alkyl, or

(ii) a 5- to 8-membered heterocyclyl-linear C_{1-6} alkyl group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, and having C_{1-6} alkyl,

is preferable.

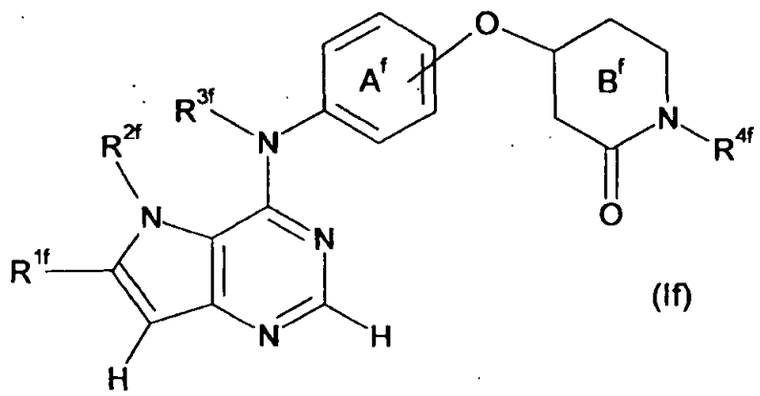
As compound (Ie), particularly preferably,

2-[4-({3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethanol,
(1Z)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one O-ethyloxime,
1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-ol,
1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one,
N-(2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide, and
N-{2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
and salts thereof can be mentioned.

[compound (If)]

The present invention provides also a compound represented by the formula (If) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (If)").



(If)

wherein each symbol is as defined above.

In the above-mentioned formula (If), as the "optionally substituted group bonded via a carbon atom,

a nitrogen atom or an oxygen atom" for R^{1f}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1f} is preferably a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom or a cyano group, particularly preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2f}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(a) $-NR^{6f}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6f} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

can be used.

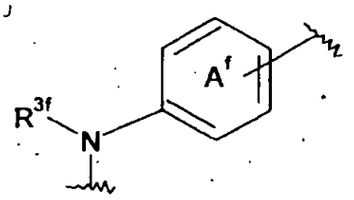
As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3f}, a C_{1-6} alkyl group is preferable.

R^{3f} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

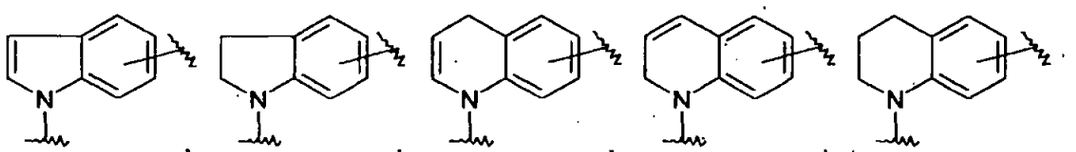
As the "ring structure" of the "optionally substituted ring structure" formed by R^{3f} bonded to the

carbon atom on the adjacent benzene ring, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

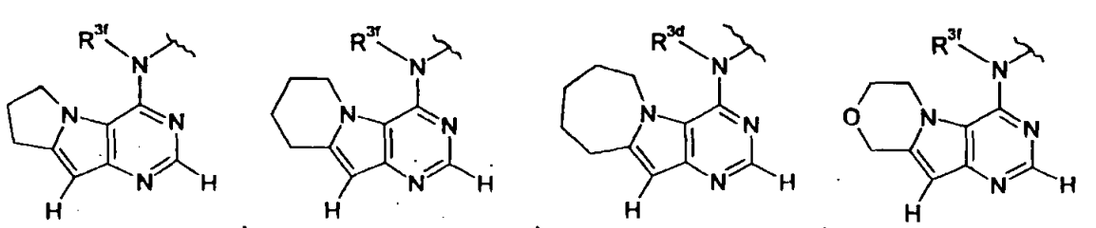


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1f} and R^{2f} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{1f} and R^{2f} bonded to each other, for example,



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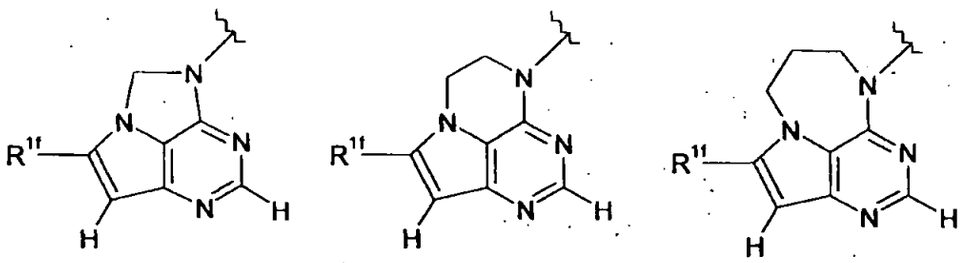
wherein each symbol is as defined above,
and the like can be mentioned.

R^{2f} and R^{3f} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2f} and R^{3f} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1f} and R^{2f}, or R^{2f} and R^{3f} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

The "benzene ring" of the "optionally substituted benzene ring" for Ring A^f optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned. Of these, halogen and methyl are preferable.

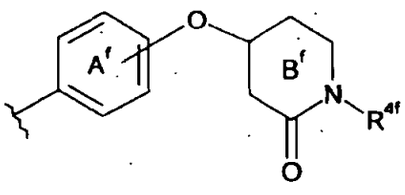
Ring A^f is preferably a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

The "piperidyl group" of the "optionally further substituted piperidyl group" for ring B^f optionally has, besides R^{4f}, 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

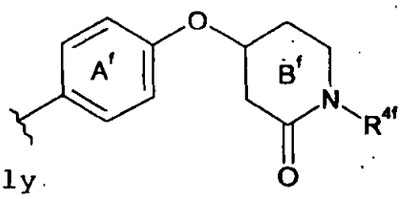
The "C_{1-6} alkyl group" of the "optionally substituted C_{1-6} alkyl group" for R^{4f} optionally has 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group U can be mentioned.

The "C_{5-8} cycloalkyl group" of the "optionally substituted C_{5-8} cycloalkyl group" for R^{4f} optionally has 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

In the above-mentioned formula, the partial structural formula



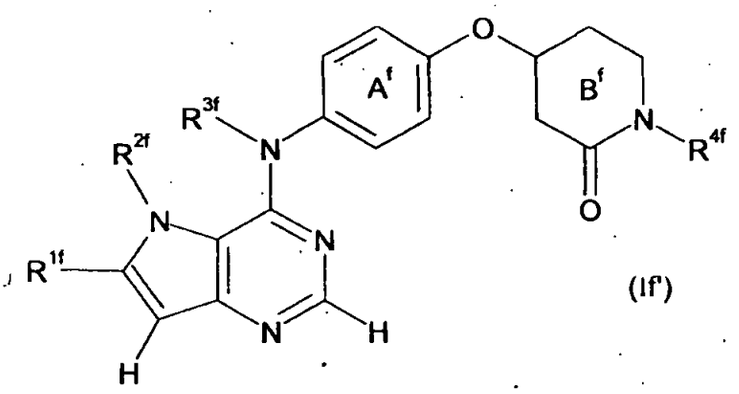
is preferably



wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (If') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (If')") can be mentioned:

[compound (If')]



(If')

wherein each symbol is as defined above.

As preferable embodiment of compound (If), compound (If) wherein

R^{1f} is a hydrogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,

R^{2f} is

(i) a C_{1-6} alkyl group, or

(ii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-NR^{6f}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6f} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3f} is a hydrogen atom or a C_{1-6} alkyl group,

ring A^f is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

ring B^f is a piperidyl group, and

R^{4f} is (i) an optionally substituted C_{1-6} alkyl group, or (ii) an optionally substituted C_{5-8} cycloalkyl group,

can be mentioned.

As another preferable embodiment of compound (If),

compound (If) wherein

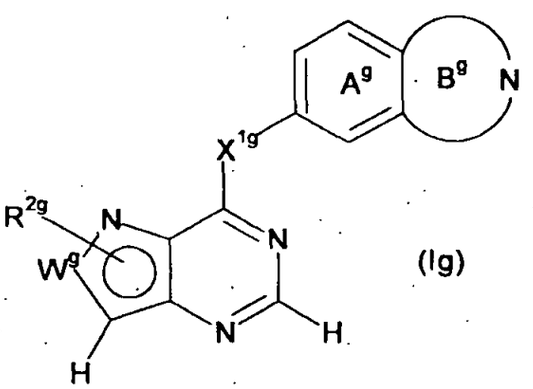
R^{3f} is a hydrogen atom, and

ring A^f is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

can be mentioned.

[compound (Ig)]

The present invention provides also a compound represented by the formula (Ig) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ig)").



(Ig)

wherein each symbol is as defined above.

In the formula (Ig), the "benzene ring" of the "optionally substituted benzene ring" for ring A^g optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

As the "nitrogen-containing heterocycle" of the "optionally substituted nitrogen-containing heterocycle" for ring B^g, for example, a 3 to 8-membered (preferably 5 or 6-membered) aromatic heterocycle or a saturated or unsaturated (preferably saturated) aliphatic heterocycle and the like can be mentioned. Of these, 3 to 8-membered

(preferably 5 or 6-membered) saturated or unsaturated (preferably saturated) aliphatic heterocyclic groups such as azetidine, pyrrolidine, piperidine, homopiperidine, heptamethylenimine, morpholine, thiomorpholine, piperazine, homopiperazine and the like, and the like can be preferably used.

The "nitrogen-containing heterocycle" optionally has 1 to 5, the same or different substituents at any substitutable positions. As the substituent, substituents similar to the above-mentioned Substituent Group V can be mentioned.

As the "aliphatic hydrocarbon group" of the "optionally substituted aliphatic hydrocarbon group" for R^{3g}, a C_{1-6} alkyl group is preferable.

The "C_{1-4} alkylene" and "-O-(C_{1-4} alkylene)-" of the "C_{1-4} alkylene or -O-(C_{1-4} alkylene)-, each of which is optionally substituted," for Y^{1g} are optionally substituted by 1 to 3 substituents selected form halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino.

X^{1g} is preferably $-NR^{3g}-$. In the formula, R^{3g} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

W^g is preferably $C(R^{1g})$.

As the "optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom" for R^{1g}, a cyano group and an optionally substituted C_{1-8} alkyl group are preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned. Of these, halogen is preferable.

R^{1g} is preferably a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group, more preferably a hydrogen atom.

As the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2g}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) $-NR^{5g}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl,

(d) hydroxy, and

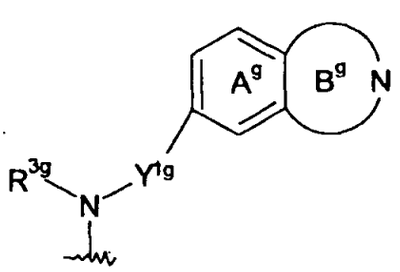
(e) amino

wherein n is an integer of 1 to 4, R^{5g} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

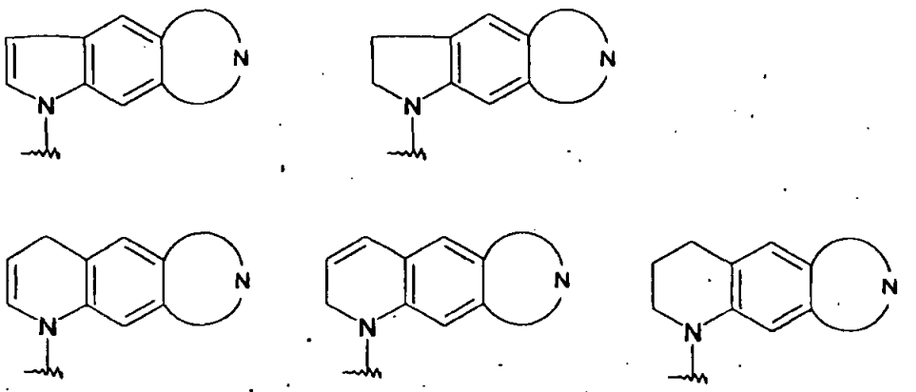
can be used.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{3g} bonded to the carbon atom on the benzene ring for ring A^g, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

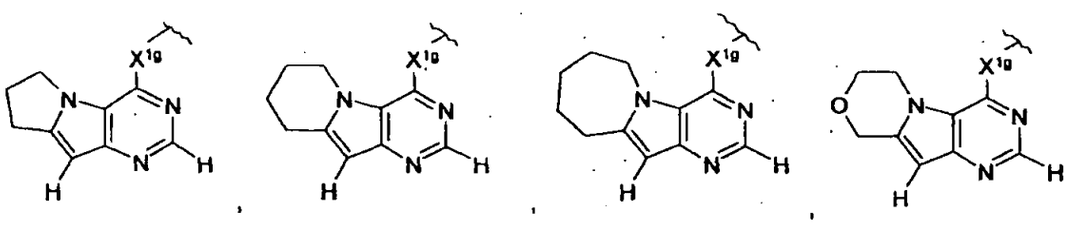


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1g} and R^{2g} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{1g} and R^{2g} bonded to each other, for example,

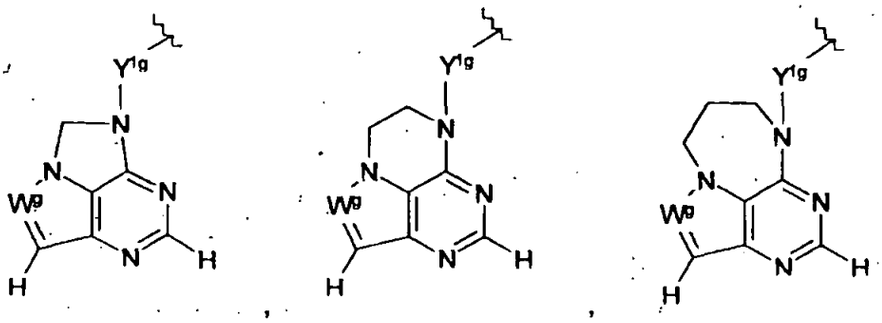


wherein each symbol is as defined above,
and the like can be mentioned.

R^{2g} and R^{3g} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered)

heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2g} and R^{3g} bonded to each other, for example,

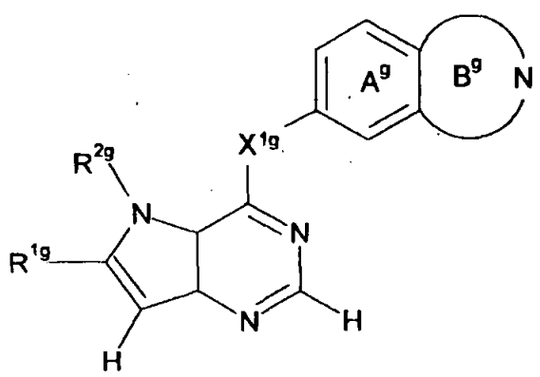


wherein each symbol is as defined above,

and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1g} and R^{2g}, or R^{2g} and R^{3g} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

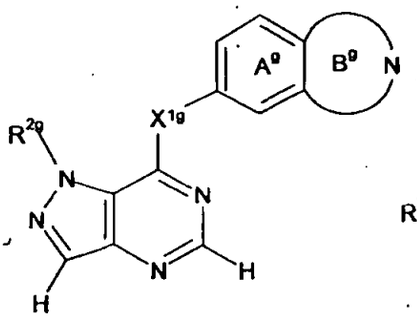
When W^g is $C(R^{1g})$, compound (Ig) is represented by the following formula (IgA) :



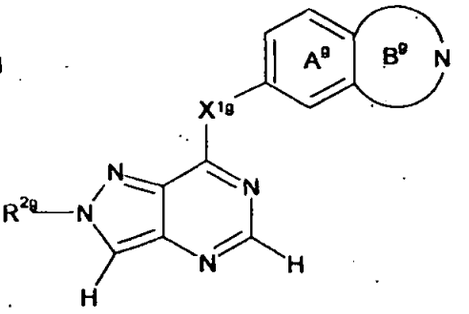
(IgA)

wherein each symbol is as defined above.

When W^g is N, compound (Ig) is represented by the following formula (IgB) or (IgC):



(IgB)

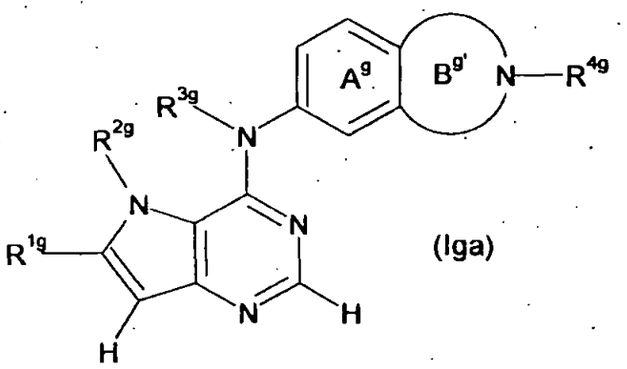


(IgC)

wherein each symbol is as defined above.

[compound (Iga)]

As preferable embodiment of compound (Ig), a compound represented by the following formula (Iga) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Iga)") can be mentioned:



(Iga)

wherein R^{4g} is an optionally substituted hydrocarbon group, ring $B^{g'}$ is a 5 or 6-membered nitrogen-containing heterocycle optionally further substituted besides R^{4g}, and the other symbols are as defined above.

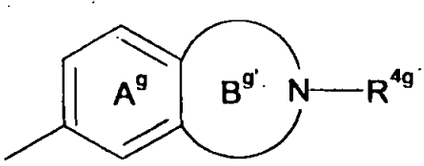
In the above-mentioned formula (Iga), as the "5 or 6-membered nitrogen-containing heterocycle" of the "optionally further substituted 5 or 6-membered nitrogen-containing heterocycle" for ring $B^{g'}$, a 5 or 6-membered "nitrogen-containing heterocycle" from the "nitrogen-containing heterocycle" of the "optionally

substituted nitrogen-containing heterocycle" for ring B^g can be mentioned.

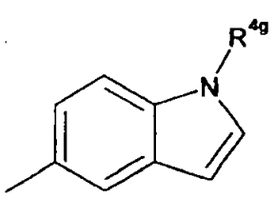
R^{4g} is preferably (i) an optionally substituted C_{6-14} aryl-C_{1-8} alkyl group, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, (iii) a C_{1-8} alkyl group, or (iv) an optionally substituted C_{6-14} aryl group, more preferably (i) a C_{6-14} aryl-C_{1-8} alkyl group optionally substituted by substituent(s) selected from the group consisting of halogen, C_{1-6} alkyl-carbamoyl and halo C_{1-6} alkoxy, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, or (iii) an optionally substituted C_{6-14} aryl group.

The "C_{6-14} aryl-C_{1-8} alkyl group" of the "optionally substituted C_{6-14} aryl-C_{1-8} alkyl group" for R^{4g}, "heterocyclyl-C_{1-8} alkyl group" of the "optionally substituted heterocyclyl-C_{1-8} alkyl group" for R^{4g} and "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for R^{4g} optionally have 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

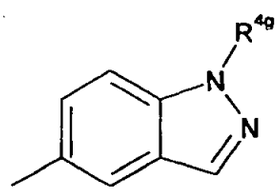
In the above-mentioned formula, the partial structural formula



is preferably



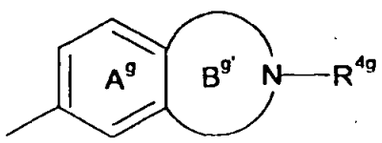
or



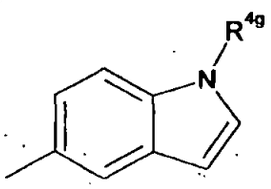
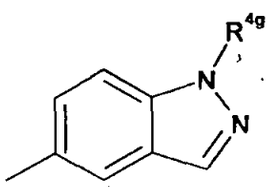
wherein each symbol is as defined above.

As preferable embodiment of compound (Ig), compound (Iga) wherein, in the above-mentioned formula (Iga),
R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2g} is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,
R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,
R^{4g} is (i) an optionally substituted C_{6-14} aryl-C_{1-8} alkyl group, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, (iii) a C_{1-8} alkyl group, or (iv) an optionally substituted C_{6-14} aryl group,
can be mentioned.

As another more preferable embodiment of compound (Ig), compound (Iga) wherein, in the above-mentioned formula (Iga),
R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2g} is
(i) a hydrogen atom,
(ii) a C_{1-6} alkyl group, or
(iii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(a) $-O-(CH_2)_n-OH$,
(b) $-NR^{5g}-CO-(CH_2)_n-OH$,
(c) $-NR^{5g}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl,
(d) hydroxy, and
(e) amino
wherein n is an integer of 1 to 4, R^{5g} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,
R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,



is the formula

 or  , and

R^{4g} is (i) a C_{6-14} aryl-C_{1-8} alkyl group optionally substituted by substituent(s) selected from the group consisting of halogen, C_{1-6} alkyl-carbamoyl and halo C_{1-6} alkoxy, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, or (iii) an optionally substituted C_{6-14} aryl group,

can be mentioned.

As compound (Ig), particularly preferably,

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide,

N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide,

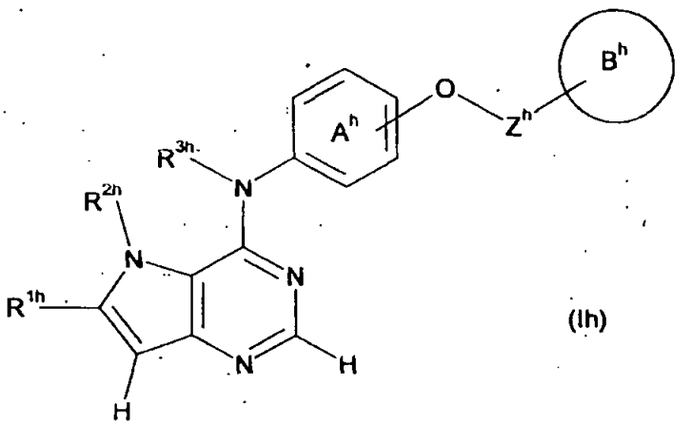
N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indazol-1-yl)methyl]benzamide, and

N-(tert-butyl)-6-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]pyridine-2-carboxamide,

and salts thereof can be mentioned.

[compound (Ih)]

The present invention provides also a compound represented by the formula (Ih) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ih)").



(Ih)

wherein each symbol is as defined above.

In the above-mentioned formula (Ih), as the "optionally substituted group bonded via a carbon atom or a sulfur atom" for R^{2h}, an optionally substituted C_{1-8} alkyl group is preferable. As the C_{1-8} alkyl group, a C_{1-6} alkyl group is preferable.

As the substituents for the alkyl group, substituents similar to the above-mentioned Substituent Group X can be mentioned, preferably, substituent(s) selected from the group consisting of

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) $-NR^{5g}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl, and

(d) hydroxy,

wherein n is an integer of 1 to 4, R^{6h} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

can be used.

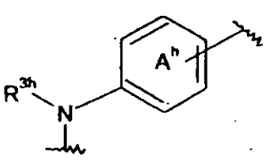
As the "aliphatic hydrocarbon group" of the

"optionally substituted aliphatic hydrocarbon group" for R^{3h}, a C_{1-6} alkyl group is preferable.

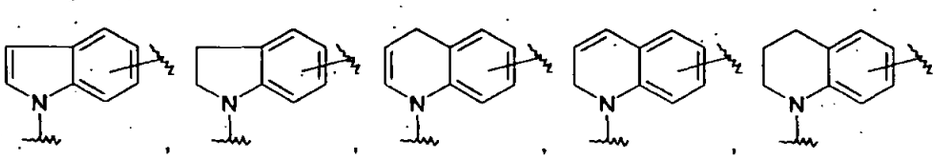
R^{3h} is preferably a hydrogen atom or a C_{1-6} alkyl group, more preferably a hydrogen atom.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{3h} bonded to the carbon atom on the adjacent benzene ring, a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5 or 6-membered) nitrogen-containing heterocycle can be mentioned.

Specifically,



wherein each symbol is as defined above, is, for example,

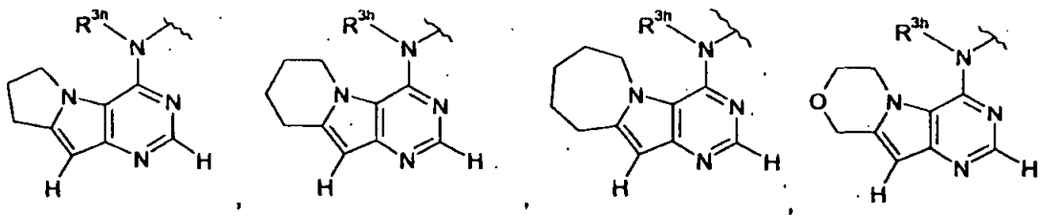


and the like.

The "ring structure" optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

R^{1h} and R^{2h} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

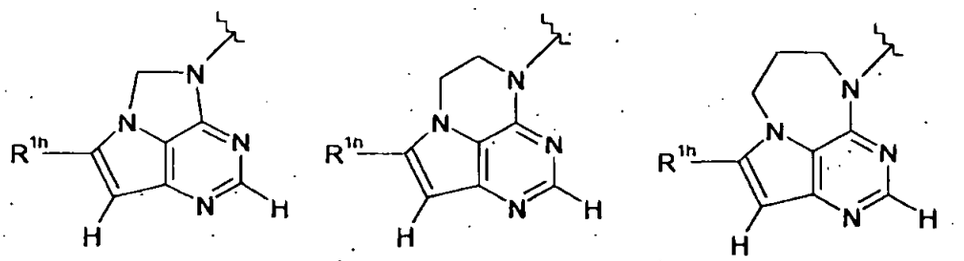
As the "ring structure" of the "optionally substituted ring structure" formed by R^{1h} and R^{2h} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

R^{2h} and R^{3h} are optionally bonded to each other to form an optionally substituted ring structure. As the "ring structure", a saturated or unsaturated (preferably saturated) 4 to 8-membered (preferably 5- to 7-membered) heterocycle can be mentioned.

As the "ring structure" of the "optionally substituted ring structure" formed by R^{2h} and R^{3h} bonded to each other, for example,



wherein each symbol is as defined above,
and the like can be mentioned.

The "ring structure" of the "optionally substituted ring structure" formed by R^{1h} and R^{2h}, or R^{2h} and R^{3h} optionally has 1 to 5 (preferably 1 to 3, more preferably 1 or 2), the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned

The "benzene ring" of the "optionally substituted benzene ring" for ring A^h optionally has 1 to 3, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be

mentioned. Of these, halogen and methyl are preferable.

Ring A^h is preferably a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl.

As the "C_{1-3} alkylene" of the "optionally substituted C_{1-3} alkylene" for Z^h, methylene is preferable.

The "C_{1-3} alkylene" of the "optionally substituted C_{1-3} alkylene" for Z^h is optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl-carbonyl, carboxy, C_{1-4} alkoxy-carbonyl, cyano, carbamoyl, sulfamoyl, nitro, amino, C_{1-4} alkyl-carbonylamino, C_{1-4} alkoxy-carbonylamino and C_{1-4} alkylsulfonylamino.

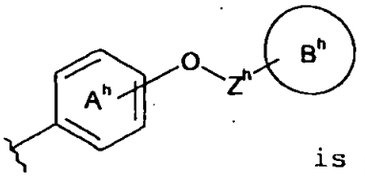
As the "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for ring B^h, a phenyl group is preferable.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for ring B^h, a pyridyl group and a piperidyl group are preferable.

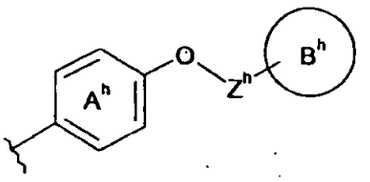
As the "C_{5-8} cycloalkyl group" of the "optionally substituted C_{5-8} cycloalkyl group" for ring B^h, a cyclohexyl group is preferable.

The "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for ring B^h, the "heterocyclic group" of the "optionally substituted heterocyclic group" for ring B^h and the "C_{5-8} cycloalkyl group" of the "optionally substituted C_{5-8} cycloalkyl group" for ring B^h optionally have 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

In the above-mentioned formula, the partial structural formula



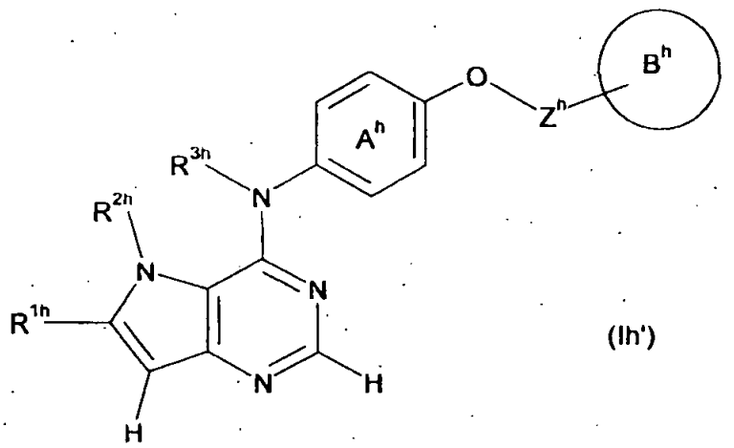
is preferably



wherein each symbol is as defined above.

As specific examples, a compound represented by the following formula (Ih') or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Ih')") can be mentioned:

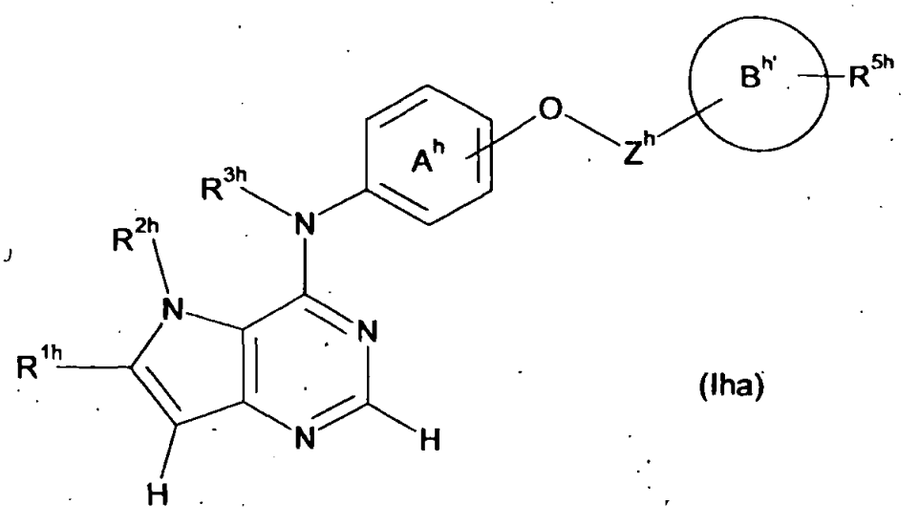
[compound (Ih')]



(Ih')

wherein each symbol is as defined above.

As preferable embodiment of compound (Ih), a compound represented by the following formula (Iha) or a salt thereof (in the present specification, hereinafter sometimes to be abbreviated as "compound (Iha)") can be mentioned:



(Iha)

wherein

R^{5h} is

(i) an optionally substituted amino group,

(ii) an optionally substituted carbamoyl group,

(iii) an optionally substituted ureido group,

(iv) an optionally substituted sulfamoyl group,

(v) an optionally substituted heterocyclic group,

(vi) an optionally substituted hydrocarbon group,

(vii) a halogen atom, or

(viii) an optionally substituted carboxyl group, and

ring $B^{h'}$ is (i) a C_{6-14} aryl group, (ii) a heterocyclic group, or (iii) a C_{5-8} cycloalkyl group, each of which is optionally further substituted besides R^{5h}, and the other symbols are as defined above.

In the above-mentioned formula (Iha), as the "optionally substituted amino group" for R^{5h}, an amino group, a C_{1-6} alkyl-amino group, an optionally halogenated C_{1-6} alkanoyl-amino group, a hydroxy-C_{1-6} alkanoyl-amino group, a C_{1-6} alkanoyl-amino group having hydroxy and halogen, a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group, a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen, a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group, a C_{3-7} cycloalkyl-carbonyl-amino group and a C_{1-6} alkoxy-carbonyl-amino group are preferable.

As the "optionally substituted carbamoyl group" for R^{5h}, a carbamoyl group, an optionally halogenated C_{1-6} alkyl-carbamoyl group, a hydroxy-C_{1-6} alkyl-carbamoyl group, a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group, a C_{3-7} cycloalkyl-carbamoyl group, and a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom are preferable.

As the "optionally substituted ureido group" for R^{5h}, a ureido group, a C_{1-6} alkyl-ureido group, a C_{3-7} cycloalkyl-ureido group, and a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom are preferable.

As the "optionally substituted sulfamoyl group" for R^{5h}, a sulfamoyl group optionally substituted by C_{1-6} alkyl is preferable.

As the "optionally substituted heterocyclic group" for R^{5h}, a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl is preferable.

As the "optionally substituted hydrocarbon group" for R^{5h}, an optionally halogenated C_{1-6} alkyl group and a C_{1-6} alkoxy-carbonyl group are preferable.

As the "optionally substituted carboxyl group" for R^{5h}, a carboxyl group is preferable.

In the above-mentioned formula (Iha), as the "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for ring $B^{h'}$, a phenyl group is preferable.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for ring $B^{h'}$, a pyridyl

group and a piperidyl group are preferable.

As the "C_{5-8} cycloalkyl group" of the "optionally substituted C_{5-8} cycloalkyl group" for ring $B^{h'}$, a cyclohexyl group is preferable.

The "C_{6-14} aryl group" of the "optionally substituted C_{6-14} aryl group" for ring $B^{h'}$, the "heterocyclic group" of the "optionally substituted heterocyclic group" for ring $B^{h'}$ and the "C_{5-8} cycloalkyl group" of the "optionally substituted C_{5-8} cycloalkyl group" for ring $B^{h'}$ optionally have besides R^{5h}, 1 to 5, the same or different substituents at any substitutable positions. As the substituents, substituents similar to the above-mentioned Substituent Group V can be mentioned.

Ring $B^{h'}$ is preferably a phenyl group, a pyridyl group or a piperidyl group, each of which is optionally further substituted besides R^{5h}.

As more preferable embodiment of compound (Ih), compound (Iha) wherein, in the above-mentioned formula (Iha),

R^{1h} is a halogen atom or an optionally halogenated C_{1-6} alkyl group,

R^{2h} is

(i) a hydrogen atom,

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

(iii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{6h}-CO-(CH_2)_n-OH$,

(c) $-NR^{6h}-CO-(CH_2)_n-SO_2$-optionally halogenated C_{1-4} alkyl, and

(d) hydroxy

wherein n is an integer of 1 to 4, R^{6h} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally

substituted by C_{1-4} alkyl,

R^{3h} is a hydrogen atom or a C_{1-6} alkyl group,

Z^h is a bond or methylene,

ring A^h is a benzene ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl,

R^{5h} is

(i) an amino group,

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

(iii) an optionally halogenated C_{1-6} alkanoyl-amino group,

(iv) a hydroxy-C_{1-6} alkanoyl-amino group,

(v) a C_{1-6} alkanoyl-amino group having hydroxy and halogen,

(vi) a C_{3-7} cycloalkyl-C_{1-6} alkanoyl-amino group,

(vii) a C_{1-6} alkanoyl-amino group having C_{3-7} cycloalkyl and halogen,

(viii) a C_{1-6} alkylsulfonyl-C_{1-6} alkanoyl-amino group,

(ix) a C_{3-7} cycloalkyl-carbonyl-amino group,

(x) a C_{1-6} alkoxy-carbonyl-amino group,

(xi) a carbamoyl group,

(xii) an optionally halogenated C_{1-6} alkyl-carbamoyl group,

(xiii) a hydroxy-C_{1-6} alkyl-carbamoyl group,

(xiv) a C_{1-6} alkoxy-C_{1-6} alkyl-carbamoyl group,

(xv) a C_{3-7} cycloalkyl-carbamoyl group,

(xvi) a 5 or 6-membered cyclic amino-carbonyl group optionally containing an oxygen atom,

(xvii) a ureido group,

(xviii) a C_{1-6} alkyl-ureido group,

(xix) a C_{3-7} cycloalkyl-ureido group,

(xx) a 5- to 8-membered heterocyclyl-ureido group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom,

(xxi) a sulfamoyl group optionally substituted by C_{1-6} alkyl,

(xxii) a 5- to 8-membered heterocyclic group containing, besides carbon atoms, 1 to 3 hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom, which is optionally substituted by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl and C_{1-6} alkoxy-carbonyl,

(xxiii) an optionally halogenated C_{1-6} alkyl group,

(xxiv) a C_{1-6} alkoxy-carbonyl group,

(xxv) a halogen atom, or

(xxvi) a carboxyl group, and

ring $B^{h'}$ is a phenyl group, a pyridyl group or a piperidyl group, each of which is optionally further substituted besides R^{5h},

can be mentioned.

As compound (Ih), particularly preferably,

N-(3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl) cyclopropanecarboxamide,

6-chloro-N-{3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-4-amine,

N-[3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide, and

N-(tert-butyl)-3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,

and salts thereof can be mentioned.

As the salts of the compounds represented by the formulas, for example, metal salts, ammonium salts,

salts with organic base, salts with inorganic acid, salts with organic acid, salts with basic or acidic amino acid and the like can be mentioned.

As preferable examples of the metal salt, for example, alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like can be mentioned.

As preferable examples of the salts with organic base, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, tromethamine[tris(hydroxymethyl)methylamine], t-butylamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like can be mentioned.

As preferable examples of salts with inorganic acid, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like can be mentioned.

As preferable examples of the salts with organic acid, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

As preferable examples of the salts with basic amino acid, for example, salts with arginine, lysine, ornithine and the like can be mentioned.

As preferable examples of the salts with acidic amino acid, for example, salts with aspartic acid, glutamic acid and the like can be mentioned.

Of these, pharmaceutically acceptable salts are preferable. When a compound contains an acidic functional group, for example, inorganic salts such as

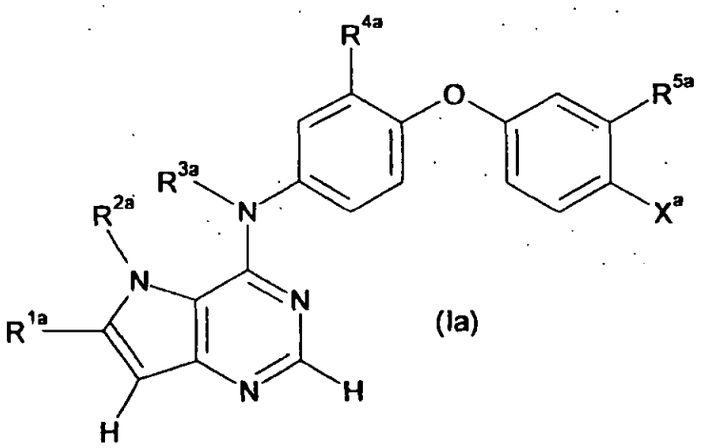
alkali metal salts (e.g., sodium salt, potassium salt etc.), alkaline earth metal salts (e.g., calcium salt, magnesium salt, barium salt etc.) and the like, ammonium salt and the like can be mentioned. And when a compound contains a basic functional group, for example, salts with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, and salts with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like can be mentioned.

[Production methods]

Hereinafter the production methods of the compounds (Ia) to (Ih) of the present invention are explained.

[Production method A]

Compound (Ia) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.



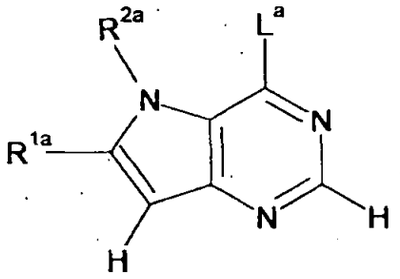
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ia) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

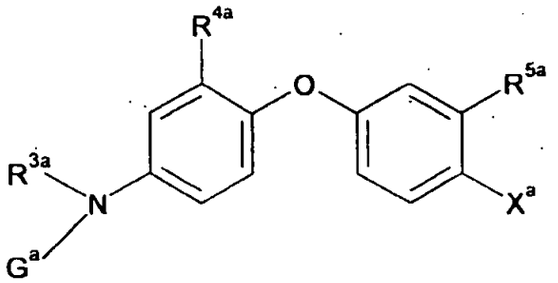
Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

Compound (Ia) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIa)

wherein L^a is a leaving group, and the other symbols are as defined above,
or a salt thereof and a compound represented by the formula:



(IIIa)

wherein G^a is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

G^a is mainly a hydrogen atom, but may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium,

calcium and the like.

Compound (IIIa) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIa) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^a, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium

ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ia) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of

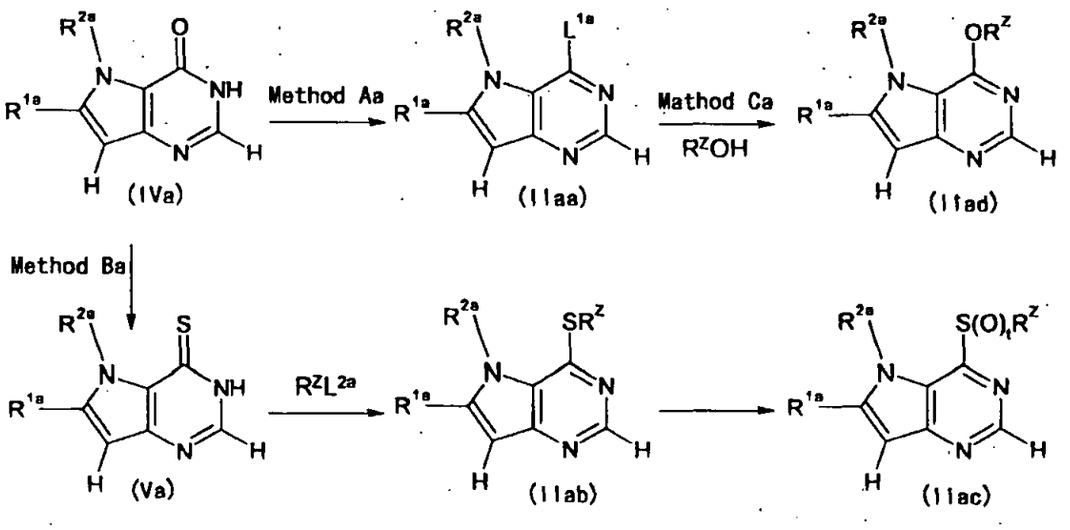
functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ia), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ia) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIa) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIa) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIaa), (IIab), (IIac) and (IIad) are encompassed in compound (IIa).



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wherein L^{1a} and L^{2a} are halogen atoms, R^2 is as defined above, and t is an integer of 1 or 2.

As Method Aa, compound (IIaa) can be produced by reacting compound (IVa) with a halogenating agent. As Method Ba, compound (IVa) is reacted with a thionating agent to give compound (Va), which is then reacted with a compound represented by R^2L^{2a} in the presence of a base to give compound (IIab), which is further subjected to an oxidation reaction to give compound (IIac). As Method Ca, compound (IIaa) is reacted with a compound represented by R^2OH in the presence of a base to give compound (IIad).

As the halogenating agent in Method Aa, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVa) to compound (Va) in Method Ba, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons

such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2a} in the production step from compound (Va) to compound (IIab) in Method Ba, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

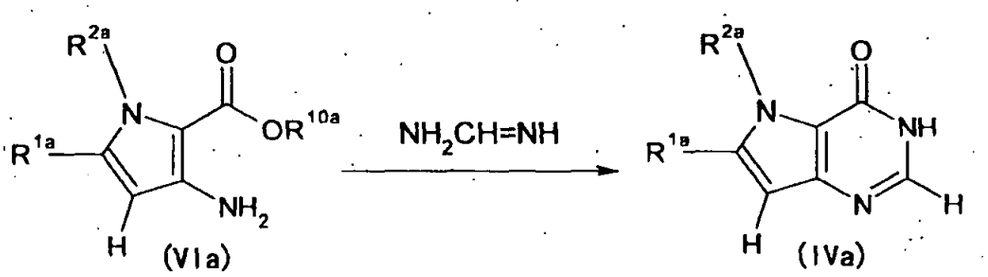
As the oxidizing agent in the production step from compound (IIab) to compound (IIac) in Method Ba, for

example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIac) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIab), and when compound (IIac) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIab). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^2OH in the production step from compound (IIaa) to compound (IIad) in Method Ca, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium

ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Furthermore, compound (IVa) can be produced by, for example, a method shown by the following formula:

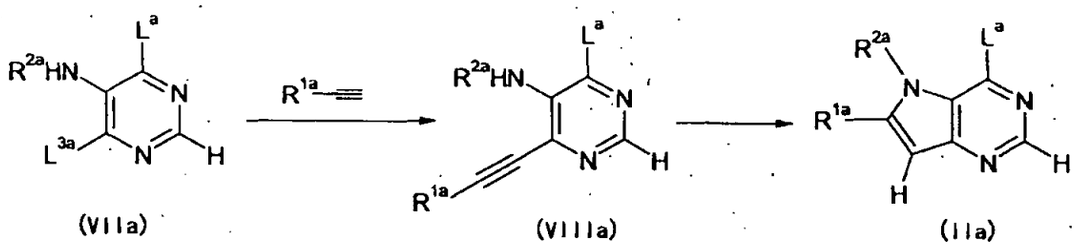


wherein R^{10a} is a C_{1-4} alkyl group, and other symbols are as defined above.

That is, compound (VIa) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVa). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-

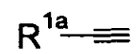
dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Compound (IIa) can be also produced by, for example, a method shown by the following formula:



wherein L^{3a} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIa) to compound (VIIIa) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIa) can be produced by reacting compound (VIIa) with about 1-3 equivalents of a compound represented by the formula:



in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate,

bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

For the production step from compound (VIIIa) to compound (IIa) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IIa). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic

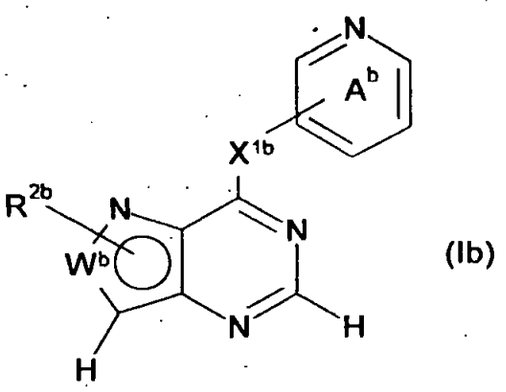
hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIa), a starting compound (IIa) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIa)

can be also produced.

[Production method B]

Compound (Ib) of the present invention can be obtained by, for example, the method shown by the following schemes or a method analogous thereto and the like.



(Ib)

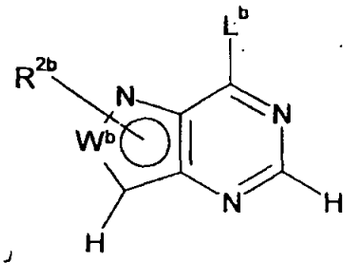
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ib) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

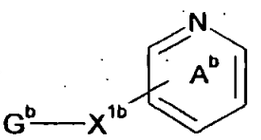
Compound (Ib) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIb)

wherein L^b is a leaving group, and the other symbols are as defined above;

or a salt thereof and a compound represented by the formula:



(IIIb)

wherein G^b is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

When X^{1b} is $-NR^{3b}-Y^{1b}-$, $-O-$ or $-S-$, G^b is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

When X^{1b} is $-CHR^{3b}-$, G^b may be a metal such as lithium, halogenated magnesium, copper, zinc and the like.

Compound (IIIb) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIb) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^b, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a

lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

Compound (Ib) wherein X^{1b} is -SO- or $-SO_2-$ can be produced by subjecting compound (Ib) wherein X^{1b} is -S- to an oxidization reaction. As the oxidizing agent in the production step, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (Ib) wherein X^{1b} is -SO- is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to the starting compound, and when compound (Ib) wherein X^{1b} is $-SO_2-$ is produced, it is used in about 2-3 equivalents relative to the starting compound. The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ib) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ib), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ib) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction

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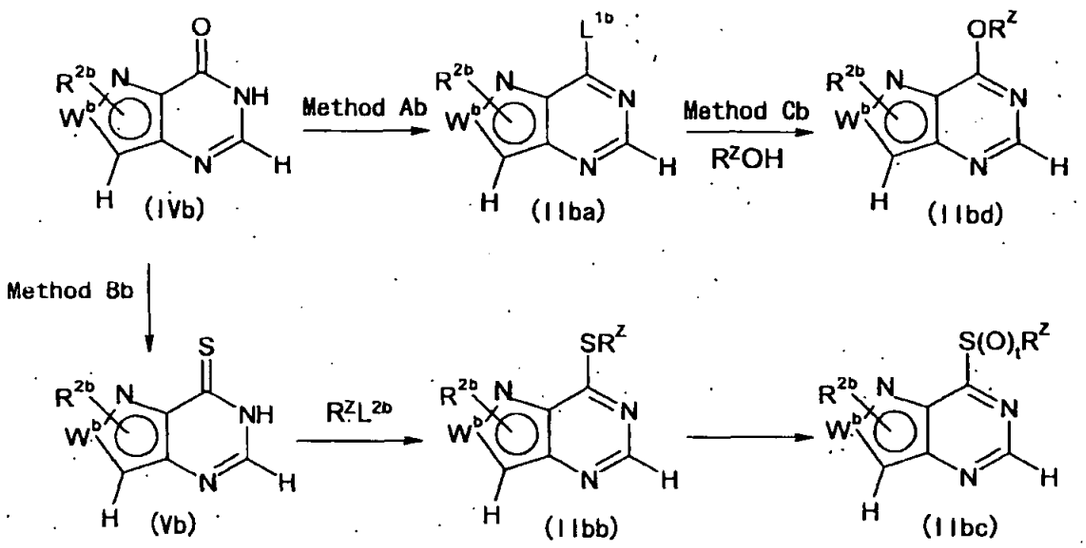
mixture.

As the starting compound (IIIb) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIb) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIba), (IIbb), (IIbc), (IIbd) and (IIbe) are encompassed in compound (IIb).



wherein L^{1b} and L^{2b} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ab, compound (IIba) can be produced by reacting compound (IVb) with a halogenating agent. As Method Bb, compound (IVb) is reacted with a thionating agent to give compound (Vb), which is then reacted with a compound represented by R^zL^{2b} in the presence of a base to give compound (IIbb), which is further subjected to an oxidation reaction to give compound (IIbc). As Method Cb, compound (IIba) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIbd).

As the halogenating agent in Method Ab, for example, about 1-100 equivalents of phosphorus

oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVb) to compound (Vb) in Method Bb, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2b} in the production step from compound (Vb) to compound (IIbb) in Method Bb, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium

hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

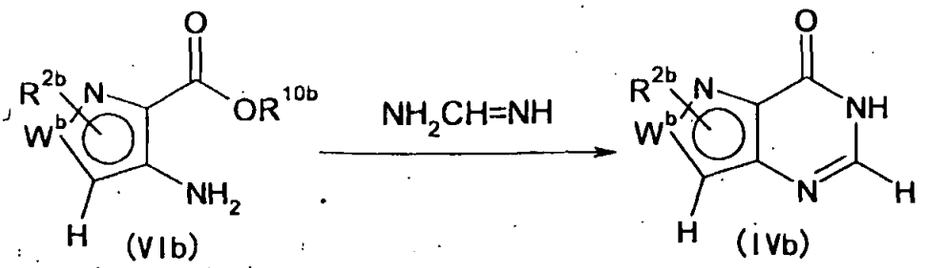
As the oxidizing agent in the production step from compound (IIbb) to compound (IIbc) in Method Bb, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIbc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIbb), and when compound (IIbc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIbb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such

as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zOH in the production step from compound (IIba) to compound (IIbd) in Method Cb, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20

hr, preferably about 1-10 hr.

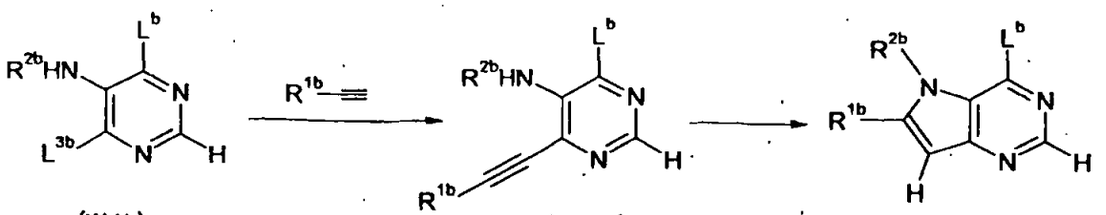
Furthermore, compound (IVb) can be produced by, for example, a method shown by the following formula:



wherein R^{10b} is a C_{1-4} alkyl group, and other symbols are as defined above.

That is, compound (VIb) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVb). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

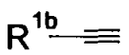
When W^b is $C(R^{1b})$, compound (IIbe) can be also produced by, for example, a method shown by the following formula:



(VIIb) (VIIIb) (IIbe)

wherein L^{3b} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIb) to compound (VIIIb) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIb) can be produced by reacting compound (VIIb) with about 1-3 equivalents of a compound represented by the formula:



in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol,

ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

For the production step from compound (VIIIb) to compound (IIbe) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IIbe). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is

carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIb), a starting compound (IIb) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIb) can be also produced.

[Production method C]

Compound (Ic) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.

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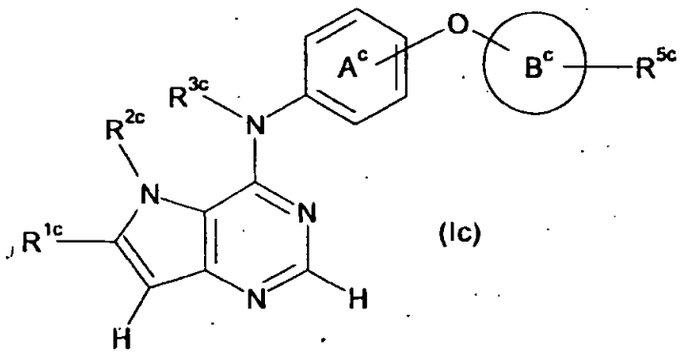


(Ic)

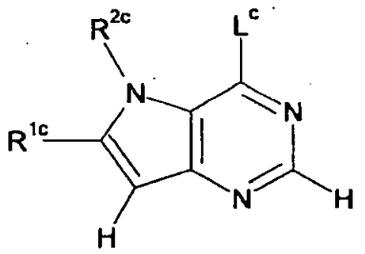
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ic) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

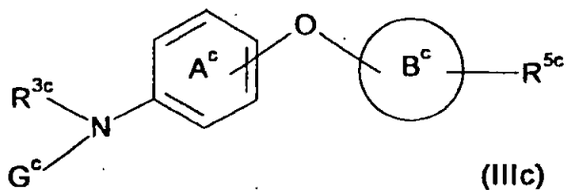
Compound (Ic) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIc)

wherein L^c is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIc)

wherein G^c is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

G^c is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (IIIc) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIc) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^c, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide,

1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ic) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of

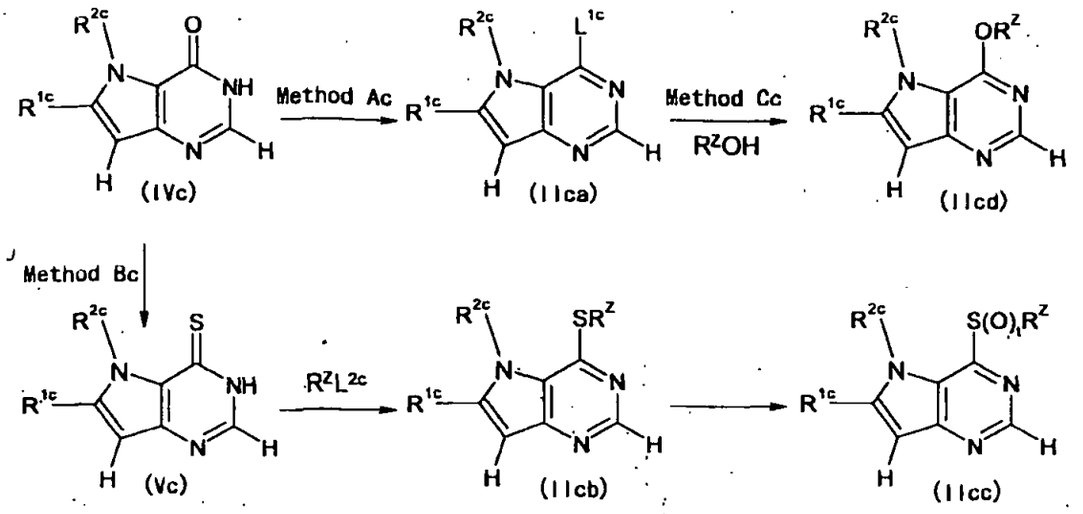
carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ic), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ic) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIc) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIc) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIca), (IIcb), (IIcc) and (IIcd) are encompassed in compound (IIc).



wherein L^{1c} and L^{2c} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ac, compound (IIca) can be produced by reacting compound (IVc) with a halogenating agent. As Method Bc, compound (IVc) is reacted with a thionating agent to give compound (Vc), which is then reacted with a compound represented by R^zL^{2c} in the presence of a base to give compound (IIcb), which is further subjected to an oxidation reaction to give compound (IIcc). As Method Cc, compound (IIca) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIcd).

As the halogenating agent in Method Ac, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene,

toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVc) to compound (Vc) in Method Bc, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2c} in the production step from compound (Vc) to compound (IIcb) in Method Bc, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol,

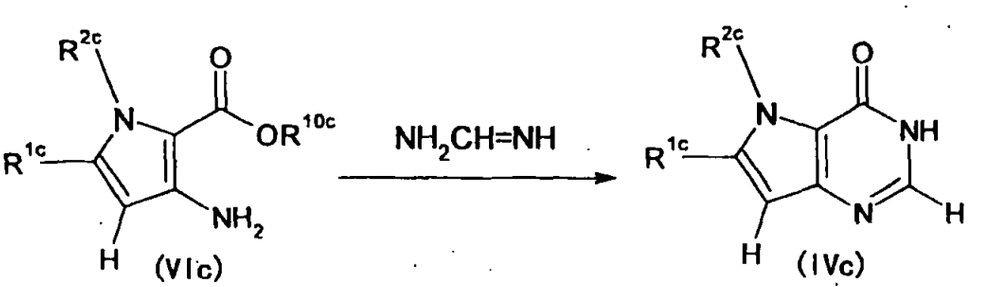
t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the oxidizing agent in the production step from compound (IIcb) to compound (IIcc) in Method Bc, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIcc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIcb), and when compound (IIcc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIcb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction

time is generally about 1-20 hr, preferably about 1-10 hr.

As R^2OH in the production step from compound (IIca) to compound (IIcd) in Method Cc, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Furthermore, compound (IVc) can be produced by, for example, a method shown by the following formula:

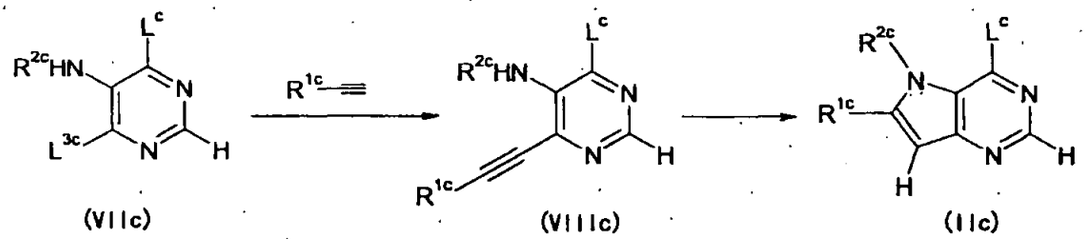


wherein R^{10c} is a C_{1-4} alkyl group, and other symbols are

as defined above.

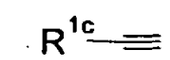
That is, compound (VIc) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVc). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Compound (IIc) can be also produced by, for example, a method shown by the following formula:



wherein L^{3c} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIc) to compound (VIIIc) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIc) can be produced by reacting compound (VIIc) with about 1-3 equivalents of a compound represented by the formula:



in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

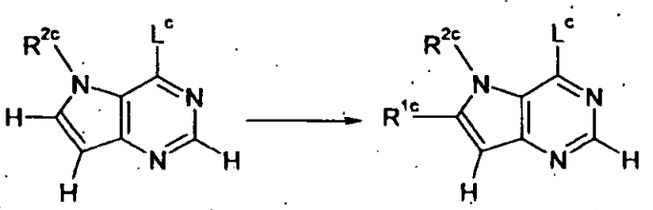
For the production step from compound (VIIIc) to compound (IIc) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper

iodide to give compound (IIc). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIc), a starting compound (IIc) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of

carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIc) can be also produced.

The starting compound (IIc) of this production method can also be produced, for example, by a method using compound (IIc'), as shown by the following scheme:



(IIc') (IIc)

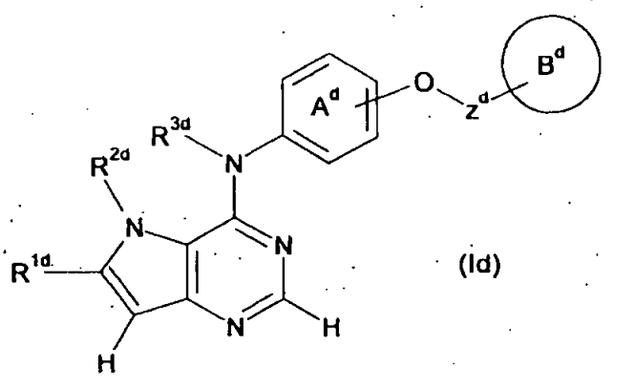
wherein each symbol is as defined above.

In this method, generally, compound (IIc') is converted to the anion by withdrawing a proton from compound (IIc') using a base, which is then reacted with a cation having R^{1c} to give compound (IIc). As the base, for example, n-butyllithium, s-butyllithium, t-butyllithium, lithium t-butoxide, lithium diisopropylamide and the like can be used. As a reagent for generating the cation, for example, p-toluenesulfonyl chloride, benzenesulfonyl bromide, p-toluenesulfonyl cyanide, S-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate, N,N-dimethylformamide and the like can be used. As the reaction solvent, for example,

halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, a mixed solvent thereof and the like can be used. The aforementioned reaction can be carried out under cooling, preferably about not more than -20°C, and the reaction time is generally about 15 min-50 hr, preferably about 30 min-4 hr.

[Production method D]

Compound (Id) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.



(Id)

wherein each symbol is as defined above.

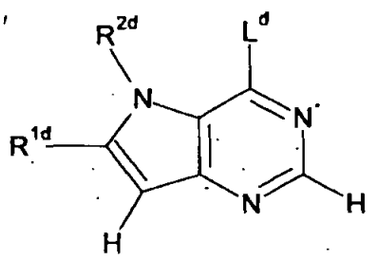
Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Id) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the

following, wherein each symbol of the compounds is as defined above.

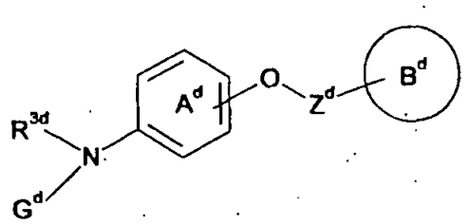
Compound (Id) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IId)

wherein L^d is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIId)

wherein G^d is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

G^d is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (IIId) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IId) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^d, a halogen atom such as chlorine, bromine, iodine

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and the like, a group represented by the formula: -$S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: -OR^z wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine

hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

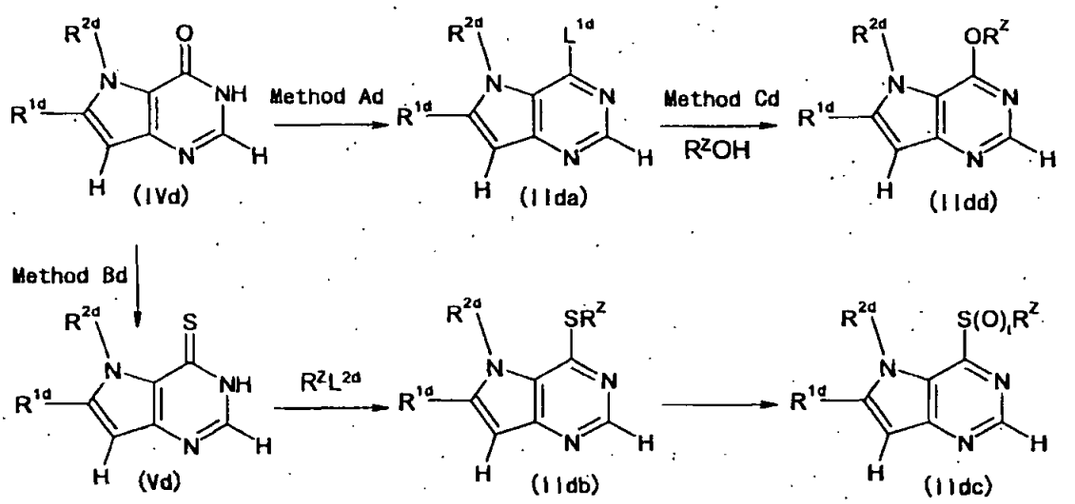
A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Id) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Id), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Id) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIId) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IId) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIda), (IIdb), (IIdc) and (IIdd) are encompassed in compound (IId).



wherein L^{1d} and L^{2d} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ad, compound (IIda) can be produced by reacting compound (IVd) with a halogenating agent. As Method Bd, compound (IVd) is reacted with a thionating agent to give compound (Vd), which is then reacted with a compound represented by R^zL^{2d} in the presence of a base to give compound (IIdb), which is further subjected to an oxidation reaction to give compound (IIdc). As Method

Cd, compound (IIda) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIdd).

As the halogenating agent in Method Ad, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVd) to compound (Vd) in Method Bd, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2d} in the production step from compound (Vd)

to compound (IIdb) in Method Bd, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

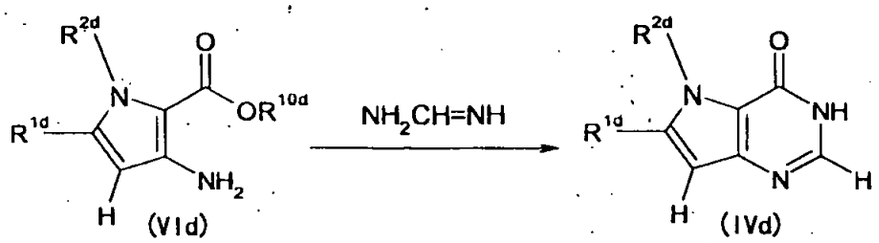
As the oxidizing agent in the production step from compound (IIdb) to compound (IIdc) in Method Bd, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIdc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIdb), and when compound (IIdc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIdb). The

reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zOH in the production step from compound (IIda) to compound (IIdd) in Method Cd, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide,

1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

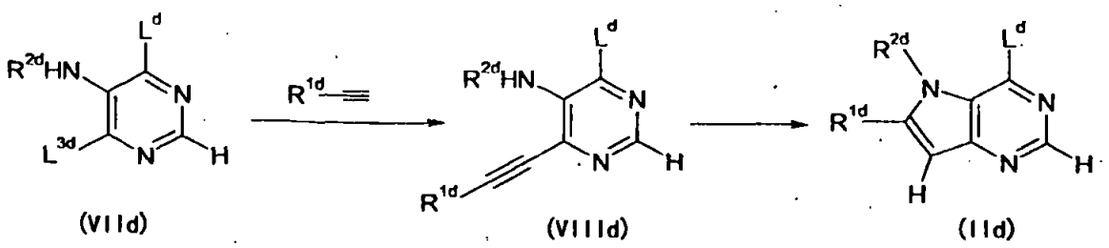
Furthermore, compound (IVd) can be produced by, for example, a method shown by the following formula:



wherein R^{10d} is a C_{1-4} alkyl group, and other symbols are as defined above.

That is, compound (VId) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVd). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

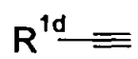
Compound (IId) can be also produced by, for example, a method shown by the following formula:



(VIId) (VIIId) (IId)

wherein L^{3d} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIId) to compound (VIIId) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIId) can be produced by reacting compound (VIId) with about 1-3 equivalents of a compound represented by the formula:



in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol,

ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

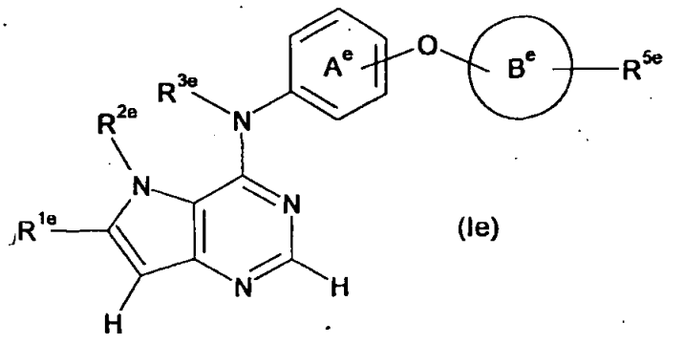
For the production step from compound (VIIId) to compound (IId) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IId). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is

carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IId), a starting compound (IId) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IId) can be also produced.

[Production method E]

Compound (Ie) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.



(Ie)

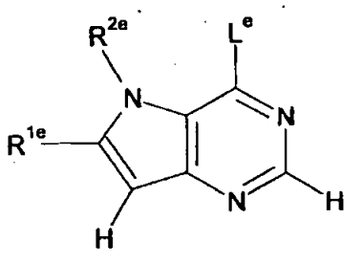
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ie) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

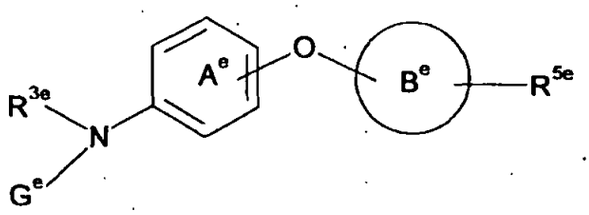
Compound (Ie) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIe)

wherein L^e is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIe)

wherein G^e is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

G^e is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (IIIe) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIe) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^e, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide,

1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ie) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of

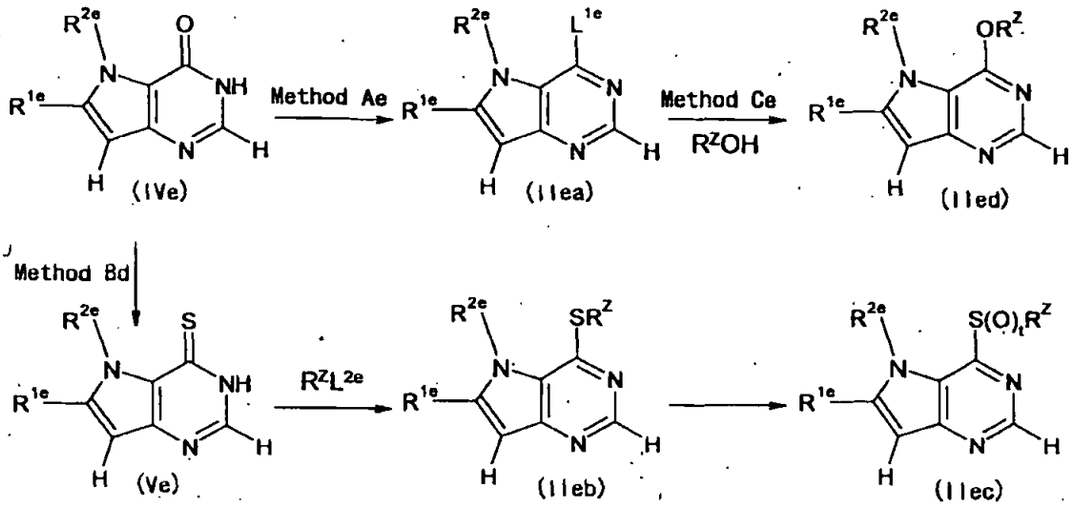
carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ie), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ie) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIe) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIe) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIea), (IIeb), (IIec) and (IIed) are encompassed in compound (IIe).



wherein L^{1e} and L^{2e} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ae, compound (IIea) can be produced by reacting compound (IVe) with a halogenating agent. As Method Be, compound (IVe) is reacted with a thionating agent to give compound (Ve), which is then reacted with a compound represented by R^zL^{2e} in the presence of a base to give compound (IIeb), which is further subjected to an oxidation reaction to give compound (IIec). As Method Ce, compound (IIea) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIed).

As the halogenating agent in Method Ae, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene,

toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVe) to compound (Ve) in Method Be, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2e} in the production step from compound (Ve) to compound (IIeb) in Method Be, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol,

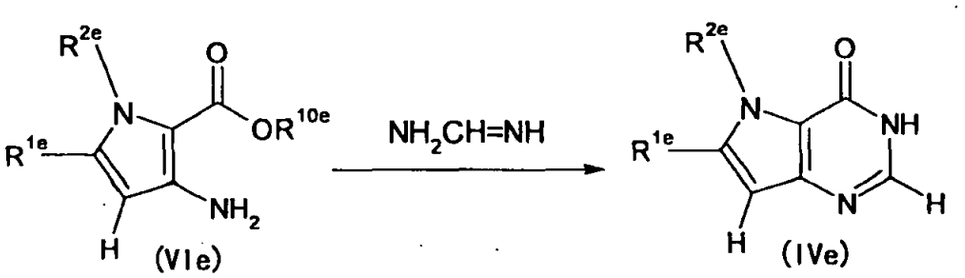
t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the oxidizing agent in the production step from compound (IIeb) to compound (IIec) in Method Be, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIec) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIeb), and when compound (IIec) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIeb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction

time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zOH in the production step from compound (IIea) to compound (IIed) in Method Cé, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Furthermore, compound (IVe) can be produced by, for example, a method shown by the following formula:

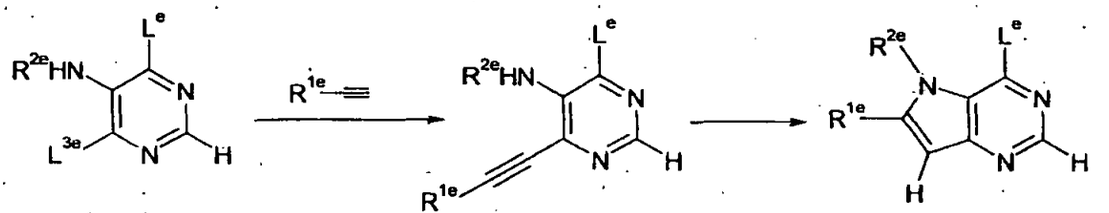


wherein R^{10e} is a C_{1-4} alkyl group, and other symbols are

as defined above.

That is, compound (VIe) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVe). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Compound (IIe) can be also produced by, for example, a method shown by the following formula:



wherein L^{3e} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIe) to compound (VIIIe) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIe) can be produced by reacting compound (VIIe) with about 1-3 equivalents of a compound represented by the formula:

R^{1e}—≡

in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

For the production step from compound (VIIIe) to compound (IIe) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper

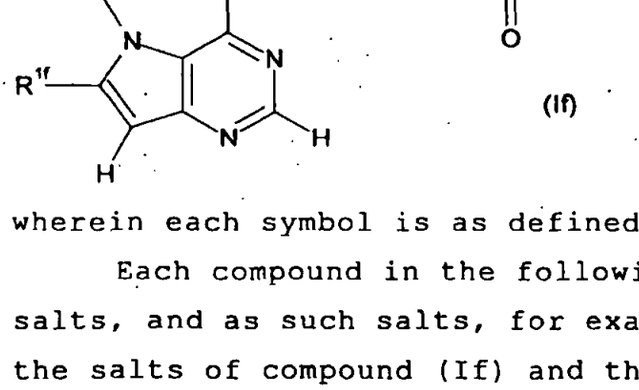
iodide to give compound (IIe). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIe), a starting compound (IIe) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of

carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIe) can be also produced.

[Production method F]

Compound (If) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.



wherein each symbol is as defined above.

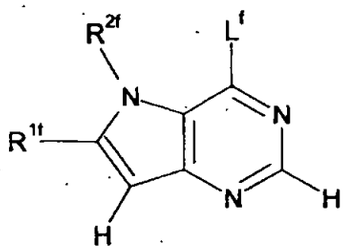
Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (If) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as

recrystallization, distillation, chromatography and the like.

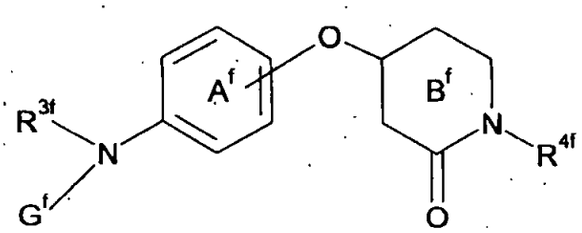
Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

Compound (If) of the present invention can be produced, for example, by reacting a compound represented by the formula;



(IIf)

wherein L^f is a leaving group, and the other symbols are as defined above,
or a salt thereof and a compound represented by the formula:



(IIIf)

wherein G^f is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

G^f is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (IIIf) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIf) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of

about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^f, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride,

isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

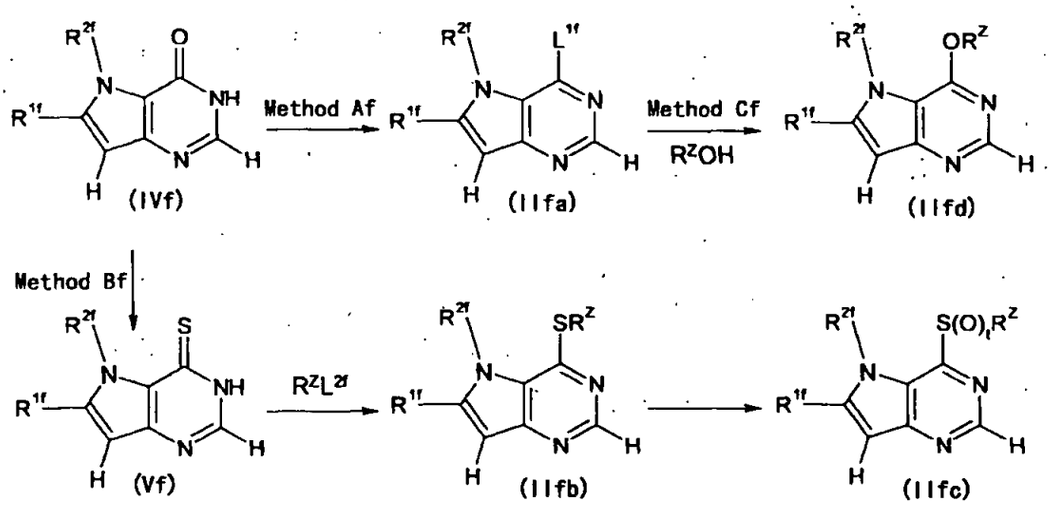
A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (If) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (If), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (If) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIf) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIf) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIfa), (IIfb), (IIfc) and (IIfd) are encompassed in compound (IIf).



wherein L^{1f} and L^{2f} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Af, compound (IIfa) can be produced by reacting compound (IVf) with a halogenating agent. As Method Bf, compound (IVf) is reacted with a thionating agent to give compound (Vf), which is then reacted with

a compound represented by R^zL^{2f} in the presence of a base to give compound (IIfb), which is further subjected to an oxidation reaction to give compound (IIfc). As Method Cf, compound (IIfa) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIfd).

As the halogenating agent in Method Af, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVf) to compound (Vf) in Method Bf, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under

heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2f} in the production step from compound (Vf) to compound (IIfb) in Method Bf, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

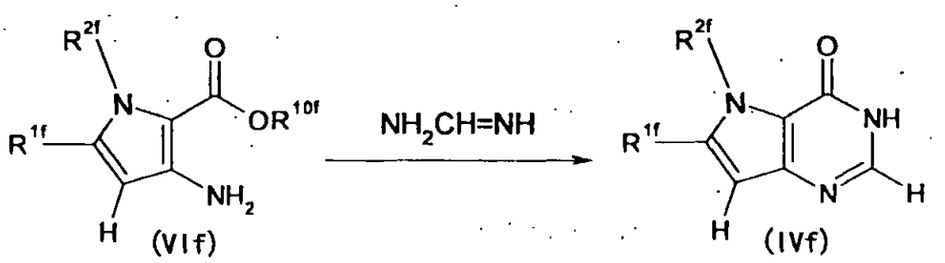
As the oxidizing agent in the production step from compound (IIfb) to compound (IIfc) in Method Bf, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIfc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5

equivalents relative to compound (IIfb), and when compound (IIfc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIfb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^2OH in the production step from compound (IIfa) to compound (IIfd) in Method Cf, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the

like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Furthermore, compound (IVf) can be produced by, for example, a method shown by the following formula:

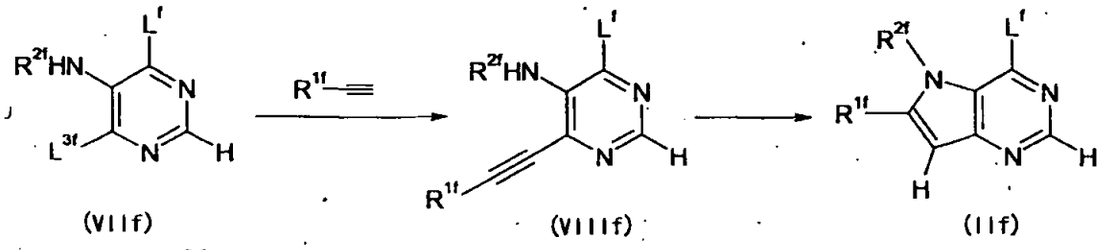


wherein R^{10f} is a C_{1-4} alkyl group, and other symbols are as defined above.

That is, compound (VIf) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVf). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20

hr, preferably about 1-10 hr.

Compound (IIf) can be also produced by, for example, a method shown by the following formula:



wherein L^{3f} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIf) to compound (VIIIf) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIf) can be produced by reacting compound (VIIf) with about 1-3 equivalents of a compound represented by the formula:

R^{1f}—≡

in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane,

chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

For the production step from compound (VIIIf) to compound (IIf) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IIf). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-

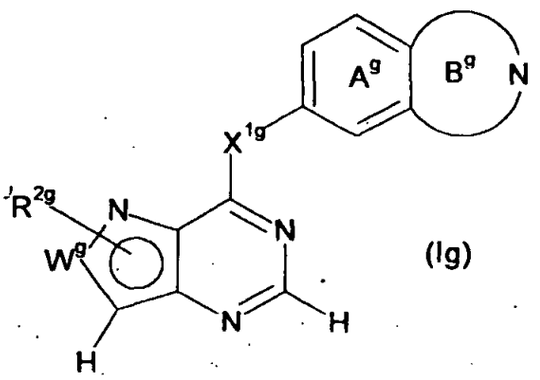
pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIf), a starting compound (IIf) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIf) can be also produced.

[Production method G]

Compound (Ig) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the

like.



(Ig)

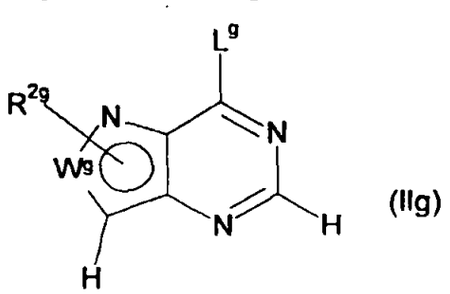
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ig) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

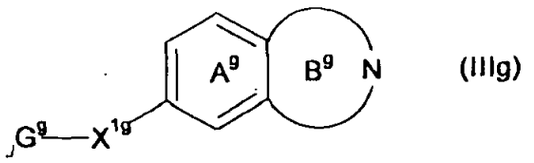
Compound (Ig) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIg)

wherein L^g is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIg)

wherein G^g is a hydrogen atom or a metal atom, and the other symbols are as defined above,
or a salt thereof.

When X^{1g} is $-NR^{3g}-Y^{1g}-$, -O- or -S-, G^g is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

When X^{1g} is $-CHR^{3g}-$, G^g may be a metal such as lithium, halogenated magnesium, copper, zinc and the like.

Compound (IIIg) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIg) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^g, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such

as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

Compound (Ig) wherein X^{1g} is -SO- or $-SO_2-$ can be produced by subjecting compound (Ig) wherein X^{1g} is -S- to an oxidization reaction. As the oxidizing agent in

the production step, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (Ig) wherein X^{1g} is -SO- is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to the starting compound, and when compound (Ig) wherein X^{1g} is $-SO_2-$ is produced, it is used in about 2-3 equivalents relative to the starting compound. The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ig) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of

carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ig), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ig) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIg) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIg) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIga), (IIgb), (IIgc), (IIgd) and (IIge) are encompassed in compound

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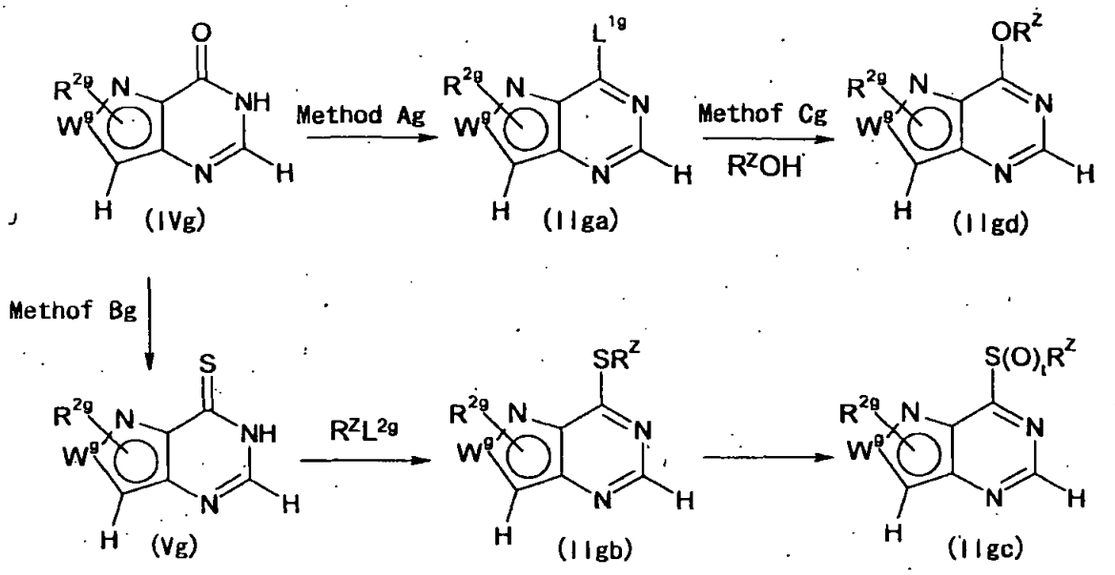
(IIg).



wherein L^{1g} and L^{2g} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ag, compound (IIga) can be produced by reacting compound (IVg) with a halogenating agent. As Method Bg, compound (IVg) is reacted with a thionating agent to give compound (Vg), which is then reacted with a compound represented by R^zL^{2g} in the presence of a base to give compound (IIgb), which is further subjected to an oxidation reaction to give compound (IIgc). As Method Cg, compound (IIga) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIgd).

As the halogenating agent in Method Ag, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane,

chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVg) to compound (Vg) in Method Bg, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zL^{2g} in the production step from compound (Vg) to compound (IIgb) in Method Bg, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic

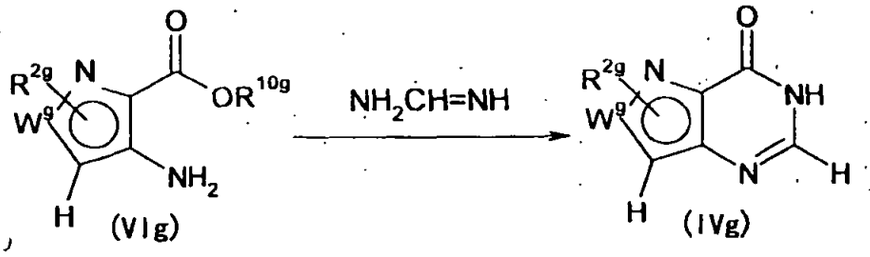
hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the oxidizing agent in the production step from compound (IIgb) to compound (IIgc) in Method Bg, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIgc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIgb), and when compound (IIgc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIgb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like

can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^2OH in the production step from compound (IIga) to compound (IIgd) in Method Cg, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

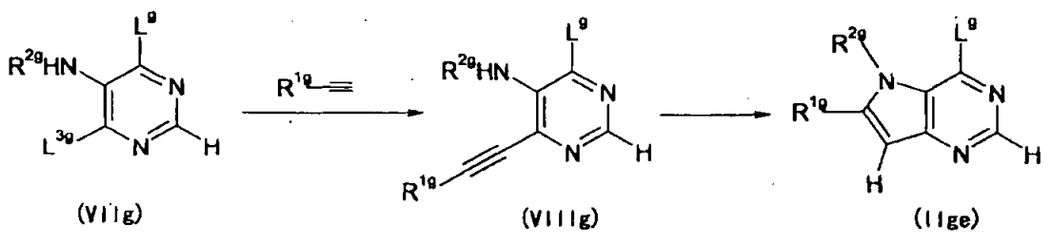
Furthermore, compound (IVg) can be produced by, for example, a method shown by the following formula:



wherein R^{10g} is a C_{1-4} alkyl group, and other symbols are as defined above.

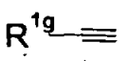
That is, compound (VIg) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVg). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

When W^9 is $C(R^{1g})$, compound (IIge) can be also produced by, for example, a method shown by the following formula:



wherein L^{3g} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIg) to compound (VIIIg) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIg) can be produced by reacting compound (VIIg) with about 1-3 equivalents of a compound represented by the formula:



in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction

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is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

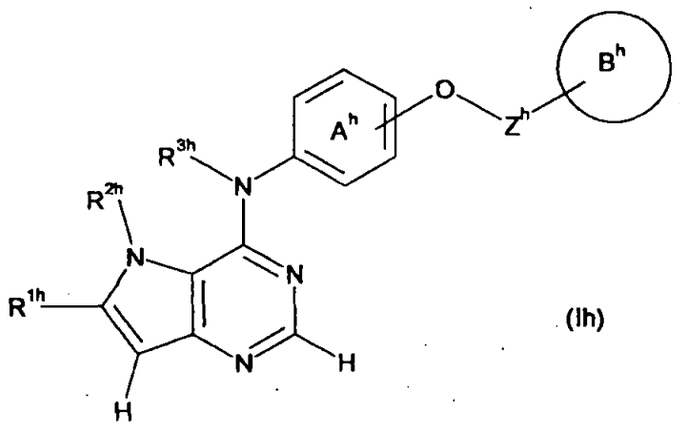
For the production step from compound (VIIIg) to compound (IIge) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IIge). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIg), a starting compound (IIg) having a different substituent can be produced by substituent conversion from, as a starting material, a

compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIg) can be also produced.

[Production method H]

Compound (Ih) of the present invention can be obtained by, for example, the method shown by the following scheme or a method analogous thereto and the like.



(Ih)

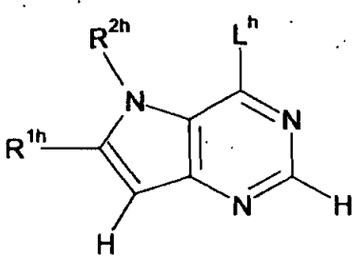
wherein each symbol is as defined above.

Each compound in the following schemes includes salts, and as such salts, for example, those similar to the salts of compound (Ih) and the like can be used.

The compound obtained in each step can be used as a reaction mixture or as a crude product in the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol of the compounds is as defined above.

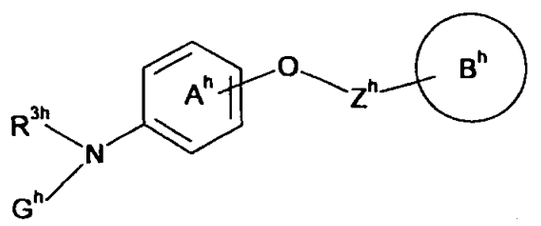
Compound (Ih) of the present invention can be produced, for example, by reacting a compound represented by the formula:



(IIh)

wherein L^h is a leaving group, and the other symbols are as defined above,

or a salt thereof and a compound represented by the formula:



(IIIh)

wherein G^h is a hydrogen atom or a metal atom, and the other symbols are as defined above,

or a salt thereof.

G^h is mainly a hydrogen atom, but it may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (IIIh) or a salt thereof is preferably used in an amount of 1-5 equivalents, preferably 1-2 equivalents, relative to compound (IIh) and the reaction is preferably carried out in a solvent. In addition, a base or an ammonium salt may be used in an amount of about 1-10 equivalents, preferably 1-2 equivalents.

In the aforementioned formula, as the leaving group for L^h, a halogen atom such as chlorine, bromine, iodine and the like, a group represented by the formula: $-S(O)_kR^z$ wherein k is an integer of 0, 1 or 2, and R^z is a lower (C_{1-4})alkyl group such as methyl, ethyl, propyl and the like, a C_{6-10} aryl group such as phenyl, tolyl and the like, or a group represented by the formula: $-OR^z$ wherein R^z is as defined above, and the like can be used.

As the solvent in the aforementioned reaction, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used.

As the base in the aforementioned reaction, an inorganic base, an organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium

hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used.

As the ammonium salt in the aforementioned reaction, pyridine hydrochloride, pyridine hydrobromide, pyridinium p-toluenesulfonate, quinoline hydrochloride, isoquinoline hydrochloride, pyrimidine hydrochloride, pyrazine hydrochloride, triazine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride, N-ethyldiisopropylamine hydrochloride and the like can be used.

The aforementioned reaction can be carried out under cooling, at room temperature or under heating (about 40-200°C, preferably about 40-160°C), and the reaction time is generally about 1-30 hr, preferably about 1-20 hr, more preferably about 1-10 hr.

A compound within the scope of the present invention can be also produced by applying means known *per se* to the obtained compound (Ih) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy group by hydrolysis of ester, conversion to carbamoyl group by amidation of carboxy group, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like

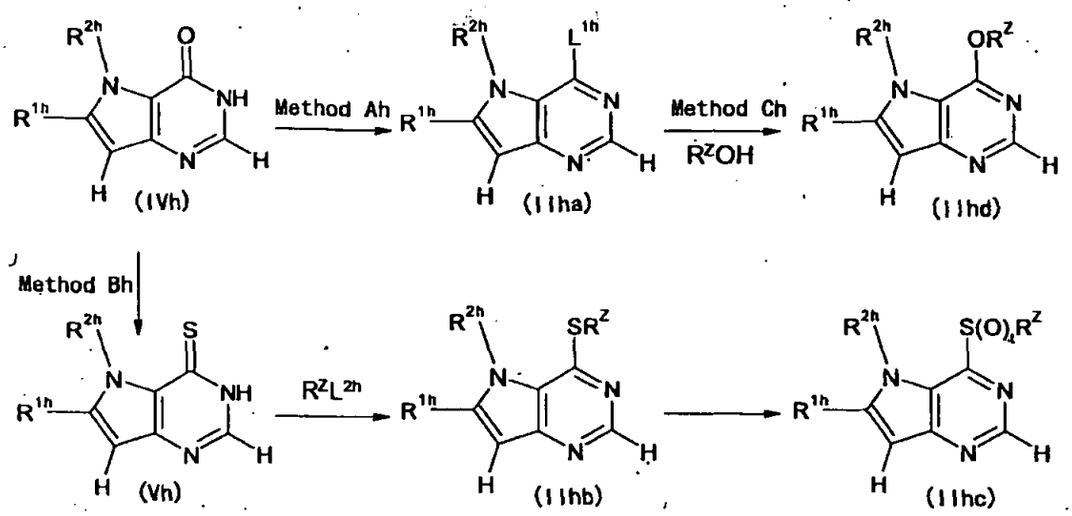
can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can be also produced.

The compound (Ih), which is a product of the reaction, may be produced as a single compound or as a mixture.

The compound (Ih) of the present invention thus obtained can be subjected to a means known *per se*, such as solvent extraction, concentration, neutralization, filtration, crystallization, recrystallization, column chromatography, high performance liquid chromatography and the like, whereby the objective compound can be isolated and purified at high purity from a reaction mixture.

As the starting compound (IIIh) of this production method, a commercially available one is used or can be produced by a means known *per se*.

The starting compound (IIh) of this production method can be produced by, for example, a method shown by the following scheme. Here, compounds (IIha), (IIhb), (IIhc) and (IIhd) are encompassed in compound (IIh).



wherein L^{1h} and L^{2h} are halogen atoms, R^z is as defined above, and t is an integer of 1 or 2.

As Method Ah, compound (IIha) can be produced by reacting compound (IVh) with a halogenating agent. As Method Bh, compound (IVh) is reacted with a thionating agent to give compound (Vh), which is then reacted with a compound represented by R^zL^{2h} in the presence of a base to give compound (IIhb), which is further subjected to an oxidation reaction to give compound (IIhc). As Method Ch, compound (IIha) is reacted with a compound represented by R^zOH in the presence of a base to give compound (IIhd).

As the halogenating agent in Method Ah, for example, about 1-100 equivalents of phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, sulfuryl chloride, phosphorus tribromide and the like can be used. In this case, the reaction may be carried out in the presence of a base such as diethylaniline, dimethylaniline, pyridine and the like. While the reaction may be carried out without solvent, as a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene,

toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetonitrile, ethyl acetate and the like may be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the thionating agent used in the production step from compound (IVh) to compound (Vh) in Method Bh, for example, about 1-5 equivalents of a Lawesson reagent, phosphorus pentasulfide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; and the like can be used. The reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As R^2L^{2h} in the production step from compound (Vh) to compound (IIhb) in Method Bh, for example, about 1-5 equivalents of methyl iodide, benzyl chloride, benzyl bromide and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol,

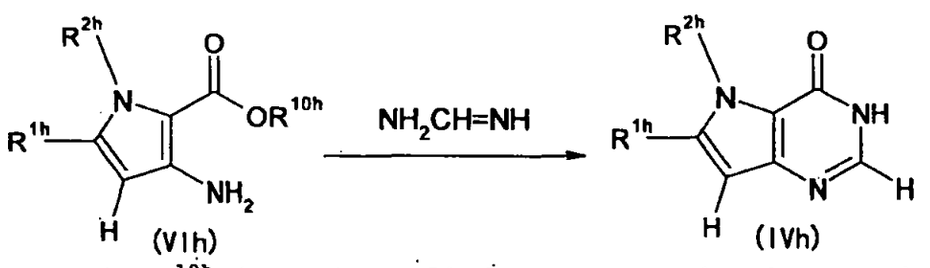
t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

As the oxidizing agent in the production step from compound (IIhb) to compound (IIhc) in Method Bh, for example, m-chloroperbenzoic acid, hydrogen peroxide, peracetic acid, t-butyl hydroperoxide, potassium peroxysulfate, potassium permanganate, sodium perborate, sodium periodate, sodium hypochlorite, halogen and the like can be used. When compound (IIhc) wherein t=1 is produced, the oxidizing agent is used in about 1-1.5 equivalents relative to compound (IIhb), and when compound (IIhc) wherein t=2 is produced, it is used in about 2-3 equivalents relative to compound (IIhb). The reaction solvent is not particularly limited as long as it does not react with the oxidizing agent and, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; carboxylic acids such as acetic acid, trifluoroacetic acid and the like; acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction

time is generally about 1-20 hr, preferably about 1-10 hr.

As R^zOH in the production step from compound (IIha) to compound (IIhd) in Method Ch, for example, about 1-10 equivalents of methanol, ethanol, phenol and the like can be used, and as the base, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, pyridine, N,N-dimethylaminopyridine, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, sodium amide, diazabicycloundecene (DBU) and the like can be used. As a reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

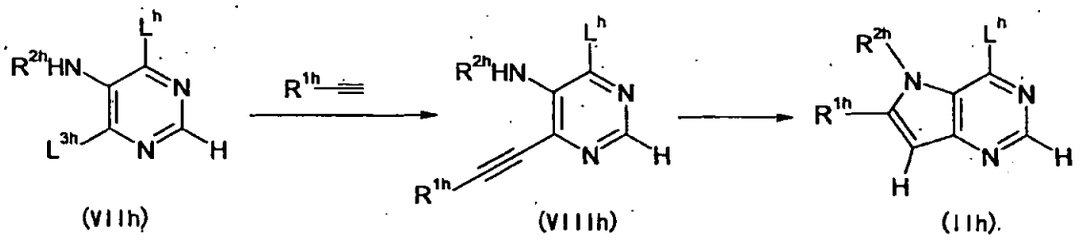
Furthermore, compound (IVh) can be produced by, for example, a method shown by the following formula:



wherein R^{10h} is a C_{1-4} alkyl group, and other symbols are as defined above.

That is, compound (VIh) is reacted with about 1-4 equivalents of formamidine or a salt thereof to give compound (IVh). As the reaction solvent, for example, alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out under cooling, at room temperature or under heating, and the reaction time is generally about 1-20 hr, preferably about 1-10 hr.

Compound (IIh) can be also produced by, for example, a method shown by the following formula:



wherein L^{3h} is a halogen atom, and other symbols are as defined above.

For the production step from compound (VIIh) to compound (VIIIh) in this method, a reaction generally known as a Sonogashira reaction or a reaction analogous thereto can be carried out, and generally, compound (VIIIh) can be produced by reacting compound (VIIh) with about 1-3 equivalents of a compound represented by the formula:

R^{1h}—≡

in the presence of a base, about 0.01-1 equivalent of a palladium catalyst and copper iodide. As the base, for example, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU), sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and the like can be used. As the palladium catalyst, for example, dichlorobis(triphenylphosphine)palladium(II), palladium on carbon, palladium(II) diacetate, bis(benzonitrile)dichloropalladium(II) and the like can be used. This reaction may be carried out in the co-presence of a tertiary phosphine compound such as triphenylphosphine, tributylphosphine and the like as a ligand. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. This reaction is carried out at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

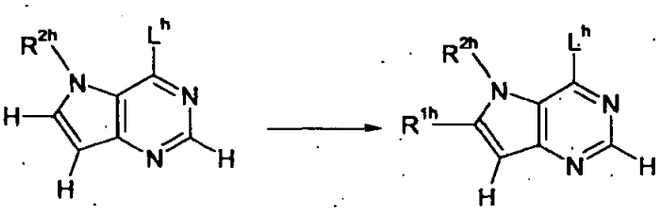
For the production step from compound (VIIIh) to compound (IIh) in this method, a cyclization reaction is generally carried out in the presence of about 1-3 equivalents of base or about 0.01-1 equivalent of copper iodide to give compound (IIh). As the base, for example, potassium t-butoxide, sodium t-butoxide, cesium t-

butoxide, sodium ethoxide, potassium hydride, sodium hydride, cesium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, N-ethyldiisopropylamine, diisopropylamine, pyridine, N,N-dimethylaminopyridine, diazabicycloundecene (DBU) and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; alcohols such as methanol, ethanol, isopropanol, t-butanol and the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; acetone, acetonitrile, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, dimethyl sulfoxide, hexamethylphosphoramide, water or a mixed solvent thereof and the like can be used. The reaction is carried out at low temperature, at room temperature or under heating, and the reaction time is generally about 1-50 hr, preferably about 1-20 hr.

Depending on the kind of the substituent of starting compound (IIh), a starting compound (IIh) having a different substituent can be produced by substituent conversion from, as a starting material, a compound produced by the above-mentioned production method. For the substituent conversion, a known general method can be used. For example, conversion to carbamoyl group by hydrolysis and amidation of ester, conversion to hydroxymethyl group by reduction of carboxy group, conversion to alcohol compound by reduction or alkylation of carbonyl group, reductive amination of carbonyl group, oximation of carbonyl group, acylation of amino group, alkylation of amino group, substitution

and amination of active halogen by amine, alkylation of hydroxy group, substitution and amination of hydroxy group and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the starting compound (IIh) can be also produced.

The starting compound (IIh) of this production method can also be produced, for example, by a method using compound (IIh'), as shown by the following scheme:



wherein each symbol is as defined above.

In this method, generally, compound (IIh') is converted to the anion by withdrawing a proton from compound (IIh') using a base, which is then reacted with a cation having R^{1h} to give compound (IIh). As the base, for example, n-butyllithium, s-butyllithium, t-butyllithium, lithium t-butoxide, lithium diisopropylamide and the like can be used. As a reagent for generating the cation, for example, p-toluenesulfonyl chloride, benzenesulfonyl bromide, p-toluenesulfonyl cyanide, S-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate, N,N-dimethylformamide and the like can be used. As the reaction solvent, for example, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and

the like; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like, a mixed solvent thereof and the like can be used. The aforementioned reaction can be carried out under cooling, preferably about not more than -20°C, and the reaction time is generally about 15 min-50 hr, preferably about 30 min-4 hr.

Thus-obtained compounds (Ia)-(Ih) can be isolated and purified by a separation means known *per se*, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

If compounds (Ia)-(Ih) are obtained as a free form, it can be converted into a desired salt by a method known *per se* or a modification thereof; conversely, if compounds (Ia)-(Ih) are obtained as a salt, it can be converted into a free form or another desired salt by a method known *per se* or a modification thereof.

When compounds (Ia)-(Ih) have isomers such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, and any isomers and mixtures are encompassed in the compound (Ia)-(Ih). For example, when compounds (Ia)-(Ih) have an optical isomer, an optical isomer separated from a racemate is also encompassed in the compound (Ia)-(Ih). These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

The compounds (Ia)-(Ih) may be a crystal, and both a single crystal and crystal mixtures are encompassed in the compound (Ia)-(Ih). Crystals can be produced by crystallization according to crystallization methods known *per se*.

The compounds (Ia)-(Ih) may be a solvate (e.g., hydrate etc.) or a non-solvate, both of which are encompassed in the compound (Ia)-(Ih).

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I and the like) is also encompassed in the compound (Ia)-(Ih).

A prodrug of the compounds (Ia)-(Ih) or salts thereof (hereinafter referred to as compound (Ia)-(Ih)) means a compound which is converted to the compounds (Ia)-(Ih) with a reaction due to an enzyme, an gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compounds (Ia)-(Ih) with oxidation, reduction, hydrolysis, etc. due to an enzyme; a compound which is converted to the compounds (Ia)-(Ih) by hydrolysis etc. due to gastric acid, etc. A prodrug for compounds (Ia)-(Ih) may be a compound obtained by subjecting an amino group in compounds (Ia)-(Ih) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino group in compounds (Ia)-(Ih) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy group in compounds (Ia)-(Ih) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in compounds (Ia)-(Ih) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting a carboxyl group in compounds (Ia)-(Ih) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in compounds (Ia)-(Ih) to an ethyl esterification, phenyl

esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Any one of these compounds can be produced from compounds (Ia)-(Ih) by a method known *per se*.

A prodrug for compounds (Ia)-(Ih) may also be one which is converted into compounds (Ia)-(Ih) under a physiological condition, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

The compounds (Ia)-(Ih) of the present invention, or a salt thereof or a prodrug thereof (hereinafter referred to as the compound of the present invention) possess tyrosine kinase-inhibiting activity and can be used for the prophylaxis or treatment of tyrosine kinase-dependent diseases in mammals. Tyrosine kinase-dependent diseases include diseases characterized by increased cell proliferation due to abnormal tyrosine kinase enzyme activity.

Particularly, the compound of the present invention specifically inhibits HER2 kinase and/or EGFR kinase and is therefore also useful as a therapeutic agent for suppressing the growth of HER2 and/or EGFR kinase-expressing cancer. Also, the compound of the present invention is useful as a preventive agent for preventing hormone-dependent cancer and the transition of hormone-dependent cancer to hormone-independent cancer.

In addition, the compound of the present invention is useful as a pharmaceutical agent because it shows low toxicity (e.g., acute toxicity, chronic toxicity,

genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity and the like), high water solubility, and is superior in stability, pharmacokinetics (absorption, distribution, metabolism, excretion and the like) and efficacy expression.

Accordingly, the compound of the present invention can be used as a safe agent for the prophylaxis or treatment of diseases due to abnormal cell proliferation such as various cancers (particularly, breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer etc.), pancreatic cancer (e.g., pencreatic duct cancer etc.), gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma etc.), colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor etc.), colon cancer (e.g., gastrointestinal stromal tumor etc.), rectal cancer (e.g., gastrointestinal stromal tumor etc.), esophagus cancer, duodenal cancer, cancer of the tongue, cancer of pharynx (e.g., nasopharyngeal carcinoma, oropharyngeal cancer, hypopharyngeal cancer etc.), salivary gland cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma etc.), neurinoma, non-small cell lung cancer, small cell lung cancer, liver cancer (e.g., primary liver cancer, Extrahepatic Bile Duct Cancer etc.), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter, transitional cell cancer etc.), cancer of the bile duct, cancer of the uterine body, endometrial carcinoma, cancer of the uterine cervix, ovarian cancer (e.g., ovarian epithelial, extragonadal

germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor etc.), urinary bladder cancer, urethral cancer, skin cancer (e.g., ocular melanoma, Merkel cell carcinoma etc.), hemangioma, malignant lymphoma, malignant melanoma, thyroid cancer (e.g., medullary thyroid carcinoma etc.), parathyroid cancer, nasal cavity cancer, paranasal sinus cancer, bone tumors (e.g., osteosarcoma, Ewing's tumor, uterus sarcoma, soft tissue sarcoma etc.), vascular fibroma, retinoblastoma, penile cancer, solid cancer in childhood, Kaposi's sarcoma, Kaposi's sarcoma derived from AIDS, maxillary tumor, fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, leukemia (e.g., acute myeloid leukemia, acute lymphoblastic leukemia etc.) etc.), atherosclerosis, angiogenesis (e.g., angiogenesis associated with growth of solid cancer and sarcoma, angiogenesis associated with tumor metastasis, angiogenesis associated with diabetic retinopathy, etc.), and viral diseases (HIV infection etc.).

Tyrosine kinase-dependent diseases further include cardiovascular diseases associated with abnormal tyrosine kinase enzyme activity. The compound of the present invention can therefore be used as an agent for prophylaxis or treatment of cardiovascular diseases such as restenosis.

The compound of the present invention is useful as an anticancer agent for the prophylaxis or treatment of cancer, especially breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer, kidney cancer and the like.

The compound of the present invention shows low toxicity and can be used as a pharmaceutical agent as it is, or as a pharmaceutical composition in admixture with a commonly known pharmaceutically acceptable carrier

etc. in mammals (e.g., humans, horses, bovines, dogs, cats, rats, mice, rabbits, pigs, monkeys and the like).

In addition to the compound of the present invention, said pharmaceutical composition may contain other active ingredients, e.g., the following hormonal therapeutic agents, anticancer agent (e.g., chemotherapeutic agents, immunotherapeutic agents, or pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors), and the like.

As a pharmaceutical agent for mammals such as humans, the compound of the present invention can be administered orally in the form of, for example, tablets, capsules (including soft capsules and microcapsules), powders, granules and the like, or parenterally in the form of injections, suppositories, pellets and the like. Examples of the "parenteral administration route" include intravenous, intramuscular, subcutaneous, intra-tissue, intranasal, intradermal, instillation, intracerebral, intrarectal, intravaginal, intraperitoneal, intratumoral, juxtaposition of tumor and administration directly to the lesion.

The dose of the compound of the present invention varies depending on the route of administration, symptoms, etc. For example, when it is administered orally as an anticancer agent to a patient (body weight 40 to 80 kg) with breast cancer or prostate cancer, its dose is, for example, 0.5 to 100 mg/kg body weight per day, preferably 1 to 50 mg/kg body weight per day, and more preferably 1 or 25 mg/kg body weight per day. This amount may be administered once or in 2 to 3 divided portions daily.

The compound of the present invention can be safely administered orally or parenterally (e.g., topical,

rectal, intravenous administrations etc.) as a single agent, or a pharmaceutical composition containing a pharmacologically acceptable carrier according to a conventional method (e.g., a method described in the Japanese Pharmacopoeia etc.), such as tablet (including sugar-coated tablet, film-coated tablet), powder, granule, capsule, liquid, emulsion, suspension, injection, suppository, sustained release preparation, plaster and the like.

And (1) administering an effective amount of a compound of the present invention and (2) a combination of 1 to 3 selected from the group consisting of (i) administering an effective amount of other anticancer agents, (ii) administering an effective amount of hormonal therapeutic agents and (iii) non-drug therapy can prevent and/or treat cancer more effectively. As the non-drug therapy, for example, surgery, radiotherapy, gene therapy, thermotherapy, cryotherapy, laser cauterization and the like are exemplified and two or more of these may be combined.

For example, the compound of the present invention can be administered to the same subject simultaneously with hormonal therapeutic agents, anticancer agents (e.g., chemotherapeutic agents, immunotherapeutic agents, or pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors) (hereafter, these are referred to as a concomitant drug).

Although the compound of the present invention exhibits excellent anticancer action even when used as a simple agent, its effect can be enhanced by using it in combination with one or more of the concomitant drug(s) mentioned above (multi-agent co-administration).

As examples of said "hormonal therapeutic agents", there may be mentioned fosfestrol, diethylstylbestrol,

chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, dienogest, asoprisnil, allylestrenol, gestrinone, nomegestrol, Tadenan, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), ER down regulator (e.g., fulvestrant, and the like), human menopausal gonadotrophin, follicle stimulating hormone, pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5α-reductase inhibitors (e.g., finasteride, dutasteride, epristeride, and the like), adrenocorticohormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), etc. and LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin) are preferable.

As examples of said "chemotherapeutic agents", there may be mentioned alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

As examples of "alkylating agents", there may be mentioned nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine

phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, and the like.

As examples of "antimetabolites", there may be mentioned mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, and the like), aminopterine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, and the like.

As examples of "anticancer antibiotics", there may be mentioned actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate, daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, and the like.

As examples of "plant-derived anticancer agents", there may be mentioned etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel (Taxol (trade mark)), docetaxel, vinorelbine, and the like.

As examples of said "immunotherapeutic agents

(BRM)", there may be mentioned picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, and the like.

The "growth factor" in said "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", there may be mentioned any substances that promote cell proliferation, which are normally peptides having a molecular weight of not more than 20,000 that are capable of exhibiting their activity at low concentrations by binding to a receptor, including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as it [e.g., EGF, heregulin, and the like], (2) insulin or substances possessing substantially the same activity as it [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as it [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGFβ (transforming growth factor β), HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), and the like], and the like.

As examples of said "growth factor receptors", there may be mentioned any receptors capable of binding to the aforementioned growth factors, including EGF receptor, heregulin receptor (HER2), insulin receptor, IGF receptor, FGF receptor-1 or FGF receptor-2, and the like.

As examples of said "pharmaceutical agents

inhibiting the action of cell growth factor", there may be mentioned HER2 antibody (trastuzumab (Herceptin (trade mark))), imatinib mesilate, ZD1839 or EGFR antibody (cetuximab (Erbitux (trade mark)) etc.), antibody against VEGF (e.g., bevacizumab (Avastin (trade mark))), VEGFR antibody, VEGFR inhibitor, EGFR inhibitor (gefitinib (Iressa (trade mark)), erlotinib (Tarceva (trade mark)) etc.) and the like.

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), angiogenesis inhibitors (e.g., thalidomide, SU11248, and the like), α-blockers (e.g., tamsulosin hydrochloride, naftopidil, urapidil, alfuzosin, terazosin, prazosin, silodosin, and the like), serine/threonine kinase inhibitor, endothelin receptor antagonist (e.g., atrasentan, and the like), proteasome inhibitor (e.g., bortezomib, and the like), Hsp 90 inhibitor (e.g., 17-AAG, and the like), spironolactone, minoxidil, 11α-hydroxyprogesterone, bone resorption inhibiting/metastasis suppressing agent (e.g., zoledronic acid, alendronic acid, pamidronic acid, etidronic acid, ibandronic acid, clodronic acid) and the like can be used.

Of those mentioned above, as the concomitant drug, LH-RH agonist (e.g., goserelin acetate, buserelin, leuprorelin, and the like), HER2 antibody (trastuzumab (Herceptin (trade mark))), EGFR antibody (cetuximab (Erbitux) (trade mark) etc.), EGFR inhibitor (erlotinib (Tarceva) (trade mark), gefitinib (Iressa (trade mark)) etc.), VEGFR inhibitor or chemotherapeutic agent

(paclitaxel(Taxol (trade mark) etc.) are preferable.

Particularly, trastuzumab (Herceptin (trade mark)), cetuximab (Erbitux (trade mark)), erlotinib (Tarceva) (trade mark)), gefitinib (Iressa (trade mark)), paclitaxel (Taxol(trade mark)) and the like preferable.

In combination of the compound of the present invention and the concomitant drug, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to the administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the administration amount clinically used, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

The administration mode of the compound of the present invention and the concomitant drug is not particularly restricted, and it is sufficient that the compound of the present invention and the concomitant drug are combined in administration. Examples of such administration mode include the following methods:

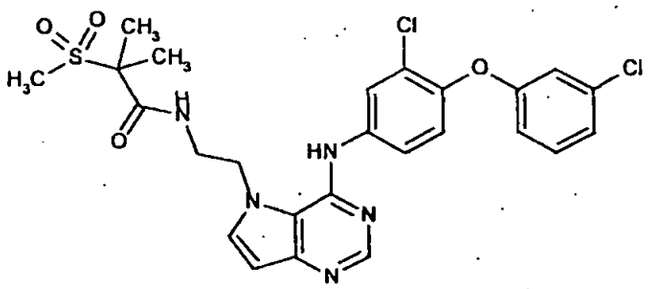
(1) The compound of the present invention and the concomitant drug are simultaneously produced to give a single preparation which is administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by the same administration route only at the different times. (4) The compound of the

present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (for example, the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order).

Examples

The present invention is explained in detail in the following by referring to Examples, Formulation Examples and Experimental Examples, which are not to be construed as limitative.

Example A-1



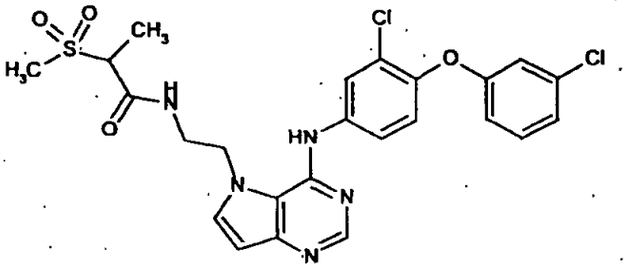
Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

To a solution of 5-(2-aminoethyl)-N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (487 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (249 mg) and 1-hydroxybenzotriazole (225 mg) in N,N-dimethylformamide (5.0 mL) were added triethylamine (0.69 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (316 mg) under ice-cooling, and the mixture was stirred at

room temperature for 15 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→90:10) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (419 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.60-3.80 (2H, m), 4.40-4.60 (2H, m), 6.46 (1H, d, J = 2.8 Hz), 6.85-7.00 (2H, m), 7.00-7.15 (2H, m), 7.15-7.30 (2H, m), 7.30-7.40 (1H, m), 7.85-7.95 (1H, m), 8.00-8.05 (1H, m), 8.36 (1H, br s), 8.54 (1H, s).

Example A-2



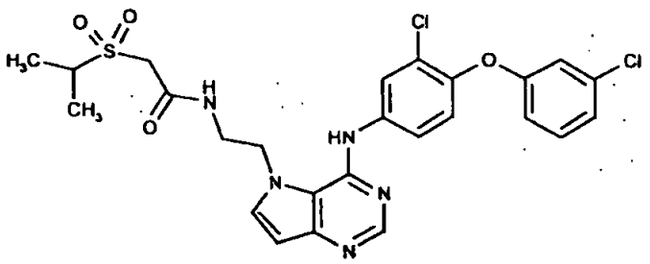
Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)propanamide

To a solution of 5-(2-aminoethyl)-N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 2-chloropropanoic acid (67 mg) and 1-hydroxybenzotriazole (90 mg) in N,N-dimethylformamide (4.0 mL) were added triethylamine (0.29 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg) under ice-cooling, and the mixture was stirred at room temperature for 17 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl

acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in N,N-dimethylformamide (2 mL), sodium methanesulfinic acid (420 mg) and pyridine (0.40 mL) were added, and the mixture was stirred at 70°C for 2 days. After cooling to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (97 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.71 (3H, d, J = 7.2 Hz), 2.98 (3H, s), 3.65-3.75 (2H, m), 3.81 (1H, q, J = 7.2 Hz), 4.45-4.55 (2H, m), 6.61 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.90-6.95 (1H, m), 7.00-7.10 (2H, m), 7.20-7.30 (1H, m), 7.30-7.40 (1H, m), 7.75-7.85 (1H, m), 7.97 (1H, d, J = 2.4 Hz), 8.28 (1H, s), 8.51 (1H, s).

Example A-3



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(isopropylsulfonyl)acetamide

(i) Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(isopropylthio)acetamide

To a solution of 5-(2-aminoethyl)-N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (300 mg), chloroacetic acid (87 mg) and 1-hydroxybenzotriazole (135 mg) in N,N-dimethylformamide (5.0 mL) were added triethylamine (0.43 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (189 mg) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in N,N-dimethylformamide (2 mL)/tetrahydrofuran (4 mL), sodium propane-2-thiolate (605 mg) was added, and the mixture was stirred at room temperature for 6 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (201 mg) as a white powder.

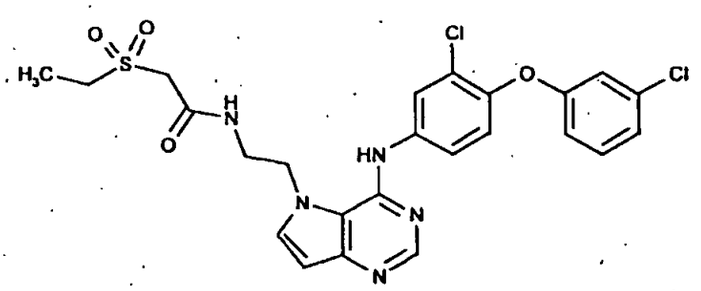
^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, d, J = 6.9 Hz), 2.80-2.90 (1H, m), 3.33 (2H, s), 3.60-3.70 (2H, m), 4.45-4.55 (2H, m), 6.62 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 8.7 Hz), 7.20-7.30 (2H, m), 7.40-7.50 (1H, m), 7.73 (1H, dd, J = 2.4, 8.7 Hz), 8.05 (1H, d, J = 2.4 Hz), 8.51 (1H, s).

(ii) Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(isopropylsulfonyl)acetamide

To a solution of N-[2-(4-{[3-chloro-4-(3-

chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(isopropylthio)acetamide in methanol (6 mL)/water (1.5 mL) was added OXONE® monopersulfate compound (339 mg), and the mixture was stirred at room temperature for 21 hr. Water was added to the reaction mixture and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from dichloromethane/methanol/diisopropyl ether to give the title compound (173 mg) as pale-yellow crystals.
^{1}H-NMR (DMSO-d_6) δ: 1.23 (6H, d, J = 6.9 Hz), 3.40-3.65 (3H, m), 4.03 (2H, s), 4.50-4.70 (2H, m), 6.58 (1H, s), 6.90-6.95 (1H, m), 6.99 (1H, s), 7.15-7.25 (1H, m), 7.30 (1H, d, J = 8.7 Hz), 7.40-7.50 (1H, m), 7.65-7.75 (1H, m), 7.79 (1H, s), 7.92 (1H, s), 8.53 (1H, s), 8.70-8.80 (1H, m), 9.28 (1H, br s).

Example A-4



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylsulfonyl)acetamide

(i) Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylthio)acetamide

Using 5-(2-aminoethyl)-N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), ethylthioacetic acid (99 mg), 1-hydroxybenzotriazole (123 mg), triethylamine (0.57

mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (173 mg) and N,N-dimethylformamide (4.0 mL) and in the same manner as in Example A-1, the title compound (186 mg) was obtained as a white powder.

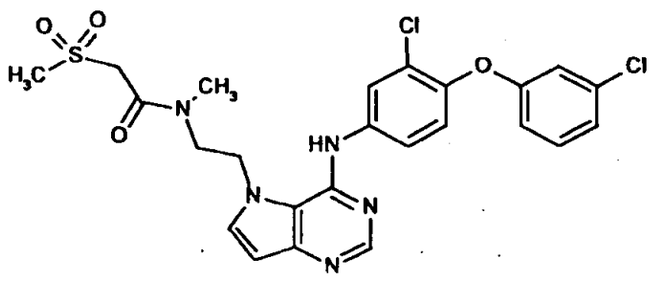
^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.5 Hz), 2.52 (2H, q, J = 7.5 Hz), 3.32 (2H, s), 3.60-3.70 (2H, m), 4.45-4.55 (2H, m), 6.62 (1H, d, J = 3.0 Hz), 6.88 (1H, d, J = 8.1 Hz), 6.95-7.00 (1H, m), 7.00-7.10 (2H, m), 7.15-7.25 (1H, m), 7.40-7.50 (1H, m), 7.70-7.80 (1H, m), 8.05-8.10 (1H, m), 8.50 (1H, s), 8.51 (1H, s).

(ii) Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylsulfonyl)acetamide

Using N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylthio)acetamide (180 mg), OXONE® monopersulfate compound (322 mg) and methanol (6 mL)/water (1.2 mL) and in the same manner as in Example A-3(ii), the title compound (149 mg) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.21 (3H, t, J = 7.2 Hz), 3.22 (2H, q, J = 7.2 Hz), 3.45-3.55 (2H, m), 4.03 (2H, s), 4.55-4.65 (2H, m), 6.55-6.60 (1H, m), 6.90-6.95 (1H, m), 6.99 (1H, s), 7.15-7.20 (1H, m), 7.29 (1H, d, J = 8.7 Hz), 7.41 (1H, t, J = 8.2 Hz), 7.65-7.75 (1H, m), 7.75-7.80 (1H, m), 7.93 (1H, s), 8.52 (1H, s), 8.72 (1H, br s), 9.22 (1H, br s).

Example A-5



Production of N-[2-(4-{[3-chloro-4-(3-

chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N-methyl-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl [2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]methylcarbamate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]methylcarbamate (2.56 g), 3-chloro-4-(3-chlorophenoxy)aniline (2.51 g) and isopropyl alcohol (25 mL) was stirred at 80°C for 18 hr. After cooling to room temperature, the mixture was stirred for 5 hr. The precipitate was collected by filtration, and washed with diisopropyl ether to give the title compound (3.72 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s), 3.01 (3H, s), 3.50-3.60 (2H, m), 4.40-4.50 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 9.0 Hz), 7.15-7.25 (2H, m), 7.90 (1H, d, J = 9.0 Hz), 8.01 (1H, br s), 8.52 (1H, s), 8.83 (1H, s).

(ii) Production of N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5-[2-(methylamino)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]methylcarbamate (3.72 g) and 10% (W/W) hydrochloric acid/methanol (30 mL) was stirred at 65°C for 24 hr. The reaction mixture was concentrated under reduced pressure, and the precipitate was collected by filtration, and washed with diethyl ether to give the title compound (2.70 g) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.50-2.60 (3H, m), 3.30-3.50 (2H, m), 5.00-5.20 (2H, m), 6.75 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.02 (1H, s), 7.21 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 8.7 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.93 (1H, s), 8.07 (1H, d, J = 3.0 Hz),

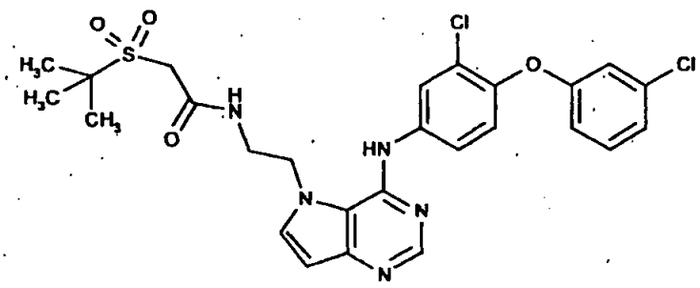
8.73 (1H, s), 9.10-9.30 (2H, m), 10.17 (1H, br s).

(iii) Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N-methyl-2-(methylsulfonyl)acetamide

Using N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5-[2-(methylamino)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), methylsulfonylacetic acid (83 mg), 1-hydroxybenzotriazole (87 mg), triethylamine (0.28 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (123 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example A-1, the title compound (164 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.17 (3H, s), 3.33 (3H, s), 3.70-3.85 (2H, m), 4.17 (2H, s), 4.45-4.55 (2H, m), 6.63 (1H, d, J = 3.0 Hz), 6.85-6.95 (2H, m), 7.00-7.10 (2H, m), 7.20-7.30 (2H, m), 7.82 (1H, dd, J = 2.7 Hz, 9.0 Hz), 7.92 (1H, d, J = 2.7 Hz), 8.44 (1H, s), 8.52 (1H, s).

Example A-6



Production of 2-(tert-butylsulfonyl)-N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]acetamide

(i) Production of 2-(tert-butylthio)-N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]acetamide

To a solution of 5-(2-aminoethyl)-N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), chloroacetic acid (58 mg) and 1-hydroxybenzotriazole (90 mg) in N,N-dimethylformamide

(4.0 mL) were added triethylamine (0.29 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in N,N-dimethylformamide (2 mL)/tetrahydrofuran (4 mL), sodium 2-methylpropane-2-thiolate (511 mg) was added, and the mixture was stirred at room temperature for 2 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (159 mg) as a white powder.

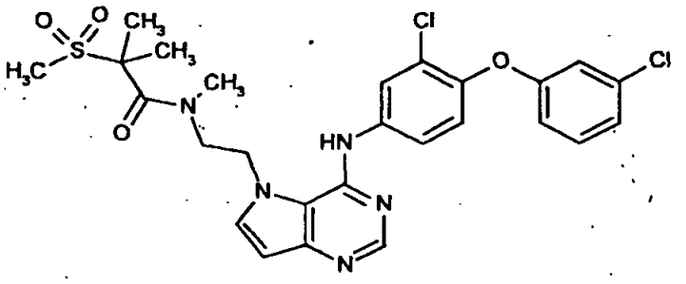
^{1}H-NMR ($CDCl_3$) δ: 1.30 (9H, s), 3.33 (2H, s), 3.60-3.70 (2H, m), 4.40-4.50 (2H, m), 6.61 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 9.0 Hz), 7.15-7.25 (2H, m), 7.45-7.55 (1H, m), 7.73 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.06 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.56 (1H, s).

(ii) Production of 2-(tert-butylsulfonyl)-N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]acetamide

Using 2-(tert-butylthio)-N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]acetamide (159 mg), OXONE® monopersulfate compound (269 mg) and methanol (5 mL)/water (1.5 mL) and in the same manner as in Example A-3(ii), the title compound (99 mg) was obtained as pale-yellow crystals.

^{1}H-NMR (95%$CDCl_3$+5%DMSO-d_6) δ: 1.43 (9H, s), 3.50-3.70 (2H, m), 4.00 (2H, s), 4.60-4.70 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (2H, m), 7.05-7.15 (2H, m), 7.31 (1H, t, J = 8.1 Hz), 7.60-7.70 (2H, m), 7.92 (1H, s), 8.49 (1H, s), 8.80-8.90 (1H, m), 9.30-9.50 (1H, m).

Example A-7



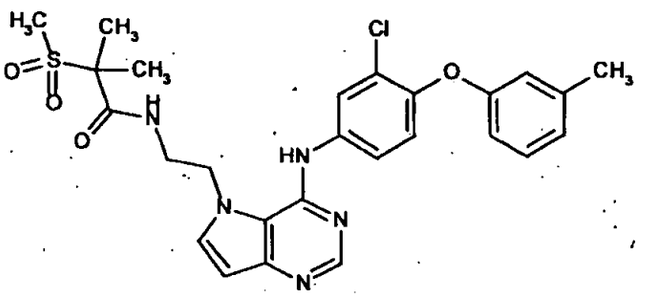
Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N,2-dimethyl-2-(methylsulfonyl)propanamide

To a solution of N-[3-chloro-4-(3-chlorophenoxy)phenyl]-5-[2-(methylamino)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg) and 2-methyl-2-(methylsulfonyl)propanoic acid (100 mg) in N,N-dimethylformamide (5.0 mL) were added triethylamine (0.28 mL) and diethyl cyanophosphonate (0.097 mL) under ice-cooling, and the mixture was stirred at room temperature for 25 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→90:10) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (94 mg) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.85 (6H, s), 2.97 (3H, s), 3.47 (3H, s), 3.70-3.80 (2H, m), 4.40-4.50 (2H, m), 6.63 (1H, d, J

= 3.6 Hz), 6.85-6.95 (2H, m), 7.00-7.05 (1H, m), 7.06 (1H, d, J = 8.7 Hz), 7.20-7.30 (2H, m), 7.90-8.00 (1H, m), 8.01 (1H, d, J = 2.4 Hz), 8.52 (1H, s), 8.69 (1H, br s).

Example A-8



Production of N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

(i) Production of 5-(2-aminoethyl)-N-[3-chloro-4-(3-methylphenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (594 mg), 3-chloro-4-(3-methylphenoxy)aniline (467 mg) and isopropyl alcohol (10 mL) was stirred at 80°C for 6 hr. To the reaction mixture was added aqueous sodium hydrogencarbonate solution, 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 (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To a solution of the residue in methanol (10 mL) was added concentrated hydrochloric acid (3 mL), and the mixture was stirred at room temperature overnight and further at 60°C for 3 hr. The reaction mixture was concentrated

under reduced pressure. Isopropyl alcohol and toluene were added to the residue, and the mixture was concentrated under reduced pressure. Methanol was added to the residue, and the mixture was concentrated under reduced pressure. Isopropyl alcohol and diisopropyl ether were added to the residue, and the precipitated solid was collected by filtration to give the title compound (805 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.31(3H, s), 3.23-3.37 (2H, m), 5.04 (2H, t, J= 6.2 Hz), 6.72-6.80 (2H, m), 6.83 (1H, m), 6.98 (1H, d, J= 7.5 Hz), 7.18 (1H, d, J= 8.9 Hz), 7.29 (1H, t, J= 7.8 Hz), 7.59 (1H, dd, J= 8.8, 2.5 Hz), 7.87 (1H, d, J= 2.5 Hz), 8.07 (1H, d, J= 3.2 Hz), 8.35 (3H, br s), 8.73 (1H, s), 10.15 (1H, br s).

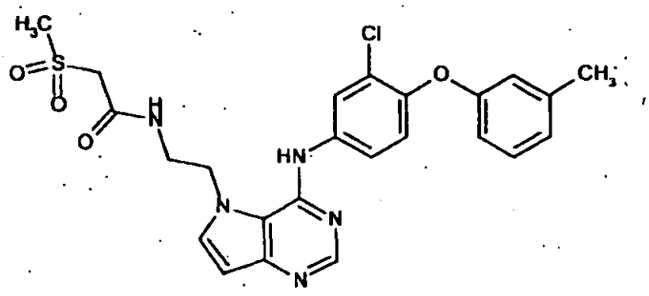
(ii) Production of N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

A mixture of 5-(2-aminoethyl)-N-[3-chloro-4-(3-methylphenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (140 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (75 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (155 mg) as a white

powder.

^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, s), 2.33 (3H, s), 2.93 (3H, s), 3.61-3.74 (2H, m), 4.41-4.51 (2H, m), 6.61 (1H, d, J= 3.3 Hz), 6.75-6.84 (2H, m), 6.89 (1H, d, J= 7.7 Hz), 7.02 (1H, d, J= 8.8 Hz), 7.16-7.24 (2H, m), 7.34 (1H, t, J= 5.8 Hz), 7.80 (1H, dd, J= 8.8 Hz, 2.5 Hz), 7.97 (1H, d, J= 2.5 Hz), 8.31 (1H, br s), 8.51 (1H, s).

Example A-9

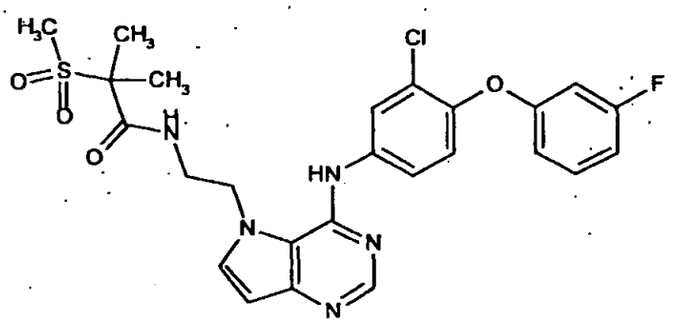


Production of N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-[3-chloro-4-(3-methylphenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (140 mg), methylsulfonylacetic acid (62 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to

give the title compound (147 mg) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.13 (3H, s), 3.63-3.76 (2H, m), 3.70 (2H, s), 4.41-4.53 (2H, m), 6.58 (1H, d, J= 3.3 Hz), 6.75-6.84 (2H, m), 6.90 (1H, d, J= 7.4 Hz), 7.01 (1H, d, J= 8.7 Hz), 7.16-7.24 (2H, m), 7.55-7.64 (1H, m), 7.69 (1H, dd, J= 8.7, 2.7 Hz), 7.89 (1H, d, J= 2.7 Hz), 8.14 (1H, br s), 8.48 (1H, s).

Example A-10



Production of N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

(i) Production of 5-(2-aminoethyl)-N-[3-chloro-4-(3-fluorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (594 mg), 3-chloro-4-(3-fluorophenoxy)aniline (475 mg) and isopropyl alcohol (10 mL) was stirred at 80°C for 6 hr. An aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. Methanol (10 mL), tetrahydrofuran (1 mL) and concentrated

hydrochloric acid (3 mL) were added to the residue, and the mixture was stirred at room temperature overnight and further stirred at 60°C for 3 hr. The reaction mixture was concentrated under reduced pressure. Isopropyl alcohol and toluene were added to the residue, and the mixture was concentrated under reduced pressure. Methanol was added to the residue, and the mixture was concentrated under reduced pressure. Isopropyl alcohol and diisopropyl ether were added to the residue and the precipitated solid was collected by filtration to give the title compound (809 mg) as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6) δ: 3.22-3.39 (2H, m), 5.09 (2H, t, J= 6.3 Hz), 6.73-6.82 (2H, m), 6.83-6.92 (1H, m), 6.96-7.05 (1H, m), 7.31 (1H, d, J= 8.9 Hz), 7.39-7.51 (1H, m), 7.66 (1H, dd, J= 2.4 Hz, 8.9 Hz), 7.93 (1H, d, J =2.4 Hz), 8.10 (1H, d, J= 3.2 Hz), 8.42 (3H, br s), 8.74 (1H, s), 10.30 (1H, br s).

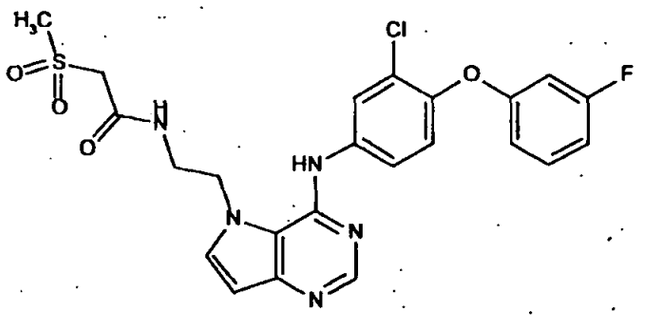
(ii) Production of N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

A mixture of 5-(2-aminoethyl)-N-[3-chloro-4-(3-fluorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (141 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (75 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective

fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (161 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.63-3.74 (2H, m), 4.42-4.53 (2H, m), 6.63 (1H, d, J= 3.3 Hz), 6.64-6.71 (1H, m), 6.74-6.82 (2H, m), 7.09 (1H, d, J= 8.9 Hz), 7.19-7.32 (2H, m), 7.37 (1H, t, J= 5.8 Hz), 7.88 (1H, dd, J= 2.7 Hz, 8.9 Hz), 8.02 (1H, d, J= 2.7 Hz), 8.36 (1H, br s), 8.53 (1H, s).

Example A-11



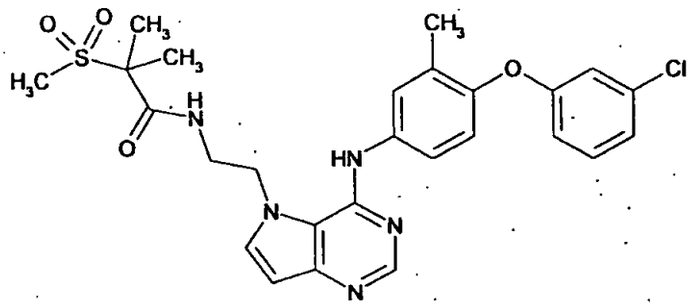
Production of N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-[3-chloro-4-(3-fluorophenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (141 mg), methylsulfonylacetic acid (62 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl

acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (146 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 3.14 (3H, s), 3.64-3.76 (2H, m), 3.98 (2H, s), 4.43-4.54 (2H, m), 6.59 (1H, d, J= 3.3 Hz), 6.63-6.70 (1H, m), 6.73-6.82 (2H, m), 7.08 (1H, d, J= 8.9 Hz), 7.18-7.31 (2H, m), 7.57-7.65 (1H, m), 7.75 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.93 (1H, d, J= 2.5 Hz), 8.19 (1H, br s), 8.49 (1H, s).

Example A-12



Production of N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

(i) Production of tert-butyl [2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.0 g) and 3-methyl-4-[3-chlorophenoxy]aniline (1.18 g) in isopropyl alcohol (10 mL) was stirred at 80°C for 12 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=8:2→ethyl

acetate) to give the title compound (1.7 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.20 (3H, s), 3.48 (2H, m), 4.45 (2H,m), 5.16 (1H, m), 6.57 (1H, d, J= 3 Hz), 6.80-7.00 (4H, m), 7.10-7.30 (2H, m), 7.68 (2H, m), 8.40 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-[4-(3-chlorophenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.6 g), 2N hydrochloric acid (23 mL) and tetrahydrofuran (46 mL) was stirred at 60°C for 20 hr. The solvent was evaporated under reduced pressure, ethanol was added, and the mixture was further concentrated. The resulting crystals were collected by filtration. The crystals were washed with isopropyl ether to give the title compound (1.35 g) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.30 (2H, m), 5.04 (2H, m), 6.72 (1H, d, J= 3 Hz), 6.80-7.00 (2H, m), 7.08 (1H, d, J= 9 Hz), 7.16 (1H, dd, J= 2 Hz, 8 Hz), 7.30-7.50 (2H, m), 7.54 (1H, m), 8.06 (1H, m), 8.40 (3H, br s), 8.68 (1H, s), 10.00 (1H, br s).

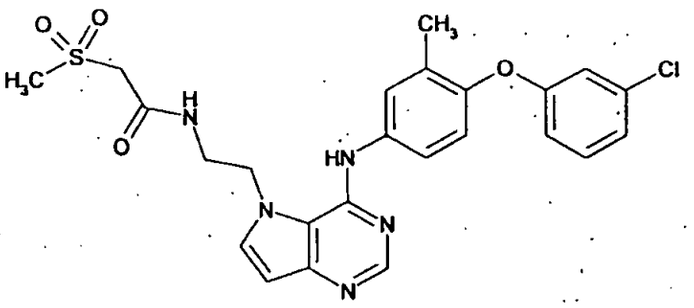
(iii) Production of N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

A mixture of 5-(2-aminoethyl)-N-[4-(3-chlorophenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (167 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (89 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 16 hr. Water was added to the

reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give the title compound (179 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.42 (6H, s), 2.14 (3H, s), 2.96 (3H, s), 3.47 (2H, q, J= 6 Hz), 4.56 (2H, t, J= 6 Hz), 6.45 (1H, d, J= 3 Hz), 6.80-6.90 (2H, m), 7.02 (1H, d, J= 9 Hz), 7.11 (1H, dd, J= 1 Hz, 8 Hz), 7.37 (1H, t, J= 8 Hz), 7.52 (1H, d, J= 3 Hz), 7.58 (2H, m), 8.20 (1H, t, J= 6 Hz), 8.28 (1H, s), 8.49 (1H, br s).

Example A-13



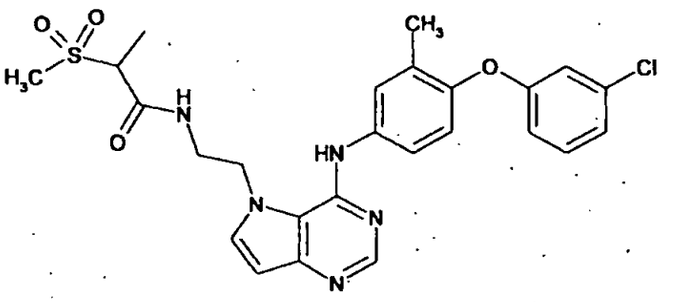
Production of N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-[4-(3-chlorophenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (167 mg), methylsulfonylacetic acid (74 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively

with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give the title compound (177 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.13 (3H, s), 3.09 (3H, s), 3.45 (2H, q, J= 6 Hz), 4.05 (2H, s), 4.55 (2H, t, J= 6 Hz), 6.46 (1H, d, J= 3 Hz), 6.80-6.95 (2H, m), 7.00 (1H, d, J= 9 Hz), 7.11 (1H, m), 7.37 (1H, t, J= 8 Hz), 7.56 (3H, m), 8.28 (1H, s), 8.52 (1H, br s), 8.66 (1H, m).

Example A-14



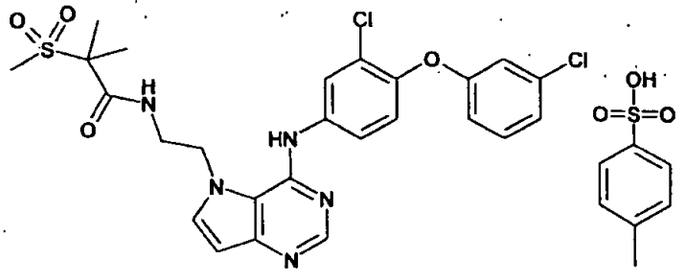
Production of N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)propanamide

A mixture of 5-(2-aminoethyl)-N-[4-(3-chlorophenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (192 mg), 2-chloropropanoic acid (0.057 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (126 mg), 1-hydroxybenzotriazole (90 mg), triethylamine (0.29 mL) and N,N-dimethylformamide (4 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by

silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=90:10), and the fraction containing 2-chloro-N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]propanamide was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (4 mL) and pyridine (0.4 mL), sodium methanesulfinic acid (420 mg) was added and the mixture was stirred at 70°C for 2 days. After cooling to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give the title compound (116 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (3H, d, J= 7 Hz), 2.13 (3H, s), 2.95 (3H, s), 3.50 (2H, m), 3.82 (1H, m), 4.53 (2H, m), 6.46 (1H, d, J= 3 Hz), 6.80-6.90 (2H, m), 7.01 (1H, d, J= 9 Hz), 7.10 (1H, d, J= 8 Hz), 7.37 (1H, t, J= 8 Hz), 7.57 (3H, m), 8.28 (1H, s), 8.49 (1H, br s), 8.59 (1H, t, J= 6 Hz).

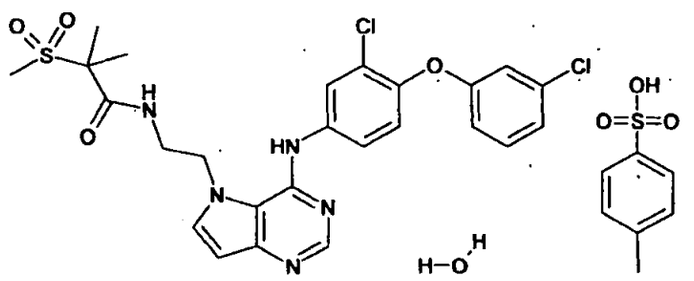
Example A-15



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide p-toluenesulfonate

Ethyl acetate (200 mL) and ethanol (70 mL) were added to N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide (9.0 g), the mixture was dissolved by heating at 65°C, and p-toluenesulfonic acid monohydrate (3.04 g) was added. The mixture was stood at room temperature under light shielding for 23 hr and the resulting crystals were collected by filtration. The crystals were washed with a small amount of ethyl acetate and diisopropyl ether to give the title compound (11.5 g) as colorless crystals.
^{1}H-NMR (DMSO-d_6) δ: 1.40 (6H, s), 2.28 (3H, s), 2.93 (3H, s), 3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.10 (2H, d, J = 7.8 Hz), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 9.0 Hz), 7.40-7.50 (3H, m), 7.60-7.70 (1H, m), 7.89 (1H, d, J = 3.0 Hz), 7.91 (1H, d, J = 1.8 Hz), 8.15-8.25 (1H, m), 8.74 (1H, s), 9.80 (1H, br s).
elemental analysis for $C_{32}H_{33}Cl_2N_5O_7S_2$
Calculated: C,52.32; H,4.53; N,9.53.
Found : C,52.35; H,4.54; N,9.49.
mp 217-218°C.

Example A-16



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide p-toluenesulfonate monohydrate

Acetone (20 mL) was added to N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-

d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide (500 mg), and the mixture was dissolved by heating at 40°C, and p-toluenesulfonic acid monohydrate (168 mg) was added. The mixture was stood at room temperature under light shielding for 4 days, and concentrated under reduced pressure. Ethyl acetate (12 mL) and ethanol (4 mL) were added to the residue, and the mixture was dissolved by heating at 60°C. The mixture was stood at room temperarure for 17 hr under light shielding, and resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether to give the title compound (543 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.40 (6H, s), 2.29 (3H, s), 2.93 (3H, s), 3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.10 (2H, d, J = 7.8 Hz), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 9.0 Hz), 7.40-7.50 (3H, m), 7.67 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.88 (1H, d, J = 3.0 Hz), 7.92 (1H, d, J = 2.4 Hz), 8.15-8.25 (1H, m), 8.73 (1H, s), 9.76 (1H, br s).

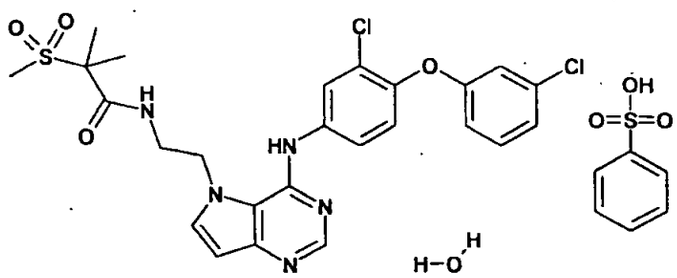
elemental analysis for $C_{32}H_{33}Cl_2N_5O_7S_2 \cdot 1.0H_2O$

Calculated: C,51.06; H,4.69; N,9.30.

Found : C,50.49; H,4.52; N,9.23.

mp 216-217°C.

Example A-17



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide benzenesulfonate monohydrate

To N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide (400 mg) were added ethyl acetate (12 mL) and ethanol (4 mL), and the mixture was dissolved by heating at 60°C, and benzenesulfonic acid monohydrate (132 mg) was added. The mixture was stood at room temperature for 17 hr under light shielding and concentrated under reduced pressure, and ethyl acetate (10 mL) was added to the residue. The mixture was stood at room temperature for 17 hr under light shielding, and resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether to give the title compound (447 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.41 (6H, s), 2.93 (3H, s), 3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.20-7.25 (1H, m), 7.25-7.35 (3H, m), 7.35 (1H, d, J = 8.4 Hz), 7.45 (1H, t, J = 8.4 Hz), 7.55-7.65 (2H, m), 7.67 (1H, dd, J = 2.4, 8.7 Hz), 7.88 (1H, d, J = 3.0 Hz), 7.93 (1H, d, J = 2.4 Hz), 8.20-8.25 (1H, m), 8.73 (1H, s), 9.74 (1H, br s).

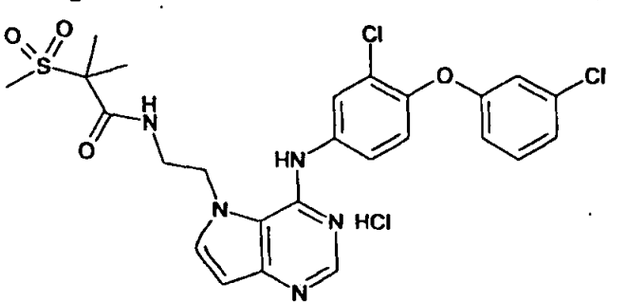
elemental analysis for $C_{31}H_{31}Cl_2N_5O_7S_2 \cdot 1.0H_2O$

Calculated: C,50.41; H,4.50; N,9.48.

Found : C,50.53; H,4.43; N,9.48.

mp 142-144°C.

Example A-18



Production of N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-

5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide hydrochloride

Acetone (20 mL) was added to N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide (400 mg), and the mixture was dissolved by heating at 40°C. 4N Hydrogen chloride/ethyl acetate solution (0.196 mL) was added. The mixture was stood at room temperature for 4 days under light shielding, and resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether to give the title compound (401 mg) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.40 (6H, s), 2.93 (3H, s), 3.50-3.65 (2H, m), 4.4.70-4.80 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 8.7 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.68 (1H, dd, J = 2.4 Hz, 8.7 Hz), 7.89 (1H, d, J = 3.0 Hz), 7.94 (1H, d, J = 2.4 Hz), 8.20-8.30 (1H, m), 8.73 (1H, s), 9.89 (1H, br s).

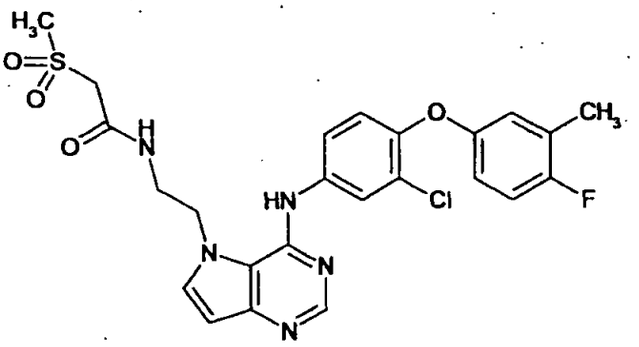
elemental analysis for $C_{25}H_{26}Cl_3N_5O_4S$

Calculated: C,50.13; H,4.38; N,11.69.

Found : C,49.70; H,4.41; N,11.48.

mp 194-195°C.

Example A-19



Production of N-(2-(4-((3-chloro-4-(4-fluoro-3-methylphenoxy)phenyl)amino)-5H-pyrrolo[3,2-d]pyrimidin-

5-yl)ethyl)-2-(methylsulfonyl)acetamide

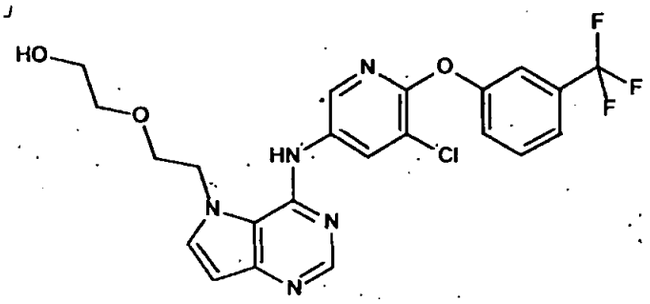
A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.00 g), 3-chloro-4-(4-fluoro-3-methylphenoxy)aniline (1.51 g) and isopropyl alcohol (10 mL) was stirred at 80°C for 12 hr. Aqueous sodium bicarbonate was added to the reaction mixture under ice-cooling and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0) to give a crude product (1.52 g). The obtained crude product (150 mg) was dissolved in tetrahydrofuran (22.2 mL). 4N Hydrogen chloride/ethyl acetate solution (11.5 mL) was added, and the mixture was stirred at 70°C for 20 hr. The solvent was evaporated under reduced pressure, ethanol was added, and the mixture was further concentrated. Diisopropyl ether was added, and the precipitated powder was collected by filtration. A mixture of the obtained powder, methylsulfonylacetic acid (74 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (7.0 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=90:10) and crystallized from diisopropyl ether to give the title compound (116 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 3.10 (3H, s), 3.46 (2H,

L68

q, J = 6.0 Hz), 4.04 (2H, s), 4.55 (2H, t, J = 6.0 Hz), 6.49-7.17 (5H, m), 7.61-7.93 (3H, m), 8.33 (1H, s), 8.65-8.66 (2H, m).

Example B-1



Production of 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 3-chloro-5-nitro-2-[3-(trifluoromethyl)phenoxy]pyridine

Under an argon atmosphere, to a solution of 3-(trifluoromethyl)phenol (0.42 g) in tetrahydrofuran (8.0 mL) was added sodium hydride (60% dispersion in mineral oil, 0.11 g) under ice-cooling. After stirring under ice-cooling for 1 hr, 2,3-dichloro-5-nitropyridine (0.50 g) was added. After stirring at room temperature for 2.5 hr, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=9:1→3:1) to give the title compound (746 mg) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 7.35-7.43 (1H, m), 7.45-7.51 (1H, m), 7.55-7.65 (1H, m), 8.61 (1H, d, J= 2.7 Hz), 8.88 (1H, d, J= 2.7 Hz).

(ii) Production of 5-chloro-6-[3-

(trifluoromethyl)phenoxy]pyridin-3-amine

A mixture of 3-chloro-5-nitro-2-[3-(trifluoromethyl)phenoxy]pyridine (746 mg), reduced iron (0.65 g), calcium chloride (0.13 g) and 15% water-containing ethanol (23 mL) was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (290 mg) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 3.65 (2H, br s), 7.20 (1H, d, J= 2.9 Hz), 7.22-7.26 (1H, m), 7.27-7.32 (1H, m), 7.37-7.40 (1H, m), 7.44-7.50 (1H, m), 7.59 (1H, d, J= 2.9 Hz).

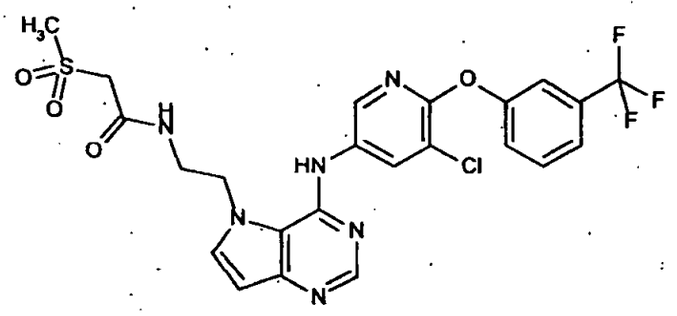
(iii) Production of 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

A solution of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (100 mg) and 5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-amine (100 mg) in isopropyl alcohol (2.0 mL) was stirred at 80°C for 16 hr. Aqueous sodium bicarbonate 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 magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=1:1→ethyl acetate) to give 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethyl benzoate (130 mg) as a colorless amorphous. To a solution of 2-{2-[4-

({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethyl benzoate (130 mg) in isopropyl alcohol-tetrahydrofuran (3 mL-2 mL) was added 1N aqueous sodium hydroxide solution (0.5 mL) at room temperature and the mixture was stirred for 3 hr. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=9:1) to give the title compound (72 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.69-3.80 (4H, m), 4.00-4.04 (2H, m), 4.54-4.59 (2H, m), 6.65 (1H, d, J= 3.3 Hz), 7.23 (1H, d, J= 3.3 Hz), 7.31-7.36 (1H, m), 7.40-7.55 (3H, m), 8.24 (1H, d, J= 2.7 Hz), 8.47 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.83 (1H, s).

Example B-2



Production of N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl {2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (189 mg)

and 5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-amine (184 mg) in isopropyl alcohol (4.0 mL) was stirred at 80°C for 20 hr. Aqueous sodium bicarbonate 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 magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:1→ethyl acetate) to give the title compound (257 mg) as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 3.43-4.54 (2H, m), 4.40-4.51 (2H, m), 5.05-5.15 (1H, m), 6.60 (1H, d, J= 3.0 Hz), 7.19 (1H, d, J= 3.0 Hz), 7.33-7.39 (1H, m), 7.41-7.53 (3H, m), 8.39 (1H, d, J= 2.4 Hz), 8.47 (1H, s), 8.64 (1H, d, J= 2.4 Hz), 8.79 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-{5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride

To a solution of tert-butyl {2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (257 mg) in tetrahydrofuran (10 mL) was added 2N hydrochloric acid (5.0 mL) at room temperature, and the mixture was stirred at 60°C for 20 hr. After concentration under reduced pressure, ethanol was added to the residue, and the mixture was concentrated again. Precipitated solid was collected by filtration and the solid was washed with diisopropyl ether to give the title compound (220 mg) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.23-3.37 (2H, m), 4.95-5.08 (2H, m), 6.74 (1H, d, J= 2.7 Hz), 7.56 (1H, d, J= 8.4 Hz), 7.64-7.74 (3H, m), 8.06 (1H, br s), 8.23-8.45 (5H, m), 8.71 (1H, s), 10.15 (1H, br s).

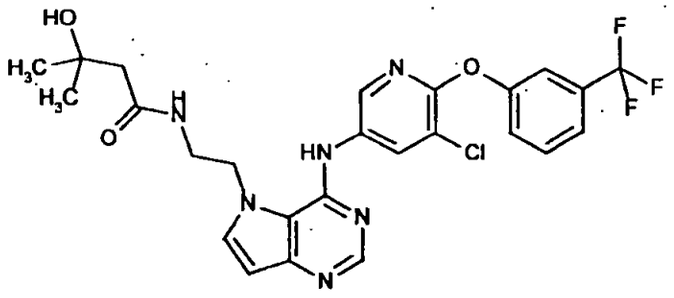
(iii) Production of N-{2-[4-({5-chloro-6-[3-

(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-{5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (95 mg), methylsulfonylacetic acid (47 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (98 mg), 1-hydroxybenzotriazole (78 mg) and triethylamine (0.12 mL) in N,N-dimethylformamide (5.0 mL) was stirred at room temperature for 14 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give the title compound (86 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.10 (3H, s), 3.62-3.78 (2H, m), 3.98 (2H, s), 4.41-4.53 (2H, m), 6.63 (1H, d, J= 3.0 Hz), 7.21 (1H, d, J= 3.0 Hz), 7.29-7.55 (5H, m), 8.41-8.50 (4H, m).

Example B-3

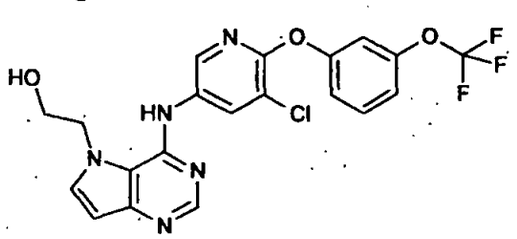


Production of N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide

Using 5-(2-aminoethyl)-N-{5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (95 mg), 3-hydroxy-3-methylbutanoic acid (46 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (98 mg), 1-hydroxybenzotriazole (78 mg), triethylamine (0.12 mL) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example B-2(iii), the title compound (73 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 2.36-2.43 (1H, m), 2.48 (2H, s), 3.55-3.66 (2H, m), 4.41-4.50 (2H, m), 6.60 (1H, d, J= 3.0 Hz), 7.18-7.22 (2H, m), 7.34-7.39 (1H, m), 7.42-7.53 (3H, m), 8.44 (1H, d, J= 2.4 Hz), 8.47 (1H, s), 8.54 (1H, d, J= 2.4 Hz), 8.97 (1H, s).

Example B-4



Production of 2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 3-chloro-5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyridine

Under an argon atmosphere, using 3-(trifluoromethoxy)phenol (0.93 g), 2,3-dichloro-5-nitropyridine (1.0 g), sodium hydride (60% dispersion in mineral oil, 0.23 g) and tetrahydrofuran (10 mL) and in the same manner as in Example B-1(i), the title compound (1.57 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 7.06-7.22 (3H, m), 7.49 (1H, t, J = 8.3 Hz), 8.59 (1H, d, J = 2.4 Hz), 8.88 (1H, d, J = 2.4 Hz).

(ii) Production of 5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine

Using 3-chloro-5-nitro-2-[3-(trifluoromethoxy)phenoxy]pyridine (1.57 g), reduced iron (1.31 g), calcium chloride (0.26 g) and 15% water-containing ethanol (50 mL) and in the same manner as in Example B-1(ii), the title compound (1.23 g) was obtained as an orange oil.

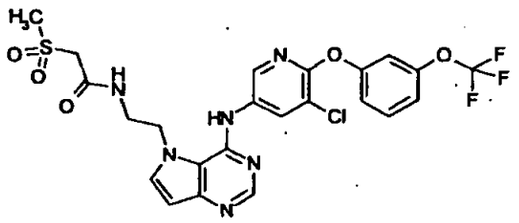
^{1}H-NMR ($CDCl_3$) δ: 3.65 (2H, br s), 6.91-7.02 (3H, m), 7.18 (1H, d, J = 2.7 Hz), 7.35 (1H, t, J = 8.1 Hz), 7.59 (1H, d, J = 2.7 Hz).

(iii) Production of 2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

A solution of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg) and 5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (101 mg) in isopropyl alcohol (2.0 mL) was stirred at 80°C for 2 days. The reaction mixture was cooled to room temperature, 1N aqueous sodium hydroxide solution (1.0 mL) was added thereto. The reaction mixture was stirred at room temperature for 4 hr, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=9:1) to give the title compound (112 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 4.11-4.19 (2H, m), 4.39-4.45 (2H, m), 4.83-4.99 (1H, m), 6.31 (1H, d, J = 3.3 Hz), 7.02-7.10 (4H, m), 7.36-7.42 (1H, m), 8.17 (1H, d, J = 2.7 Hz), 8.31 (1H, s), 8.34 (1H, d, J = 2.7 Hz), 9.44 (1H, s).

Example B-5



Production of N-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl {2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (300 mg), 5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (308 mg) and isopropyl alcohol (3.0 mL) and in the same manner as in Example B-2(i), the title compound (372 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 3.45-3.53 (2H, m), 4.43-4.49 (2H, m), 5.10 (1H, t, J = 5.4 Hz), 6.60 (1H, d, J = 3.0 Hz), 7.02-7.12 (3H, m), 7.18 (1H, d, J = 3.0 Hz), 7.36-7.42 (1H, m), 8.38 (1H, d, J = 2.4 Hz), 8.47 (1H, s), 8.65 (1H, d, J = 2.4 Hz), 8.77 (1H, br s).

(ii) Production of 5-(2-aminoethyl)-N-{5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride

Using tert-butyl {2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (350 mg), 2N hydrochloric acid (5.0 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example B-2(ii), the title compound (294 mg) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.34 (2H, m), 4.91-5.03 (2H, m), 6.66-6.76 (1H, m), 7.20-7.32 (3H, m), 7.59 (1H, t, J =

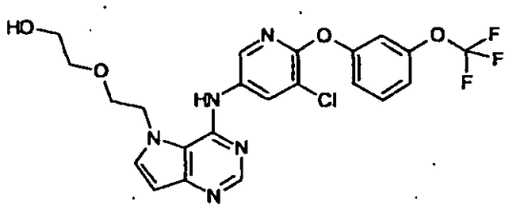
8.1 Hz), 8.01 (1H, br s), 8.12-8.37 (5H, m), 8.68 (1H, br s), 9.94-10.06 (1H, m).

(iii) Production of N-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 5-(2-aminoethyl)-N-{5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (90 mg), methylsulfonylacetic acid (43 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (90 mg), 1-hydroxybenzotriazole monohydrate (72 mg), triethylamine (0.12 mL) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example B-2(iii), the title compound (59 mg) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.10 (3H, s), 3.64-3.75 (2H, m), 3.98 (2H, s), 4.43-4.53 (2H, m), 6.62 (1H, d, J = 3.0 Hz), 7.03-7.13 (3H, m), 7.15-7.23 (2H, m), 7.41 (1H, t, J = 8.4 Hz), 8.42 (1H, s), 8.44-8.47 (2H, m), 8.49 (1H, s).

Example B-6



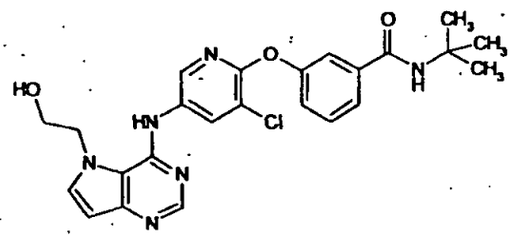
Production of 2-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (100 mg), 5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-amine (80 mg), isopropyl alcohol (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example B-4(iii), the title compound (71 mg) was

obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.77 (1H, br s), 3.66-3.80 (4H, m), 4.01 (2H, t, J = 4.5 Hz), 4.56 (2H, t, J = 4.5 Hz), 6.64 (1H, d, J = 3.3 Hz), 7.01-7.09 (3H, m), 7.22 (1H, d, J = 3.3 Hz), 7.36-7.42 (1H, m), 8.25 (1H, d, J = 2.7 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.49 (1H, s), 8.83 (1H, s).

Example B-7



Production of N-(tert-butyl)-3-[(3-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}pyridin-2-yl)oxy]benzamide

(i) Production of methyl 3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzoate

Using methyl 3-hydroxybenzoate (0.83 g), 2,3-dichloro-5-nitropyridine (1.0 g), sodium hydride (60% dispersion in mineral oil, 0.24 g) and tetrahydrofuran (10 mL) and in the same manner as in Example B-1(i), the title compound (1.61 g) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 7.37-7.41 (1H, m), 7.52-7.57 (1H, m), 7.84-7.86 (1H, m), 7.98-8.02 (1H, m), 8.58 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 2.7 Hz).

(ii) Production of 3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzoic acid

To a solution of methyl 3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzoate (1.61 g) in isopropyl alcohol (20 mL) and tetrahydrofuran (10 mL) was added 1N aqueous sodium hydroxide solution (6.0 mL) at room temperature. After stirring at room temperature for 24 hr, 1N hydrochloric acid (6.0 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 magnesium sulfate. After concentration under reduced pressure, the resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether to give the title compound (0.62 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 7.42-7.48 (2H, m), 7.57-7.63 (1H, m), 7.90-7.94 (1H, m), 8.06-8.08 (1H, m), 8.60-8.61 (1H, m), 8.88 (1H, d, J = 2.4 Hz).

(iii) Production of N-(tert-butyl)-3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzamide

To a solution of 3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzoic acid (0.62 g) and N,N-dimethylformamide (0.1 mL) in tetrahydrofuran (12 mL) was added thionyl chloride (0.23 mL) at room temperature. After stirring at room temperature for 2 hr, the mixture was concentrated under reduced pressure. A solution of the residue in tetrahydrofuran (10 mL) was added dropwise to a solution of tert-butylamine (0.3 g) and triethylamine (0.89 mL) in tetrahydrofuran (5.0 mL) at 0°C. After stirring at room temperature for 20 hr, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=9:1→2:1) to give the title compound (0.61 g) as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 5.93 (1H, br s), 7.28-7.32 (1H, m), 7.52 (1H, t, J = 8.0 Hz), 7.57 (1H, t, J = 2.1 Hz), 7.62-7.65 (1H, m), 8.59 (1H, d, J = 2.4 Hz), 8.87 (1H, d, J = 2.4 Hz).

(iv) Production of 3-[(5-amino-3-chloropyridin-2-yl)oxy]-N-(tert-butyl)benzamide

Using N-(tert-butyl)-3-[(3-chloro-5-nitropyridin-2-yl)oxy]benzamide (570 mg), reduced iron (0.46 g), calcium chloride (90 mg) and 15% water-containing ethanol (17 mL) and in the same manner as in Example B-1(ii), the title compound (373 mg) was obtained as pale-yellow crystals.

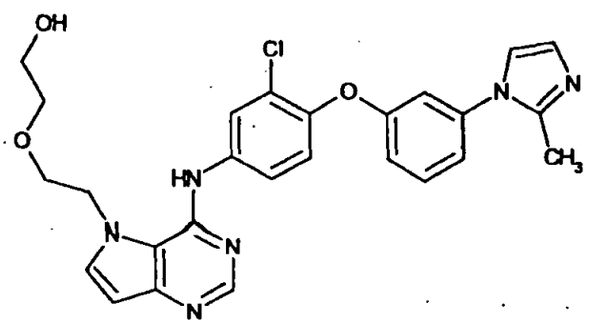
^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 3.63 (2H, br s), 5.91 (1H, br s), 7.15-7.19 (2H, m), 7.36-7.47 (3H, m), 7.56 (1H, d, J = 2.7 Hz).

(v) Production of N-(tert-butyl)-3-[(3-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}pyridin-2-yl)oxy]benzamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (80 mg), 3-[(5-amino-3-chloropyridin-2-yl)oxy]-N-(tert-butyl)benzamide (85 mg), isopropyl alcohol (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example B-4(iii), the title compound (78 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 4.11 (2H, t, J = 4.5 Hz), 4.41 (2H, t, J = 4.5 Hz), 5.44-5.56 (1H, m), 5.98 (1H, s), 6.30 (1H, d, J = 3.0 Hz), 7.06 (1H, d, J = 3.0 Hz), 7.20-7.28 (1H, m), 7.37-7.43 (1H, m), 7.46-7.50 (2H, m), 8.09 (1H, d, J = 2.7 Hz), 8.28 (1H, s), 8.31 (1H, d, J = 2.7 Hz), 9.57 (1H, s).

Example C-1



Production of 2-{2-[4-({3-chloro-4-[3-(2-methyl-1H-

imidazol-1-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2-methyl-1H-imidazole

To a solution of 3-(2-methyl-1H-imidazol-1-yl)phenol (1.10 g) and 3-chloro-4-fluoronitrobenzene (1.28 g) in N,N-dimethylformamide (10 mL) was added potassium carbonate (1.31 g) and the mixture was stirred at room temperature for 18 hr. Brine was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate twice, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (1.86 g) as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 7.00-7.25 (6H, m), 7.54 (1H, t, J = 8.2 Hz), 8.12 (1H, dd, J = 2.7, 9.0 Hz), 8.41 (1H, d, J = 2.4 Hz).

(ii) Production of 3-chloro-4-[3-(2-methyl-1H-imidazol-1-yl)phenoxy]aniline

To a solution of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2-methyl-1H-imidazole (1.86 g) in ethyl acetate (30 mL)/methanol (2 mL) was added 5% platinum-activated carbon (0.37 g) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 3.5 hr, the platinum-activated carbon was filtered off, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0) to give the title compound (1.26 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.73 (2H, br s), 6.58

(1H, dd, J = 2.7, 8.7 Hz), 6.74 (1H, t, J = 2.1 Hz), 6.79 (1H, d, J = 2.4 Hz), 6.9-7.05 (5H, m), 7.37 (1H, t, J = 8.1 Hz).

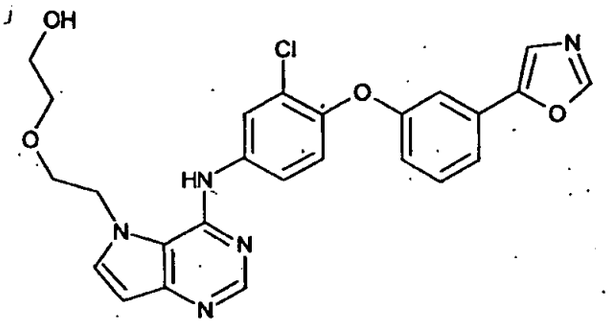
(iii) Production of 2-{2-[4-({3-chloro-4-[3-(2-methyl-1H-imidazol-1-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (207 mg), 3-chloro-4-[3-(2-methyl-1H-imidazol-1-yl)phenoxy]aniline (180 mg), 1-methyl-2-pyrrolidone (4.0 mL) and pyridine hydrochloride (139 mg) was stirred at 120°C for 17 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (2.6 mL) and tetrahydrofuran (5 mL) and the mixture was stirred at room temperature for 3 days. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) and the obtained solid was collected by filtration and washed with diisopropyl ether to give the title compound (158 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.70-3.75 (2H, m), 3.75-3.85 (2H, m), 4.02 (2H, t, J = 4.4 Hz), 4.57 (2H, t, J = 4.4 Hz), 6.64 (1H, d, J = 3.0 Hz), 6.80-6.85 (1H, m),

6.95-7.05 (4H, m), 7.11 (2H, d, J = 9.0 Hz), 7.22 (1H, d, J = 3.6 Hz), 7.40 (1H, t, J = 8.4 Hz), 7.64 (1H, dd, J = 2.4, 9.0 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.53 (1H, s), 8.82 (1H, s).

Example C-2



Production of 2-{2-[4-({3-chloro-4-[3-(1,3-oxazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 5-[3-(benzyloxy)phenyl]-1,3-oxazole

To a solution of 3-(benzyloxy)benzaldehyde (2.12 g) and p-toluenesulfonylmethyl isocyanide (1.95 g) in methanol (40 mL) was added potassium carbonate (1.66 g) under ice-cooling, and the mixture was stirred at room temperature for 20 min and refluxed for 1 hr. After concentration under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→50:50) to give the title compound (2.04 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 5.12 (2H, s), 6.90-7.00 (1H, m), 7.25-7.50 (9H, m), 7.91 (1H, s).

(ii) Production of 3-(1,3-oxazol-5-yl)phenol

To a solution of 5-[3-(benzyloxy)phenyl]-1,3-oxazole (2.01 g) in methanol (10 mL)/tetrahydrofuran (10 mL) was added 10% palladium-activated carbon (0.40 g)

and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 hr. The palladium-activated carbon was filtered off, and the filtrate was concentrated under reduced pressure. The precipitate was washed with diisopropyl ether and hexane to give the title compound (1.25 g) as pale-gray crystals.

^{1}H-NMR (95%$CDCl_3$+5%DMSO-d_6) δ: 6.80-6.90 (1H, m), 7.10-7.20 (2H, m), 7.24 (1H, t, J = 8.0 Hz), 7.31 (1H, s), 7.94 (1H, s), 9.13 (1H, s).

(iii) Production of 5-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-oxazole

To a solution of 3-(1,3-oxazol-5-yl)phenol (1.20 g) and 3-chloro-4-fluoronitrobenzene (1.45 g) in N,N-dimethylformamide (10 mL) was added potassium carbonate (1.54 g) and the mixture was stirred at room temperature for 18 hr. To the reaction mixture was added brine under ice-cooling, and the mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was recrystallized from ethyl acetate/diisopropyl ether/hexane to give the title compound (2.00 g) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 6.96 (1H, t, J = 9.0 Hz), 7.00-7.10 (1H, m), 7.35-7.45 (2H, m), 7.45-7.60 (2H, m), 7.93 (1H, s), 8.08 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.40 (1H, d, J = 3.0 Hz).

(iv) Production of 3-chloro-4-[3-(1,3-oxazol-5-yl)phenoxy]aniline

Using 5-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-oxazole (1.95 g), 5% platinum-activated carbon (0.33 g) and ethyl acetate (30 mL)/methanol (5 mL) and in the same manner as in Example C-1(ii), the title compound (1.80 g) was obtained as pale-yellow crystals.

^{1}H-NMR (95%$CDCl_3$+5%DMSO-d_6) δ: 6.8-6.9 (2H, m), 6.95-7.05 (2H, m), 7.15-7.2 (2H, m), 7.3-7.4 (3H, m), 7.91 (1H,

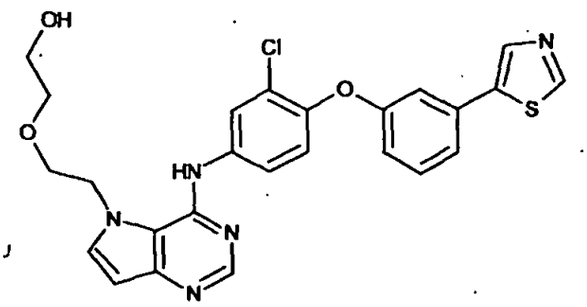
s), 8.09 (1H, s).

(v) Production of 2-{2-[4-({3-chloro-4-[3-(1,3-oxazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (346 mg), 3-chloro-4-[3-(1,3-oxazol-5-yl)phenoxy]aniline (344 mg) and isopropyl alcohol (10 mL) was stirred at 80°C for 18 hr. Aqueous sodium bicarbonate was added to the reaction mixture under ice-cooling and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). 1N Aqueous sodium hydroxide solution (0.8 mL) and tetrahydrofuran (4.0 mL) were added to the obtained compound, and the mixture was stirred at room temperature for 2 days. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate, and the extract was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (26 mg) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 3.70-3.75 (2H, m), 3.75-3.85 (2H, m), 4.03 (2H, t, J = 4.5 Hz), 4.58 (2H, t, J = 4.5 Hz), 6.64 (1H, d, J = 3.0 Hz), 6.90-6.95 (1H, m), 7.08 (1H, d, J = 9.0 Hz), 7.22 (1H, d, J = 3.3 Hz), 7.25-7.30 (1H, m), 7.30-7.40 (3H, m), 7.61 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.89 (2H, d, J = 2.1 Hz), 8.53 (1H, s), 8.78 (1H, s).

Example C-3



Production of 2-{2-[4-({3-chloro-4-[3-(1,3-thiazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 5-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-thiazole

Using 3-(1,3-thiazol-5-yl)phenol (343 mg), 3-chloro-4-fluoronitrobenzene (429 mg), potassium carbonate (401 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example C-1(i), the title compound (624 mg) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 6.96 (1H, t, J = 9.3 Hz), 7.00-7.10 (1H, m), 7.30-7.35 (1H, m), 7.50-7.55 (2H, m), 8.07 (1H, d, J = 2.7 Hz), 8.10-8.15 (1H, m), 8.41 (1H, d, J = 2.4 Hz), 8.79 (1H, d, J = 0.6 Hz).

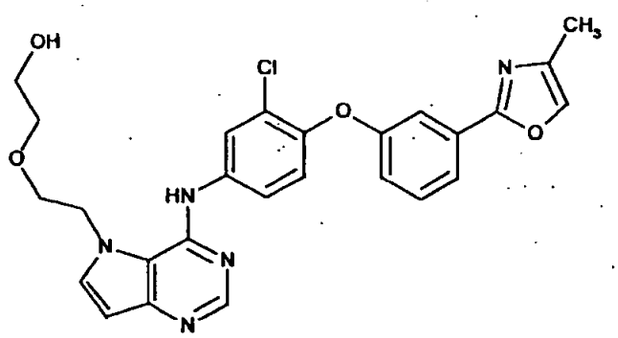
(ii) Production of 2-{2-[4-({3-chloro-4-[3-(1,3-thiazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

A mixture of the compound obtained using 5-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-thiazole (624 mg), 5% platinum-activated carbon (312 mg) and ethyl acetate (10 mL) and in the same manner as in Example C-1(ii), 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (450 mg) and isopropyl alcohol (10 mL) was stirred at 80°C for 20 hr. Aqueous sodium bicarbonate was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated

and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (2.2 mL) and tetrahydrofuran (5 mL) and the mixture was stirred at room temperature for 2 days. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) and further washed with diisopropyl ether to give the title compound (63.5 mg) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 3.70-3.85 (4H, m), 4.00-4.10 (2H, m), 4.50-4.60 (2H, m), 6.64 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 7.08 (1H, d, J = 8.7 Hz), 7.20-7.40 (4H, m), 7.61 (1H, dd, J = 2.4, 8.7 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.06 (1H, s), 8.53 (1H, s), 8.75 (1H, s), 8.78 (1H, s).

Example C-4



Production of 2-{2-[4-({3-chloro-4-[3-(4-methyl-1,3-oxazol-2-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 2-(3-methoxyphenyl)-4-methyl-1,3-oxazole

A suspension of 3-methoxybenzamide (4.91 g) and chloroacetone (3.61 g) in toluene (30 mL) was stirred at 110°C for 2 days. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=10:90→30:70) to give the title compound (1.54 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 3.88 (3H, s), 6.95-7.05 (1H, m), 7.35 (1H, t, J = 8.0 Hz), 7.40-7.45 (1H, m), 7.50-7.65 (2H, m).

(ii) Production of 3-(4-methyl-1,3-oxazol-2-yl)phenol

A solution (10 mL) of 2-(3-methoxyphenyl)-4-methyl-1,3-oxazole (1.54 g) in 48% hydrobromic acid was refluxed for 24 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=10:90→40:60) to give the title compound (1.14 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 6.09 (1H, br s), 6.90-7.00 (1H, m), 7.30 (1H, t, J = 8.0 Hz), 7.40-7.45 (1H, m), 7.50-7.60 (2H, m).

(iii) Production of 2-[3-(2-chloro-4-nitrophenoxy)phenyl]-4-methyl-1,3-oxazole

Using 3-(4-methyl-1,3-oxazol-2-yl)phenol (1.09 g), 3-chloro-4-fluoronitrobenzene (1.21 g), potassium carbonate (1.29 g) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-1(i), the title

compound (1.86 g) was obtained as a pale-yellow oil.
^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 6.94 (1H, t, J = 9.2 Hz), 7.10-7.20 (1H, m), 7.40-7.45 (1H, m), 7.53 (1H, t, J = 8.0 Hz), 7.70-7.75 (1H, m), 7.85-7.95 (1H, m), 8.07 (1H, dd, J = 2.6, 9.2 Hz), 8.40 (1H, d, J = 2.6 Hz).

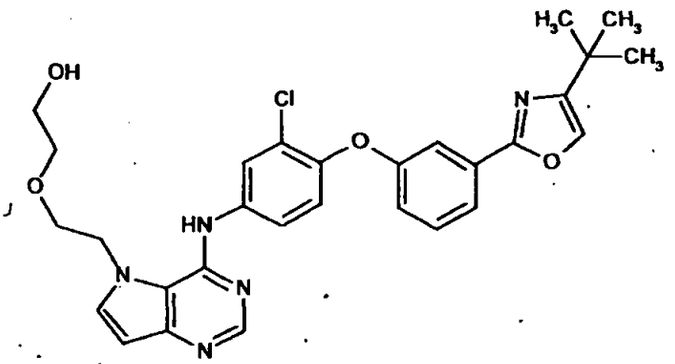
(iv) Production of 3-chloro-4-[3-(4-methyl-1,3-oxazol-2-yl)phenoxy]aniline

Using 2-[3-(2-chloro-4-nitrophenoxy)phenyl]-4-methyl-1,3-oxazole (1.86 g), 5% platinum-activated carbon (0.31 g) and ethyl acetate (20 mL) and in the same manner as in Example C-1(ii), the title compound (0.41 g) was obtained as a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 6.96 (1H, d, J = 6.9 Hz), 6.95-7.00 (1H, m), 7.36 (1H, t, J = 8.0 Hz), 7.35-7.40 (1H, m), 7.50-7.55 (1H, m), 7.70-7.75 (1H, m).

(v) Production of 2-{2-[4-({3-chloro-4-[3-(4-methyl-1,3-oxazol-2-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (392 mg), 3-chloro-4-[3-(4-methyl-1,3-oxazol-2-yl)phenoxy]aniline (410 mg) and isopropyl alcohol (10 mL), the reaction was carried out in the same manner as in Example C-2(v). Then, the obtained compound was reacted in the same manner as in Example C-2(v) and using 1N aqueous sodium hydroxide solution (4.7 mL) and tetrahydrofuran (10 mL) to give the title compound (371 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.65-3.85 (4H, m), 4.02 (2H, t, J = 4.4 Hz), 4.57 (2H, t, J = 4.4 Hz), 6.62 (1H, d, J = 3.2 Hz), 7.05-7.15 (2H, m), 7.20 (1H, d, J = 3.0 Hz), 7.30-7.45 (2H, m), 7.50-7.55 (1H, m), 7.62 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.70-7.75 (1H, m), 7.90 (1H, d, J = 2.6 Hz), 8.52 (1H, s), 8.79 (1H, s).

Example C-5



Production of 2-{2-[4-({4-[3-(4-tert-butyl-1,3-oxazol-2-yl)phenoxy]-3-chlorophenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 4-tert-butyl-2-(3-methoxyphenyl)-1,3-oxazole

Using 3-methoxybenzamide (1.51 g), 1-bromopinacolone (2.15 g) and toluene (10 mL) and in the same manner as in Example C-4(i), the title compound (2.01 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (9H, s), 3.88 (3H, s), 6.96 (1H, dd, J = 2.6 Hz, 8.4 Hz), 7.30-7.40 (2H, m), 7.55-7.65 (2H, m).

(ii) Production of 3-(4-tert-butyl-1,3-oxazol-2-yl)phenol

Using 4-tert-butyl-2-(3-methoxyphenyl)-1,3-oxazole (2.01 g) and 48% hydrobromic acid (10 mL) and in the same manner as in Example C-4(ii), the title compound (0.62 g) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.31 (9H, s), 5.20-5.50 (1H, m), 6.90 (1H, dd, J = 1.8 Hz, 8.0 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.36 (1H, s), 7.45-7.55 (1H, m), 7.58 (1H, d, J = 7.2 Hz).

(iii) Production of 4-tert-butyl-2-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-oxazole

Using 3-(4-tert-butyl-1,3-oxazol-2-yl)phenol (1.48 g), 3-chloro-4-fluoronitrobenzene (1.26 g), potassium

carbonate (1.41 g) and N,N-dimethylformamide (12 mL) and in the same manner as in Example C-1(i), the title compound (2.13 g) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.31 (9H, s), 6.92 (1H, t, J = 9.3 Hz), 7.10-7.20 (1H, m), 7.37 (1H, s), 7.51 (1H, t, J = 8.1 Hz), 7.75-7.80 (1H, m), 7.94 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iv) Production of 4-[3-(4-tert-butyl-1,3-oxazol-2-yl)phenoxy]-3-chloroaniline

Using 4-tert-butyl-2-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-oxazole (1.12 g), 5% platinum-activated carbon (0.19 g) and ethyl acetate (20 mL)/methanol (4 mL) and in the same manner as in Example C-1(ii), the title compound (985 mg) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.30 (9H, s), 3.68 (2H, br s), 6.58 (1H, dd, J = 2.6, 8.4 Hz), 6.80 (1H, d, J = 2.6 Hz), 6.85-6.95 (2H, m), 7.33 (2H, t, J = 8.4 Hz), 7.55-7.60 (1H, m), 7.70-7.75 (1H, m).

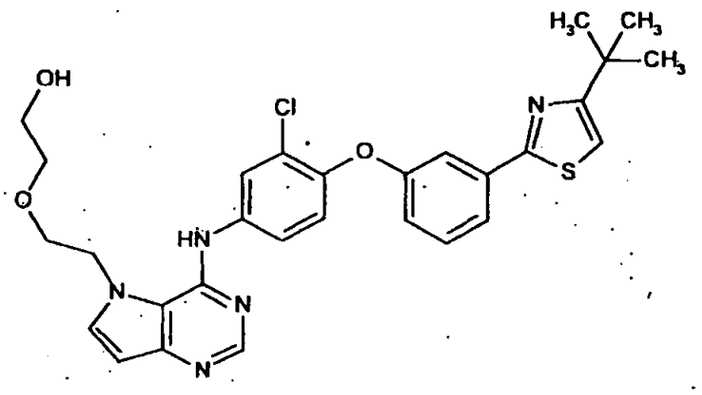
(v) Production of 2-{2-[4-({4-[3-(4-tert-butyl-1,3-oxazol-2-yl)phenoxy]-3-chlorophenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (444 mg), 4-[3-(4-tert-butyl-1,3-oxazol-2-yl)phenoxy]-3-chloroaniline (660 mg) and isopropyl alcohol (10 mL), the reaction was carried out in the same manner as in Example C-2(v). Then, the obtained compound was reacted in the same manner as in Example C-2(v) and using 1N aqueous sodium hydroxide solution (6.0 mL) and tetrahydrofuran (12 mL) to give the title compound (316 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.30 (9H, s), 3.70-3.80 (4H, m), 4.02 (2H, t, J = 4.2 Hz), 4.56 (2H, t, J = 4.2 Hz), 6.62 (1H, d, J = 3.3 Hz), 7.00 (1H, dd, J = 2.4 Hz, 8.4 Hz), 7.05 (1H, d, J = 8.7 Hz), 7.20 (1H, d, J = 3.3 Hz), 7.34 (1H,

s), 7.37 (1H, t, J = 7.8 Hz), 7.59 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.60-7.65 (1H, m), 7.75 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.77 (1H, s).

Example C-6



Production of 2-{2-[4-({4-[3-(4-tert-butyl-1,3-thiazol-2-yl)phenoxy]-3-chlorophenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 3-methoxybenzenecarbothioamide

A mixture of 3-methoxybenzonitrile (9.32 g), O, O-diethyl dithiophosphate (11.85 mL) and 4N hydrochloric acid (70 mL) was stirred at room temperature for 20 hr. The precipitate was collected by filtration, and washed with ethyl acetate and diisopropyl ether to give the title compound (8.51 g) as a pale-green powder.

^{1}H-NMR ($CDCl_3$) δ: 3.27 (2H, br s), 3.89 (3H, s), 7.10-7.20 (1H, m), 7.36 (1H, t, J = 7.8 Hz), 7.40-7.50 (1H, m), 7.50-7.60 (1H, m).

(ii) Production of 4-tert-butyl-2-(3-methoxyphenyl)-1,3-thiazole

A solution of 3-methoxybenzenecarbothioamide (4.18 g) and 1-bromopinacolone (4.48 g) in ethanol (50 mL) was stirred at room temperature for 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After concentration

under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=0:100→10:90) to give the title compound (4.91 g) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 3.88 (3H, s), 6.88 (1H, s), 6.90-7.00 (1H, m), 7.32 (1H, t, J = 8.1 Hz), 7.50-7.60 (2H, m).

(iii) Production of 3-(4-tert-butyl-1,3-thiazol-2-yl)phenol

Using 4-tert-butyl-2-(3-methoxyphenyl)-1,3-thiazole (4.91 g) and 48% hydrobromic acid (30 mL) and in the same manner as in Example C-4(ii), the title compound (3.59 g) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s), 5.08 (1H, s), 6.80-6.85 (1H, m), 6.89 (1H, s), 7.28 (1H, t, J = 8.0 Hz), 7.45-7.55 (2H, m).

(iv) Production of 4-tert-butyl-2-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-thiazole

Using 3-(4-tert-butyl-1,3-thiazol-2-yl)phenol (3.13 g), 3-chloro-4-fluoronitrobenzene (2.48 g), potassium carbonate (2.78 g) and N,N-dimethylformamide (24 mL) and in the same manner as in Example C-1(i), the title compound (1.49 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s), 6.93 (2H, t, J = 4.6 Hz), 7.05-7.15 (1H, m), 7.49 (1H, t, J = 8.0 Hz), 7.75-7.80 (1H, m), 7.80-7.90 (1H, m), 8.06 (1H, dd, J = 2.6, 8.8 Hz), 8.40 (1H, d, J = 2.6 Hz).

(v) Production of 4-[3-(4-tert-butyl-1,3-thiazol-2-yl)phenoxy]-3-chloroaniline

Using 4-tert-butyl-2-[3-(2-chloro-4-nitrophenoxy)phenyl]-1,3-thiazole (1.49 g), 5% platinum-activated carbon (0.25 g) and ethyl acetate (10 mL) and in the same manner as in Example C-1(ii), the title compound (1.37 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s), 3.68 (2H, br s), 6.58

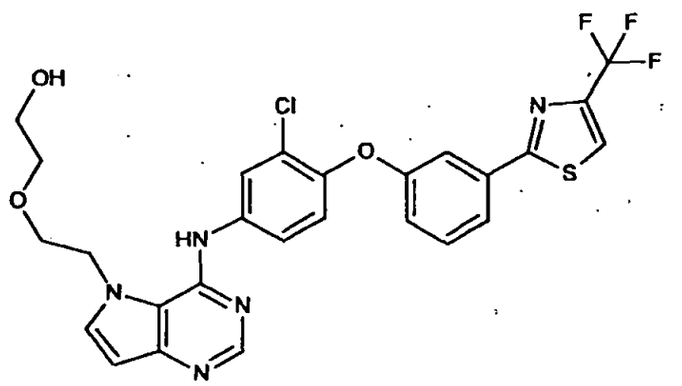
(1H, dd, J = 2.8, 8.6 Hz), 6.80-6.95 (4H, m), 7.30 (1H, t, J = 8.1 Hz), 7.55-7.65 (2H, m).

(vi) Production of 2-{2-[4-({4-[3-(4-tert-butyl-1,3-thiazol-2-yl)phenoxy]-3-chlorophenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (277 mg), 4-[3-(4-tert-butyl-1,3-thiazol-2-yl)phenoxy]-3-chloroaniline (359 mg) and isopropyl alcohol (5.0 mL), the reaction was carried out in the same manner as in Example C-2(v). Then, the obtained compound was reacted in the same manner as in Example C-2(v) and using 1N aqueous sodium hydroxide solution (3.7 mL) and tetrahydrofuran (7.5 mL) to give the title compound (163 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 3.70-3.80 (4H, m), 4.02 (2H, t, J = 4.5 Hz), 4.57 (2H, t, J = 4.5 Hz), 6.63 (1H, d, J = 3.3 Hz), 6.89 (1H, s), 6.92 (1H, d, J = 2.4 Hz), 7.05 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.34 (1H, t, J = 8.4 Hz), 7.58 (1H, dd, J = 2.4 Hz, 8.7 Hz), 7.65-7.70 (2H, m), 7.89 (1H, d, J = 2.4 Hz), 8.52 (1H, s), 8.75 (1H, s).

Example C-7



Production of 2-{2-[4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol

(i) Production of 2-(3-methoxyphenyl)-4-(trifluoromethyl)-1,3-thiazole

Using 3-methoxybenzenecarbothioamide (4.18 g), 3-bromo-1,1,1-trifluoroacetone (4.77 g) and ethanol (50 mL) and in the same manner as in Example C-6(ii), the title compound (4.29 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 6.95-7.05 (1H, m), 7.37 (1H, d, J = 8.2 Hz), 7.50-7.60 (2H, m), 7.73 (1H, d, J = 1.0 Hz).

(ii) Production of 3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenol

Using 2-(3-methoxyphenyl)-4-(trifluoromethyl)-1,3-thiazole (4.23 g) and 48% hydrobromic acid (30 mL) and in the same manner as in Example C-4(ii), the title compound (4.61 g) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 5.10-5.50 (1H, m), 6.90-7.00 (1H, m), 7.33 (1H, t, J = 8.1 Hz), 7.50-7.60 (2H, m), 7.73 (1H, s).

(iii) Production of 2-[3-(2-chloro-4-nitrophenoxy)phenyl]-4-(trifluoromethyl)-1,3-thiazole

Using 3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenol (4.00 g), 3-chloro-4-fluoronitrobenzene (3.01 g), potassium carbonate (3.38 g) and N,N-dimethylformamide (20 mL) and in the same manner as in Example C-1(i), the title compound (4.82 g) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 6.96 (1H, t, J = 9.0 Hz), 7.15-7.25 (1H, m), 7.55 (1H, t, J = 8.1 Hz), 7.75-7.80 (2H, m), 7.85 (1H, t, J = 8.1 Hz), 8.09 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iv) Production of 3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}aniline

Using 2-[3-(2-chloro-4-nitrophenoxy)phenyl]-4-(trifluoromethyl)-1,3-thiazole (2.00 g), 5% platinum-

activated carbon (0.33 g) and ethyl acetate (15 mL) and in the same manner as in Example C-1(ii), the title compound (1.87 g) was obtained as a colorless oil.

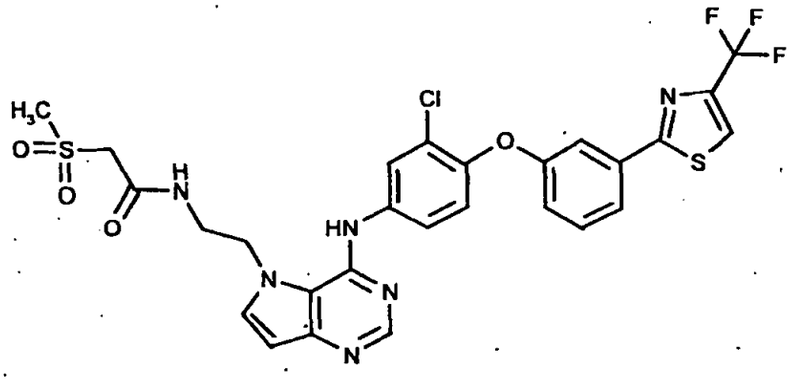
^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.81 (1H, d, J = 2.7 Hz), 6.94 (2H, d, J = 8.7 Hz), 7.36 (1H, t, J = 8.1 Hz), 7.50-7.55 (1H, m), 7.63 (1H, d, J = 7.5 Hz), 7.73 (1H, s).

(v) Production of 2-(2-{4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (262 mg), 3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}aniline (338 mg) and isopropyl alcohol (5.0 mL), the reaction was carried out in the same manner as in Example C-2(v). Then, the obtained compound was reacted in the same manner as in Example C-2(v) and using 1N aqueous sodium hydroxide solution (3.4 mL) and tetrahydrofuran (7 mL) to give the title compound (173 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 3.70-3.85 (4H, m), 4.02 (2H, t, J = 4.5 Hz), 4.57 (2H, t, J = 4.5 Hz), 6.63 (1H, d, J = 3.3 Hz), 7.00-7.10 (1H, m), 7.08 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.6-7.65 (2H, m), 7.67 (1H, d, J = 7.8 Hz), 7.74 (1H, s), 7.91 (1H, d, J = 2.7 Hz), 8.52 (1H, s), 8.79 (1H, s).

Example C-8



Production of N-(2-{4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl (2-{4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.01 g), 3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}aniline (1.51 g) and isopropyl alcohol (10 mL) was stirred at 80°C for 12 hr. To the reaction mixture was added aqueous sodium bicarbonate under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The obtained solid was collected by filtration, washed with diisopropyl ether and hexane to give the title compound (1.88 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 3.45-3.55 (2H, m), 4.45-4.55 (2H, m), 5.05-5.15 (1H, m), 6.61 (1H, d, J = 1.5

title compound (5.16 g) as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 5.13 (1H, s), 7.03-7.08 (1H, m), 7.10 (1H, s), 7.25-7.46 (11H, m), 7.58-7.62 (1H, m), 7.70-7.76 (1H, m).

(ii) Production of diphenylmethyl 3-(2-chloro-4-nitrophenoxy)benzoate

A mixture of 2-chloro-1-fluoro-4-nitrobenzene (2.81 g), diphenylmethyl 3-hydroxybenzoate (5.16 g), potassium carbonate (3.32 g) and N,N-dimethylformamide (50 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, diisopropyl ether was added to the obtained residue, and the precipitated solid was collected by filtration to give the title compound (6.93 g) as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ: 6.90 (1H, d, J= 9.3 Hz), 7.12 (1H, s), 7.27-7.46 (11H, m), 7.55 (1H, t, J= 8.0 Hz), 7.82 (1H, m), 8.02-8.11 (2H, m), 8.40 (1H, d, J= 2.7 Hz).

(iii) Production of diphenylmethyl 3-(4-amino-2-

title compound (3.58 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) δ: 3.69 (2H, br s), 6.57 (1H, dd, J= 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.91 (1H, d, J= 8.6 Hz), 7.04-7.10 (2H, m), 7.26-7.44 (11H, m), 7.62-7.65 (1H, m), 7.78-7.83 (1H, m).

(iv) Production of 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (1.04 g), diphenylmethyl 3-(4-amino-2-chlorophenoxy)benzoate (1.29 g) and isopropyl alcohol (20 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added trifluoroacetic acid (10 mL) and anisole (10 mL) and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure. 4N Hydrogen chloride/ethyl acetate solution was added to the residue, and the mixture was concentrated under reduced pressure. Ethyl acetate and acetonitrile were added to the residue and the precipitated solid was collected by filtration to give the title compound (1.24 g) as a white powder.
^{1}H-NMR (DMSO-d_6) δ: 3.76-3.83 (2H, m), 3.91 (2H, t, J= 4.7 Hz), 4.27-4.33 (2H, m), 4.89 (2H, m), 6.60-6.64 (1H, m), 7.22 (1H, d, J= 8.8 Hz), 7.26-7.75 (10H, m), 7.91 (1H, d, J= 2.5 Hz), 8.01 (1H, d, J= 3.0 Hz), 8.64 (1H, s), 9.91 (1H, m).

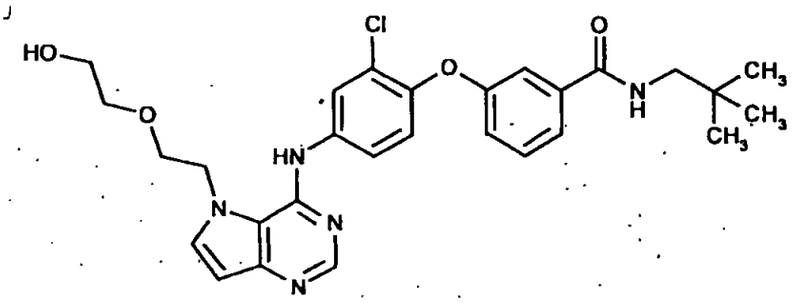
(v) Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide

A mixture of 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), tert-butylamine (0.038 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. To the residue were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diethyl ether to give the title compound (106 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.36 (1H, br s), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.53-4.60 (2H, m), 5.96

(1H, br s), 6.61 (1H, d, J= 3.0 Hz), 7.03 (1H, d, J= 8.8 Hz), 7.05-7.12 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.27-7.37 (3H, m), 7.57 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.91 (1H, d, J= 2.5 Hz), 8.51 (1H, s), 8.79 (1H, br s).

Example C-10

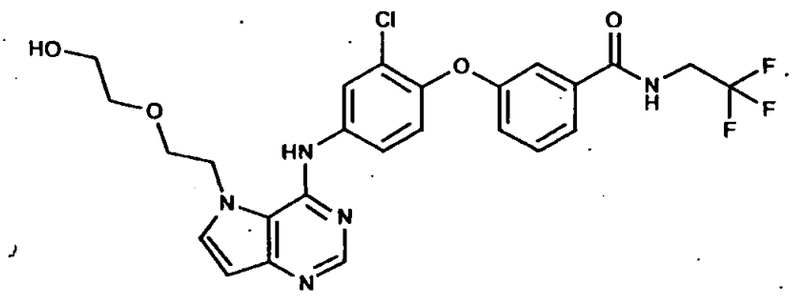


Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2,2-dimethylpropyl)benzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), neopentylamine (0.042 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (116 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.97 (9H, s), 2.30 (1H, br s), 3.25 (2H, d, J= 6.3 Hz), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.53-4.60 (2H, m), 6.14-6.26 (1H, m), 6.61 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 8.8 Hz), 7.06-7.12 (1H, m), 7.21 (1H, d, J= 3.3 Hz), 7.32-7.44 (3H, m), 7.57 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.90 (1H, d, J= 2.5 Hz), 8.51 (1H, s), 8.79 (1H, br s).

Example C-11

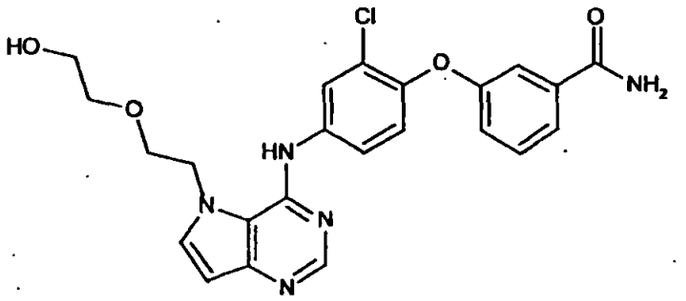


Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2,2,2-trifluoroethyl)benzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), 2,2,2-trifluoroethylamine (0.029 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (125 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 2.11 (1H, br s), 3.70-3.82 (4H, m), 3.99-4.17 (4H, m), 4.54-4.62 (2H, m), 6.61 (1H, d, J= 3.0 Hz), 6.67-6.78 (1H, m), 7.03 (1H, d, J= 8.8 Hz), 7.14-7.20 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.33 (1H, m), 7.40 (1H, t, J= 8.0 Hz), 7.46-7.51 (1H, m), 7.55 (1H, dd, J= 8.8, 2.6 Hz), 7.88 (1H, d, J= 2.6 Hz), 8.46 (1H, s), 8.78 (1H, br s).

Example C-12



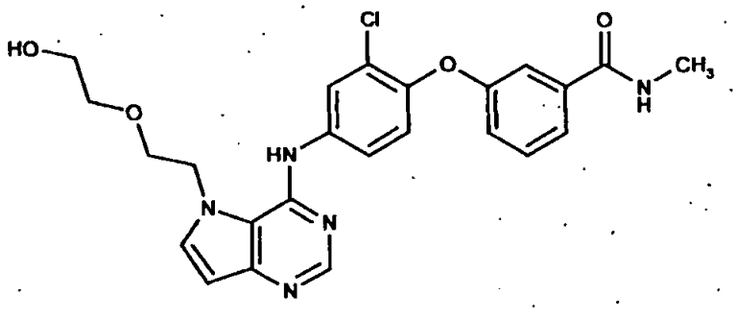
Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide

To a solution of 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg) in N,N-dimethylformamide (3 mL) were added triethylamine (0.050 mL) and 1,1'-carbonylbis(1H-imidazole) (58 mg) and the mixture was stirred at room temperature for 0.5 hr. 7N ammonia/methanol (0.086 mL) was added and the mixture was stirred at room temperature for 4 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. To the residue were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected

to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethanol-ethyl acetate to give the title compound (95 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.49 (4H, m), 3.84 (2H, t, J= 4.4 Hz), 4.65 (2H, t, J= 4.4 Hz), 4.72 (1H, t, J= 4.4 Hz), 6.52 (1H, d, J= 2.7 Hz), 7.08-7.15 (1H, m), 7.21 (1H, d, J= 8.7 Hz), 7.36-7.50 (3H, m), 7.58-7.72 (3H, m), 7.98-8.08 (2H, m), 8.35 (1H, s), 8.97 (1H, br s).

Example C-13



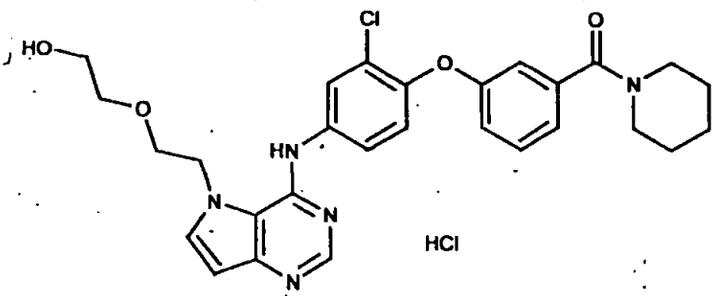
Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-methylbenzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), N,N-dimethylformamide (3 mL), triethylamine (0.050 mL), 1,1'-carbonylbis(1H-imidazole) (58 mg), 2M methylamine/tetrahydrofuran (0.30 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-12, the title compound (114 mg) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.76 (3H, d, J= 4.5 Hz), 3.50 (4H, m), 3.84 (2H, t, J= 4.4 Hz), 4.65 (2H, t, J= 4.4 Hz), 4.72 (1H, t, J= 4.5 Hz), 6.52 (1H, d, J= 3.0 Hz), 7.07-7.15 (1H, m), 7.20 (1H, d, J= 8.7 Hz), 7.34 (1H, m),

7.46 (1H, t, J= 7.8 Hz), 7.52-7.60 (1H, m), 7.61-7.73 (2H, m), 8.01 (1H, d, J= 2.7 Hz), 8.35 (1H, s), 8.44-8.53 (1H, m), 8.97 (1H, br s).

Example C-14



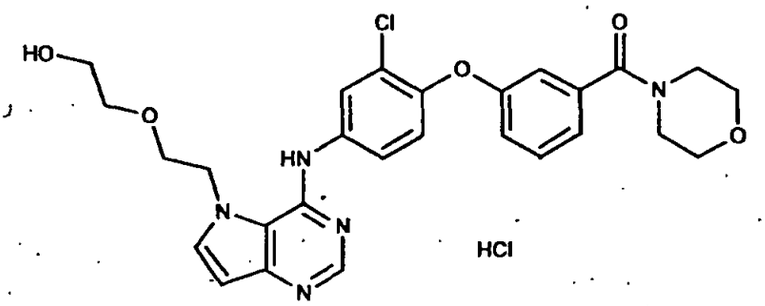
Production of 2-{2-[4-({3-chloro-4-[3-(piperidin-1-ylcarbonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol hydrochloride

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), N,N-dimethylformamide (3 mL), triethylamine (0.050 mL), 1,1'-carbonylbis(1H-imidazole) (58 mg), piperidine (0.059 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-12, 2-{2-[4-({3-chloro-4-[3-(piperidin-1-ylcarbonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol was obtained. The compound was dissolved in ethyl acetate-ethanol and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (126 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.34-1.68 (6H, m), 3.15-3.75 (8H, m), 3.84 (2H, t, J= 4.5 Hz), 4.81 (2H, m), 6.70 (1H, d, J= 3.0 Hz), 6.86 (1H, m), 7.04-7.10 (1H, m), 7.12 (1H, d, J= 7.7 Hz), 7.31 (1H, d, J= 8.8 Hz), 7.44-7.51 (1H, m), 7.64 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.97 (1H, d, J= 2.5

Hz), 8.02 (1H, d, J= 3.3 Hz), 8.74 (1H, s), 9.90 (1H, br s).

Example C-15



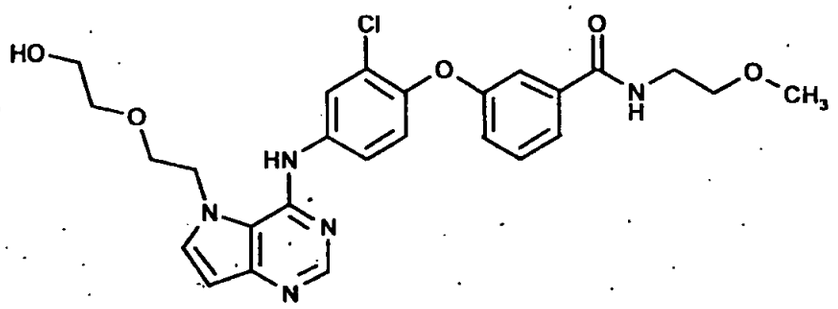
Production of 2-{2-[4-({3-chloro-4-[3-(morpholin-4-ylcarbonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol hydrochloride

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), morpholine (0.031 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), 2-{2-[4-({3-chloro-4-[3-(morpholin-4-ylcarbonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol was obtained. The compound was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (116 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.80 (12H, m), 3.85 (2H, t, J= 4.4 Hz), 4.81 (2H, t, J= 4.4 Hz), 6.70 (1H, d, J= 3.0 Hz), 6.94 (1H, m), 7.05-7.12 (1H, m), 7.15-7.21 (1H, m), 7.30 (1H, d, J= 8.8 Hz), 7.45-7.53 (1H, m), 7.64 (1H,

dd, J= 2.5 Hz, 8.8 Hz), 7.97 (1H, d, J= 2.5 Hz), 8.02 (1H, d, J= 3.3 Hz), 8.74 (1H, s), 9.90 (1H, br s).

Example C-16

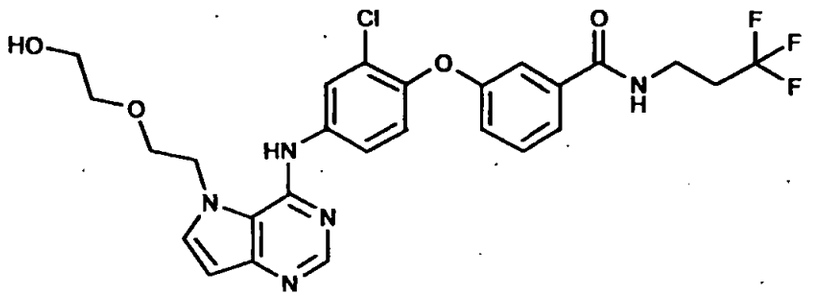


Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2-methoxyethyl)benzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), 2-methoxyethylamine (0.031 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (134 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 2.07-2.31 (1H, m), 3.38 (3H, s), 3.51-3.66 (4H, m), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.54-4.60 (2H, m), 6.51-6.59 (1H, m), 6.62 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 8.8 Hz), 7.08-7.13 (1H, m), 7.21 (1H, d, J= 3.3 Hz), 7.31-7.46 (3H, m), 7.58 (1H, dd, J= 8.8, 2.8 Hz), 7.90 (1H, d, J= 2.8 Hz), 8.51 (1H, s), 8.78 (1H, br s).

Example C-17



Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(3,3,3-trifluoropropyl)benzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), 3,3,3-trifluoropropylamine hydrochloride (53 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.092 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (150 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 2.08 (1H, br s), 2.37-2.54 (2H, m), 3.64-3.83 (6H, m), 3.99-4.06 (2H, m), 4.55-4.61 (2H, m), 6.48-6.58 (1H, m), 6.62 (1H, d, J= 3.2 Hz), 7.04 (1H, d, J= 9.0 Hz), 7.11-7.17 (1H, m), 7.22 (1H, d, J= 3.2 Hz), 7.27 (1H, m), 7.34-7.45 (2H, m), 7.57 (1H, dd, J= 2.5 Hz, 9.0 Hz), 7.89 (1H, d, J= 2.5 Hz), 8.50 (1H, s), 8.78 (1H, br s).

Example C-18

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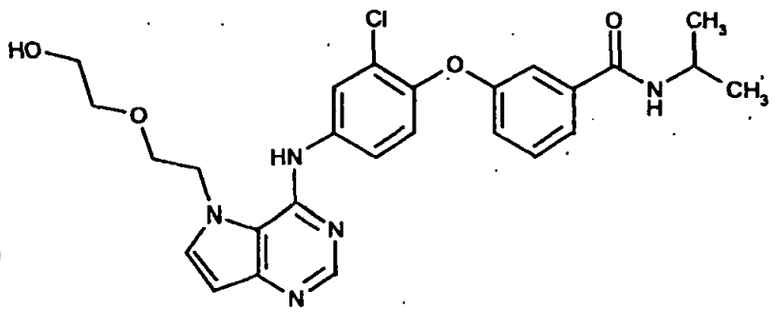
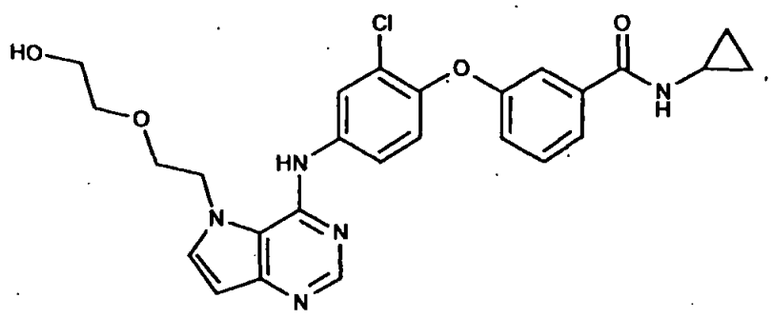


Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-isopropylbenzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), isopropylamine (0.031 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (125 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, d, J= 6.6 Hz), 2.13-2.37 (1H, m), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.18-4.31 (1H, m), 4.53-4.60 (2H, m), 5.92-6.02 (1H, m), 6.62 (1H, d, J= 3.0 Hz), 7.03 (1H, d, J=8.8 Hz), 7.06-7.12 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.30-7.42 (3H, m), 7.56 (1H, dd, J= 2.8 Hz, 8.8 Hz), 7.90 (1H, d, J= 2.8 Hz), 8.50 (1H, s), 8.78 (1H, br s).

Example C-19



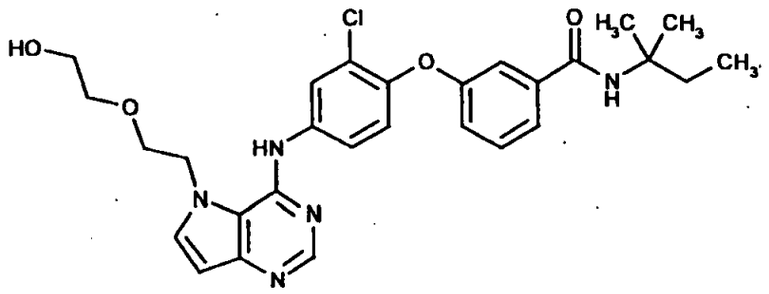
Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-cyclopropylbenzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), cyclopropylamine (0.025 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (118 mg) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.52-0.73 (4H, m), 2.76-2.87 (1H, m), 3.49 (4H, m), 3.84 (2H, t, J= 4.6 Hz), 4.65 (2H, t, J= 4.6 Hz), 4.72 (1H, t, J= 4.6 Hz), 6.52 (1H, d, J= 3.2 Hz), 7.06-7.12 (1H, m), 7.19 (1H, d, J=8.9 Hz), 7.35 (1H, m), 7.44 (1H, t, J= 7.8 Hz), 7.52-7.58 (1H, m), 7.64 (1H, dd, J= 8.9, 2.5 Hz), 7.69 (1H, d, J= 3.2 Hz), 8.00 (1H, d, J= 2.5 Hz), 8.34 (1H, s), 8.49 (1H, d, J= 4.1 Hz), 8.97 (1H, br s).

Example C-20

L90

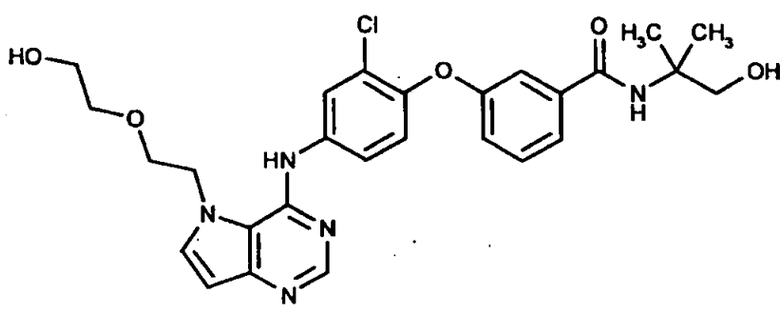


Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(1,1-dimethylpropyl)benzamide

Using 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid hydrochloride (183 mg), tert-amylamine (0.042 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (69 mg), 1-hydroxybenzotriazole (55 mg), triethylamine (0.050 mL), N,N-dimethylformamide (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and in the same manner as in Example C-9(v), the title compound (135 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J= 7.5 Hz), 1.40 (6H, s), 1.83 (2H, q, J= 7.5 Hz), 3.70-3.80 (4H, m), 3.99-4.05 (2H, m), 4.54-4.60 (2H, m), 5.84 (1H, br s), 6.63 (1H, d, J= 3.2 Hz), 7.02-7.12 (2H, m), 7.21 (1H, d, J= 3.2 Hz), 7.28-7.39 (3H, m), 7.58 (1H, dd, J= 8.8, 2.7 Hz), 7.91 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.79 (1H, br s).

Example C-21



dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from methanol-acetonitrile-diethyl ether to give the title compound (2.58 g) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.32 (9H, s), 3.22-3.32 (2H, m), 4.51 (2H, t, J= 6.2 Hz), 6.49 (1H, d, J= 3.0 Hz), 7.10-7.20 (1H, m), 7.24-7.34 (3H, m), 7.52 (1H, t, J= 8.0 Hz), 7.61 (1H, m), 7.67 (1H, d, J= 7.7 Hz), 7.75-7.84 (1H, m), 7.97 (1H, m), 8.33 (1H, s), 8.66 (1H, br s).

(iii) Production of 3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-(tert-butyl)benzamide dihydrochloride

A mixture of 3-{4-[(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}benzoic acid (524 mg), tert-butylamine (0.126 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (230 mg), 1-hydroxybenzotriazole (184 mg) and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added ethanol (2 mL) and 4N hydrogen chloride/ethyl acetate solution (2 mL) and the mixture was stirred at room temperature overnight. Ethyl acetate was added to the reaction mixture, and the precipitated solid was collected by filtration to give the title compound (427 mg) as a pale-yellow powder.

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^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 3.23-3.37 (2H, m), 4.96-5.06 (2H, m), 6.74 (1H, d, J= 3.3 Hz), 7.17 (1H, dd, J= 2.6 Hz, 8.1 Hz), 7.25 (1H, d, J= 8.8 Hz), 7.35 (1H, m), 7.47 (1H, t, J= 7.8 Hz), 7.58-7.66 (2H, m), 7.85 (1H, s), 7.90 (1H, m), 8.05 (1H, m), 8.27 (3H, br s), 8.74 (1H, s), 10.04 (1H, br s).

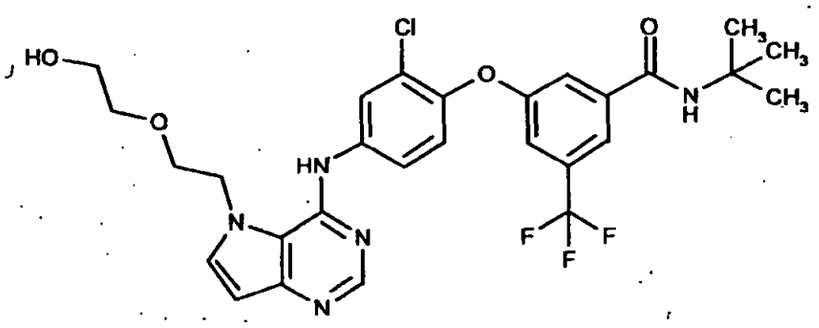
(iv) Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-{[(methylsulfonyl)acetyl]amino}ethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide hydrochloride

A mixture of 3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-(tert-butyl)benzamide dihydrochloride (166 mg), methylsulfonylacetic acid (62 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (121 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 3.06 (3H, s), 3.50-3.61 (2H, m), 4.07 (2H, s), 4.67-4.77 (2H, m), 6.67 (1H, d, J= 3.1 Hz), 7.13-7.20 (1H, m), 7.25 (1H, d, J= 8.9 Hz), 7.37 (1H, m), 7.47 (1H, t, J= 8.0 Hz), 7.60-7.69 (2H,

m), 7.85 (1H, s), 7.93 (1H, d, J= 2.5 Hz), 7.96 (1H, d, J= 3.1 Hz), 8.74 (1H, s), 8.78-8.87 (1H, m), 9.99 (1H, br s).

Example C-23



Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-5-(trifluoromethyl)benzamide

(i) Production of methyl 3-hydroxy-5-(trifluoromethyl)benzoate

3-Amino-5-(trifluoromethyl)benzoic acid (2.80 g) was dissolved in concentrated sulfuric acid (50 g) and water (50 mL) and the mixture was cooled to -10°C. Water (120 mL) was added, and an aqueous solution (20 mL) of sodium nitrite (0.942 g) was added dropwise. Water (10 mL) was added, and the mixture was stirred at -10°C for 10 min and at 0°C for 30 min. The mixture was further stirred with heating under reflux for 1 hr. After allowing to cool, 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 methanol (30 mL). Concentrated hydrochloric acid (0.9 mL) was added and the mixture was stirred with heating under reflux overnight. The reaction mixture was concentrated under reduced pressure, aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was

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extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=10:90→30:70). The objective fractions were concentrated under reduced pressure to give the title compound (1.86 g) as a pale-yellow powder.
^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 5.49 (1H, s), 7.29 (1H, m), 7.70 (1H, m), 7.87 (1H, m).

(ii) Production of methyl 3-(4-amino-2-chlorophenoxy)-5-(trifluoromethyl)benzoate

A mixture of 2-chloro-1-fluoro-4-nitrobenzene (1.48 g), methyl 3-hydroxy-5-(trifluoromethyl)benzoate (1.86 g), potassium carbonate (1.75 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=5:95→15:85). The objective fractions were concentrated under reduced pressure. To the residue were added ethyl acetate (30 mL) and 5% platinum-activated carbon (90 mg) and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 hr. The catalyst was filtered off, and the filtrate was concentrated and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=15:85→35:65). The objective fractions were concentrated under reduced pressure. Hexane was added to the residue, and the precipitated solid was

collected by filtration to give the title compound (2.50 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 3.76 (2H, br s), 3.92 (3H, s), 6.61 (1H, dd, J= 8.6, 2.7 Hz), 6.81 (1H, d, J= 2.7 Hz), 6.94 (1H, d, J= 8.6 Hz), 7.31 (1H, m), 7.64 (1H, m), 7.95 (1H, m).

(iii) Production of methyl 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoate

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (346 mg), methyl 3-(4-amino-2-chlorophenoxy)-5-(trifluoromethyl)benzoate (346 mg) and isopropyl alcohol (5 mL) was stirred at 80°C for 5 hr. 2-[2-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (69 mg) was added, and the mixture was further stirred at 80°C for 3 hr. The reaction mixture was concentrated under reduced pressure, aqueous sodium hydrogencarbonate solution was added, 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure to give the title compound (609 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 3.95-4.00 (2H, m), 4.06-4.12 (2H, m), 4.47-4.53 (2H, m), 4.56-4.63 (2H, m), 6.64 (1H, d, J= 3.3 Hz), 6.83 (1H, d, J= 8.8 Hz), 7.24 (1H, d, J= 3.3 Hz), 7.29-7.43 (4H, m), 7.45-7.52 (1H, m), 7.69 (1H, m), 7.77-7.83 (2H, m), 7.92 (1H, d, J= 2.5 Hz), 8.00 (1H, m), 8.52 (1H, s), 8.83 (1H, br s).

(iv) Production of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-

yl}amino)phenoxy]-5-(trifluoromethyl)benzoic acid

To methyl 3-{4-[(5-{2-[2-(benzoyloxy)ethoxy]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoate (609 mg) were added methanol (12 mL) and 1N aqueous sodium hydroxide solution (3 mL) and the mixture was stirred at room temperature overnight. Water and 1N hydrochloric acid (3 mL) were 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, ethanol-acetonitrile-diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration to give the title compound (416 mg) as a white powder.

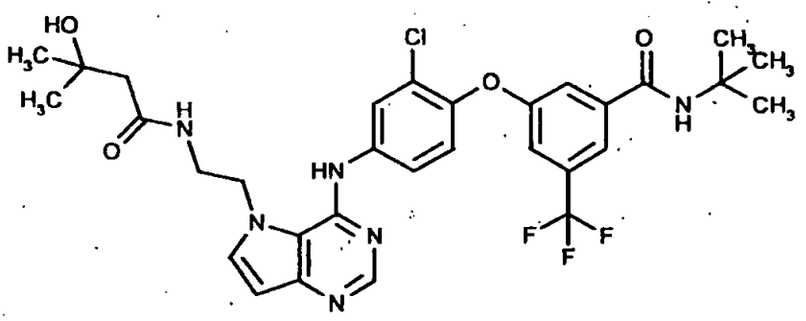
^{1}H-NMR (DMSO-d_6) δ: 3.50 (4H, m), 3.85 (2H, t, J= 4.4 Hz), 4.56-4.88 (1H, m), 4.68 (2H, t, J= 4.4 Hz), 6.54 (1H, d, J= 3.0 Hz), 7.38 (1H, d, J= 8.7 Hz), 7.52 (1H, m), 7.59-7.80 (3H, m), 7.90 (1H, m), 8.05 (1H, m), 8.40 (1H, s), 9.11 (1H, br s).

(v) Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-5-(trifluoromethyl)benzamide

A mixture of 3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-5-(trifluoromethyl)benzoic acid (322 mg), tert-butylamine (0.126 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (138 mg), 1-hydroxybenzotriazole (153 mg) and N,N-dimethylformamide (5 mL) was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diethyl ether to give the title compound (247 mg) as white crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.70-4.82 (4H, m), 4.02 (2H, t, J= 4.4 Hz), 4.57 (2H, t, J= 4.4 Hz), 6.00 (1H, br s), 6.61 (1H, d, J= 3.2 Hz), 7.06 (1H, d, J= 8.8 Hz), 7.21 (1H, d, J= 3.2 Hz), 7.29 (1H, m), 7.44 (1H, m), 7.57 (1H, m), 7.62 (1H, dd, J= 2.8 Hz, 8.8 Hz), 7.93 (1H, d, J= 2.8 Hz), 8.51 (1H, s), 8.87 (1H, br s).

Example C-24



Production of N-(tert-butyl)-3-{2-chloro-4-[(5-{2-[(3-hydroxy-3-methylbutanoyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}-5-(trifluoromethyl)benzamide

(i) Production of methyl 3-{4-[(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.48 g), methyl 3-(4-amino-2-chlorophenoxy)-5-(trifluoromethyl)benzoate (1.73 g) and isopropyl alcohol (20 mL) was stirred at 80°C for 5 hr. tert-Butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (0.30 g) was added and the mixture was further stirred at 80°C for 3 hr. The reaction mixture was concentrated

under reduced pressure, aqueous sodium hydrogencarbonate solution was added 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added acetone and diisopropyl ether, and the precipitated solid was collected by filtration to give the title compound (2.06 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 3.45-3.55 (2H, m), 3.93 (3H, s), 4.44-4.54 (2H, m), 5.10-5.18 (1H, m), 6.61 (1H, d, J= 3.2 Hz), 7.11 (1H, d, J= 8.9 Hz), 7.20 (1H, d, J= 3.2 Hz), 7.39 (1H, m), 7.77 (1H, m), 7.96 (1H, dd, J= 8.9, 2.5 Hz), 8.00 (1H, s), 8.07 (1H, d, J= 2.5 Hz), 8.53 (1H, s), 8.67 (1H, br s).

(ii) Production of 3-{4-[(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoic acid

To methyl 3-{4-[(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoate (2.42 g) were added methanol (10 mL), tetrahydrofuran (10 mL) and 1N aqueous sodium hydroxide solution (8 mL) and the mixture was stirred at room temperature overnight. To the reaction mixture were added water and 1N hydrochloric acid (8 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 residue was crystallized from methanol-diethyl ether to give the

title compound (2.03 g) as white crystals.
^{1}H-NMR (DMSO-d_6) δ: 1.32 (9H, s), 3.20-3.36 (2H, m), 4.53 (2H, t, J= 6.4 Hz), 6.51 (1H, d, J= 3.0 Hz), 7.10-7.23 (1H, m), 7.39 (1H, d, J= 8.7 Hz), 7.54 (1H, m), 7.63 (2H, m), 7.80-7.90 (1H, m), 7.90 (1H, m), 8.02 (1H, m), 8.35 (1H, s), 8.73 (1H, br s).

(iii) Production of 3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-(tert-butyl)-5-(trifluoromethyl)benzamide dihydrochloride

A mixture of 3-{4-[(5-{2-[(tert-butoxycarbonyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-2-chlorophenoxy}-5-(trifluoromethyl)benzoic acid (888 mg), tert-butylamine (0.189 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (345 mg), 1-hydroxybenzotriazole (276 mg) and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=70:30→100:0→methanol:ethyl acetate=10:90). The objective fractions were concentrated under reduced pressure. To the residue were added ethanol (1 mL) and 4N hydrogen chloride/ethyl acetate solution (5 mL) and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, ethanol and diethyl ether were added, and the precipitated solid was collected by filtration to give the title compound (815 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.37 (9H, s), 3.23-3.38 (2H, m), 5.06

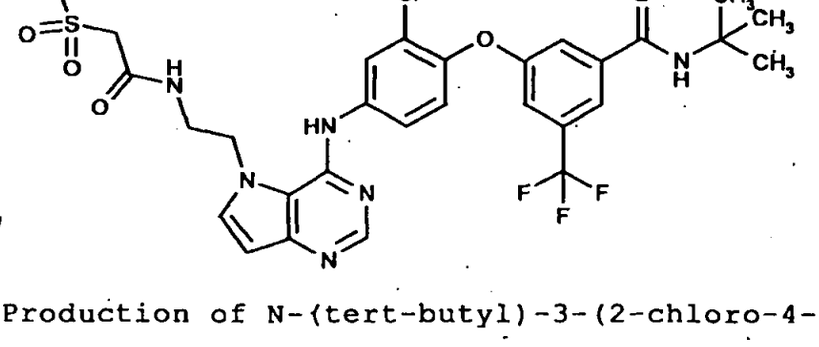
(2H, m), 6.76 (1H, d, J= 3.0 Hz), 7.37-7.44 (1H, m), 7.52 (1H, m), 7.59 (1H, m), 7.66-7.75 (1H, m), 7.94-8.55 (7H, m), 8.76 (1H, s), 9.95-10.04 (1H, m).

(iv) Production of N-(tert-butyl)-3-{2-chloro-4-[(5-{2-[(3-hydroxy-3-methylbutanoyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}-5-(trifluoromethyl)benzamide

A mixture of 3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-(tert-butyl)-5-(trifluoromethyl)benzamide dihydrochloride (186 mg), 3-hydroxy-3-methylbutanoic acid (53 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (152 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, s), 1.48 (9H, s), 2.48 (2H, s), 3.54-3.66 (2H, m), 4.41-4.53 (2H, m), 6.01 (1H, br s), 6.57 (1H, d, J= 3.3 Hz), 7.07 (1H, d, J= 9.0 Hz), 7.18 (1H, d, J= 3.3 Hz), 7.25-7.35 (2H, m), 7.48 (1H, m), 7.62 (1H, m), 7.78 (1H, dd, J= 2.4 Hz, 9.0 Hz), 8.10 (1H, d, J= 2.4 Hz), 8.49 (1H, s), 8.72 (1H, br s).

Example C-25



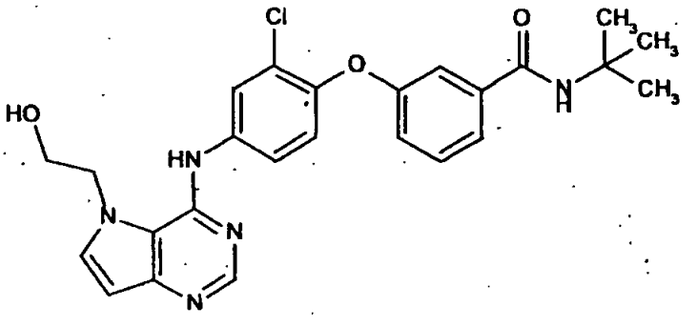
Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-{[(methylsulfonyl)acetyl]amino}ethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-5-(trifluoromethyl)benzamide

A mixture of 3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-(tert-butyl)-5-(trifluoromethyl)benzamide dihydrochloride (186 mg), methylsulfonylacetic acid (62 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85) and basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (146 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.14 (3H, s), 3.60-3.74 (2H, m), 4.00 (2H, s), 4.40-4.54 (2H, m), 6.06 (1H, br s), 6.58 (1H, d, J= 3.0 Hz), 7.08 (1H, d, J= 8.8 Hz),

7.21 (1H, d, J= 3.0 Hz), 7.35 (1H, m), 7.46 (1H, m), 7.58 (1H, m), 7.78 (1H, dd, J= 2.3 Hz, 8.8 Hz), 7.87-7.96 (1H, m), 7.97 (1H, d, J= 2.3 Hz), 8.29 (1H, br s), 9.46 (1H, s).

Example C-26



Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide

(i) Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (1.51 g), methyl 3-(4-amino-2-chlorophenoxy)benzoate (1.39 g) and isopropyl alcohol (20 mL) was stirred at 80°C overnight. Aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added methanol (30 mL) and 1N aqueous sodium hydroxide solution (13.5 mL) and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, water and 1N hydrochloric acid (13.5 mL) were added, and the mixture

was extracted with ethyl acetate-tetrahydrofuran. The extract was washed with water and the solvent was evaporated under reduced pressure. The residue was crystallized from acetonitrile-diethyl ether to give the title compound (1.88 g) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.88 (2H, m), 4.50-4.60 (2H, m), 6.31 (1H, br s), 6.52 (1H, d, J= 3.0 Hz), 7.23-7.34 (3H, m), 7.51 (1H, t, J= 8.0 Hz), 7.59-7.71 (3H, m), 7.99 (1H, d, J= 2.7 Hz), 8.35 (1H, s), 9.90 (1H, br s).

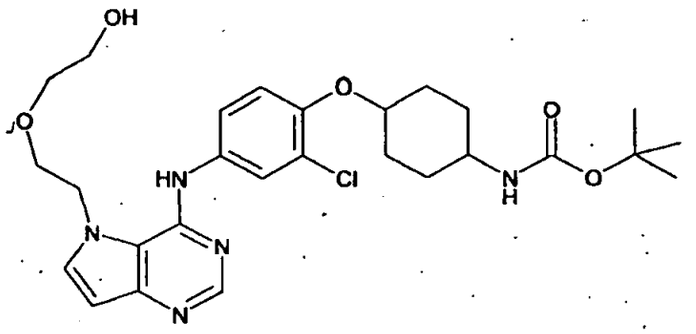
(ii) Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide

A mixture of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (850 mg), tert-butylamine (0.420 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (466 mg), 1-hydroxybenzotriazole (368 mg) and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80) and basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (630 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.66 (1H, br s), 4.08-4.16 (2H, m), 4.35-4.42 (2H, m), 5.99 (1H, br s), 6.16 (1H, d, J= 3.3 Hz), 6.98-7.03 (2H, m), 7.04-7.12 (1H,

m), 7.30-7.37 (3H, m), 7.41 (1H, dd, J= 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J= 2.6 Hz), 8.23 (1H, s), 9.68 (1H, br s).

Example C-27



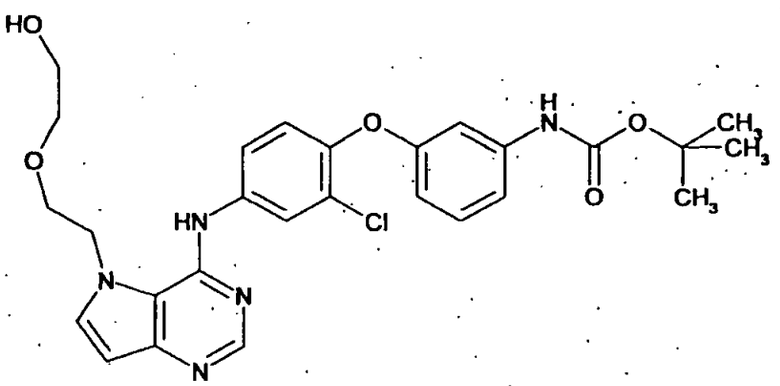
Production of tert-butyl {4-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]cyclohexyl}carbamate

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (300 mg), tert-butyl [4-(4-amino-2-chlorophenoxy)cyclohexyl]carbamate(384 mg) and isopropyl alcohol (7.0 mL) was stirred at 80°C overnight. The reaction mixture was concentrated under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were added 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 subjected to silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20). The objective fractions were concentrated under reduced pressure. The crude product was dissolved in methanol (5.0 mL) and tetrahydrofuran (1.0 mL), 1N aqueous sodium hydroxide solution (2.5 mL) was added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give the title compound (163 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.52 (4H, m), 1.38 (9H, s), 1.82-2.14 (4H, m), 3.25-3.32 (4H, m), 3.81 (2H, t, J= 4.9 Hz), 4.15-4.29 (1H, m), 4.60-4.72 (3H, m), 6.48 (1H, d, J= 3 Hz), 6.80-6.83 (1H, m), 7.17 (1H, d, J= 9 Hz), 7.46-7.49 (1H, m), 7.63 (1H, d, J= 3 Hz), 7.77 (1H, d, J= 3 Hz), 8.26 (1H, s), 8.68 (1H, br s).

Example C-28



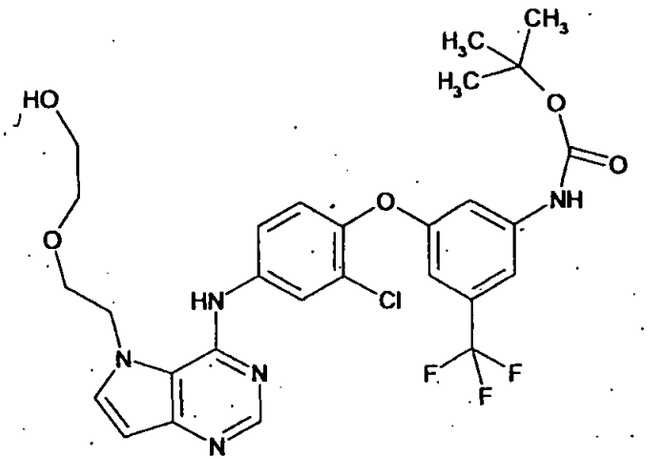
Production of tert-butyl {3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}carbamate

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (165 mg), tert-butyl [3-(4-amino-2-chlorophenoxy)phenyl]carbamate (200 mg), isopropyl alcohol (7.0 mL), methanol (5.0 mL), tetrahydrofuran (1.0 mL) and 1N aqueous sodium hydroxide solution (2.5 mL) and in the same manner as in Example C-27, the title compound (90 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.45 (9H, s), 3.49 (4H, s), 3.83 (2H, t, J= 4.7 Hz), 4.63-4.72 (3H, m), 6.51 (2H, d, J= 3 Hz),

7.12-7.24 (4H, m), 7.63-7.69 (2H, m), 7.99 (1H, s), 8.34 (1H, s), 8.93 (1H, s), 9.43 (1H, s).

Example C-29

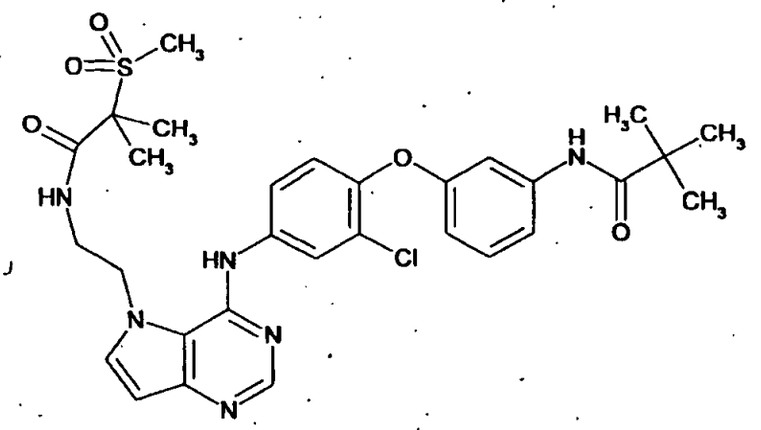


Production of tert-butyl [3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-5-(trifluoromethyl)phenyl]carbamate

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (206 mg), tert-butyl [3-(4-amino-2-chlorophenoxy)-5-(trifluoromethyl)phenyl]carbamate (300 mg), isopropyl alcohol (10 mL), methanol (2.0 mL), tetrahydrofuran (1.0 mL) and 1N aqueous sodium hydroxide solution (2.0 mL) and in the same manner as in Example C-27, the title compound (53 mg) was obtained as crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.53 (9H, s), 3.72-3.82 (5H, m), 4.02 (2H, t, J= 4.9 Hz), 4.58 (2H, t, J= 4.9 Hz), 6.36 (1H, d, J= 2.1 Hz), 6.58 (2H, d, J= 4.7 Hz), 6.66 (1H, d, J= 3.2 Hz), 7.07 (1H, d, J= 8.9 Hz), 7.23-7.25 (2H, m), 7.62 (1H, dt, J= 8.9, 2.1 Hz), 7.87 (1H, s), 8.54 (1H, s), 8.79 (1H, s).

Example C-30



Production of N-[3-(2-chloro-4-{[5-(2-{[2-methyl-2-(methylsulfonyl)propanoyl]amino}ethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2,2-dimethylpropanamide

(i) Production of 5-(2-aminoethyl)-N-[4-(3-aminophenoxy)-3-chlorophenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (267 mg) and tert-butyl [3-(4-amino-2-chlorophenoxy)phenyl]carbamate (430 mg) in 1-methyl-2-pyrrolidone (15 mL) was stirred at 120°C for 5 hr. After cooling to room temperature, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=19:1→3:2→ethyl acetate) to give a brown solid. To a solution of the obtained solid in tetrahydrofuran (20 mL) was added 2N hydrochloric acid (10 mL) at room temperature, and the mixture was stirred at 60°C for 20 hr. After concentration under reduced pressure, ethanol was added and the mixture was further concentrated. Diisopropyl ether was added to the residue and the resulting crystals were collected by filtration. The

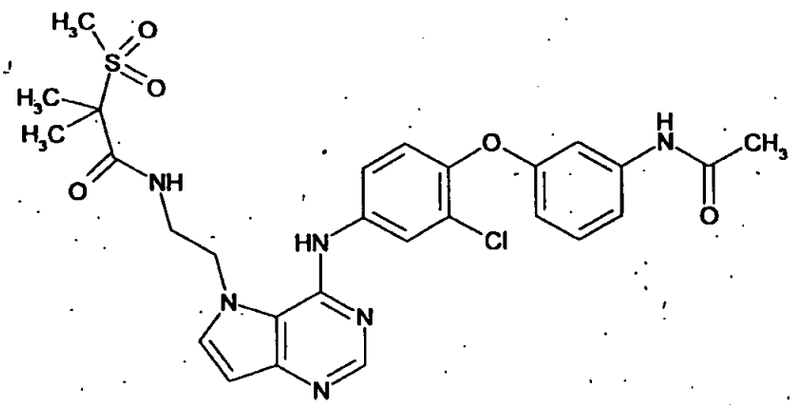
crystals were washed with diisopropyl ether to give the title compound (342 mg) as pale-yellow crystals.
^{1}H-NMR (DMSO-d_6) δ: 3.26-3.34 (2H, m), 5.04-5.13 (2H, m), 6.76-7.05 (4H, m), 7.28-7.69 (3H, m), 7.94 (1H, s), 8.11 (1H, s), 8.45 (3H, br s), 8.76 (1H, s), 10.39 (2H, br s).

(ii) Production of N-[3-(2-chloro-4-{[5-(2-{[2-methyl-2-(methylsulfonyl)propanoyl]amino}ethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2,2-dimethylpropanamide

A mixture of 5-(2-aminoethyl)-N-[4-(3-aminophenoxy)-3-chlorophenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (114 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (210 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (380 mg), 1-hydroxybenzotriazole (41 mg), triethylamine (1.0 mL) and tetrahydrofuran (5.0 mL) was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The obtained crude product was dissolved in tetrahydrofuran (5.0 mL), N-methylmorpholine (1.0 mL) and 2,2-dimethylpropanoyl chloride (0.25 mL) were added, and the mixture was stirred for 1 hr. Under ice-cooling, saturated aqueous sodium hydrogencarbonate was added, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated, and the residue was separated and purified by silica gel column chromatography (eluent, ethyl

6.49 (1H, d, J= 3.2 Hz), 6.73-6.76 (1H, m), 7.17-7.76 (6H, m), 7.99 (1H, d. J= 3.2 Hz), 8.22 (1H, br s), 8.34 (1H, s), 8.66 (1H, s), 9.52 (1H, s).

Example C-33



Production of N-{2-[4-({4-[3-(acetylamino)phenoxy]-3-chlorophenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-methyl-2-(methylsulfonyl)propanamide

A mixture of N-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide (91 mg), triethylamine (0.2 mL), acetic anhydride (0.3 mL) and tetrahydrofuran (7.0 mL) was stirred at room temperature for 1 hr. Under ice-cooling, saturated aqueous sodium hydrogencarbonate was added, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated, and the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20), and crystallized from diethyl ether/ethyl acetate to give the title compound (84 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.41(6H, s), 2.00 (3H, s), 2.96 (3H, s), 3.39-3.50 (2H, m), 4.55-4.59 (2H, m), 6.49 (1H, d, J= 3.2 Hz), 6.63-6.68 (1H, m), 7.23-7.30 (4H, m), 7.59 (1H, s), 7.72-7.75 (1H, m), 7.96 (1H, s), 8.20 (1H, br s), 8.34 (1H, s), 8.65 (1H, s), 10.00 (1H, s).

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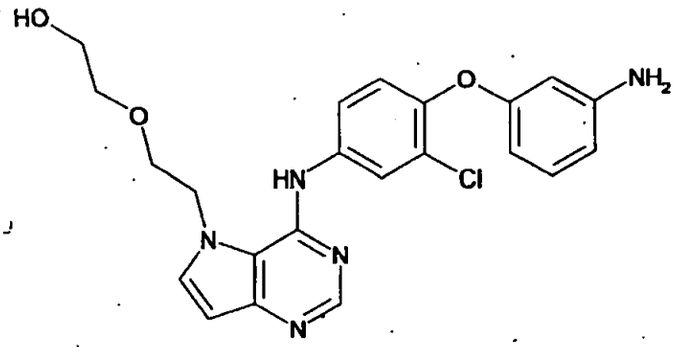
Example C-34

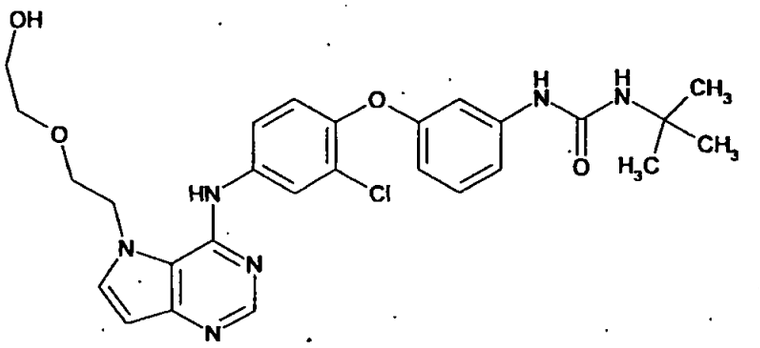


Production of 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol

tert-Butyl {3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}carbamate (120 mg) was dissolved in methanol (7.0 mL), 4N hydrogen chloride/ethyl acetate solution (8.0 mL) was added and the mixture was stirred for 5 hr. 8N aqueous sodium hydroxide solution (8.0 mL) and water (10 mL) were added, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated, and the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20), and crystallized from diethyl ether/ethyl acetate to give the title compound (59 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.49 (4H, s), 3.81-3.85 (2H, m), 4.62-4.65 (2H, t, J= 4.8Hz), 4.71 (1H, m), 5.32 (2H, m), 6.06-6.09 (2H, m), 6.27 (1H, d, J= 8.8 Hz), 6.51 (1H, d, J= 3.0 Hz), 6.94-6.70 (1H, m), 7.11 (1H, d, J= 8.8 Hz), 7.56-7.60 (1H, m), 7.70 (1H, d, J= 3.0 Hz), 7.95 (1H, s), 8.34 (1H, s), 8.93 (1H, s).

Example C-35



Production of N-(tert-butyl)-N'-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}urea

(i) Production of 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (206 mg), tert-butyl [3-(4-amino-2-chlorophenoxy)phenyl]carbamate (300 mg) and isopropyl alcohol (7.0 mL) was stirred at 80°C for 12 hr. The reaction mixture was concentrated under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were added 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 subjected to silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→0:100). The objective fractions were concentrated under reduced pressure. The crude product was dissolved in methanol (8.0 mL), and using 4N hydrogen chloride/ethyl acetate solution (8.0 mL) and in the same manner as in Example C-34, the title compound (370 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.76-3.80 (2H, m), 3.87-3.94 (2H, m), 4.22-4.35 (2H, m), 4.85-4.93 (2H, m), 6.62-6.77 (3H, m), 6.87-7.18 (3H, m), 7.30-7.71 (8H, m), 7.90 (1H, s), 8.01

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(1H, s), 8.65 (1H, s).

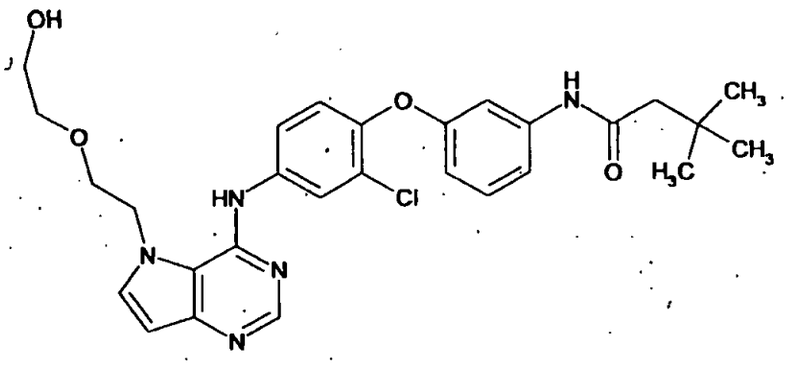
(ii) Production of N-(tert-butyl)-N'-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}urea

2-[2-(4-{[4-(3-Aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (200 mg) was suspended in toluene (10 mL), triethylamine (0.9 mL) and 2-isocyanato-2-methylpropane (0.4 mL) were added, and the mixture was stirred at 120°C for 6 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was dissolved in methanol (6.0 mL) and tetrahydrofuran (6.0 mL). 1N Aqueous sodium hydroxide solution (3.0 mL) was added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (74 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.26 (9H, s), 3.49 (4H, s), 3.83 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 5.93 (1H, s), 6.43-6.52 (2H, m), 6.96-7.21 (4H, m),

7.60-7.69 (2H, m), 7.98 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.35 (1H, s), 8.92 (1H, s).

Example C-36



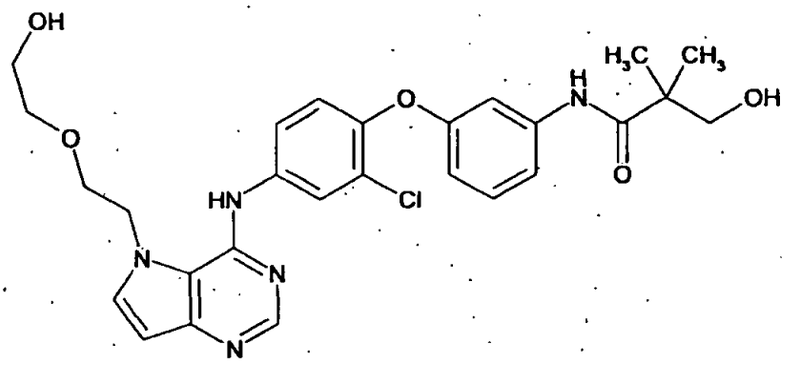
Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-3,3-dimethylbutanamide

A mixture of 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (270 mg), triethylamine (1.9 mL), 3,3-dimethylbutanoyl chloride (0.3 mL) and tetrahydrofuran (20 mL) was stirred at room temperature for 1 hr. Under ice-cooling, saturated aqueous sodium hydrogencarbonate was added, and the mixture was extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20). The objective fractions were concentrated under reduced pressure. The residue was dissolved in methanol (6.0 mL) and tetrahydrofuran (6.0 mL). 1N Aqueous sodium hydroxide solution (2.0 mL) was added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (126 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.00 (9H, s), 2.15 (2H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.68-6.70 (1H, m), 7.16-7.37 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.85 (1H, s).

Example C-37



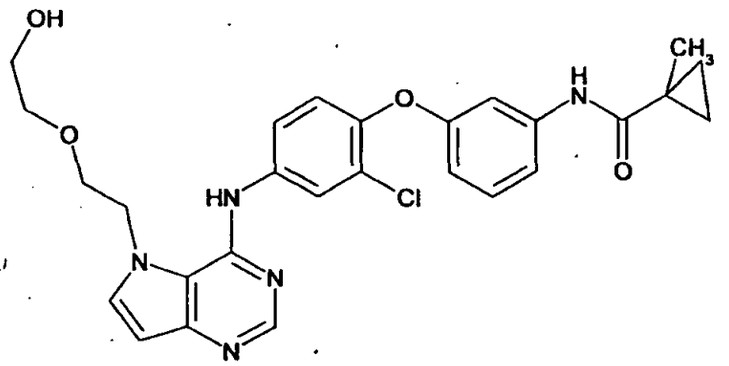
Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-3-hydroxy-2,2-dimethylpropanamide

A mixture of 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (260 mg), 3-hydroxy-2,2-dimethylpropanoic acid (200 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (621 mg), 1-hydroxybenzotriazole (70 mg), triethylamine (2.0 mL) and tetrahydrofuran (15 mL) was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The obtained crude product was dissolved in methanol (6.0 mL) and tetrahydrofuran (6.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) was added, and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (84 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.30 (6H, s), 3.49 (4H, s), 3.56 (2H, br s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, s), 4.73 (1H, m), 6.50 (1H, d, J= 3.2 Hz), 6.64 (1H, d, J= 7.7 Hz), 7.15-7.38 (4H, m), 7.62-7.70 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.90 (1H, s).

Example C-38

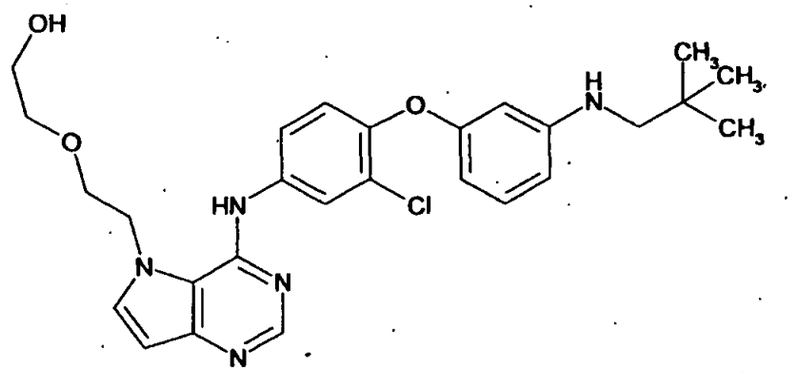


Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-1-methylcyclopropanecarboxamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (200 mg), 1-methylcyclopropanecarboxylic acid (179 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (600 mg), 1-hydroxybenzotriazole (70 mg), triethylamine (2.3 mL), tetrahydrofuran (20 mL), 1N aqueous sodium hydroxide solution (2.0 mL), tetrahydrofuran (6.0 mL) and ethanol (6.0 mL) and in the same manner as in Example C-37, the title compound (69 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.59-0.62 (2H, m), 1.04-1.08 (2H, m), 1.37 (3H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.60-6.70 (1H, m), 7.15 (1H, d, J= 6.0 Hz), 7.23-7.41 (3H, m), 7.60-7.64 (1H, m), 7.70 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.36 (1H, s), 8.98 (1H, s), 9.22 (1H, s).

Example C-39



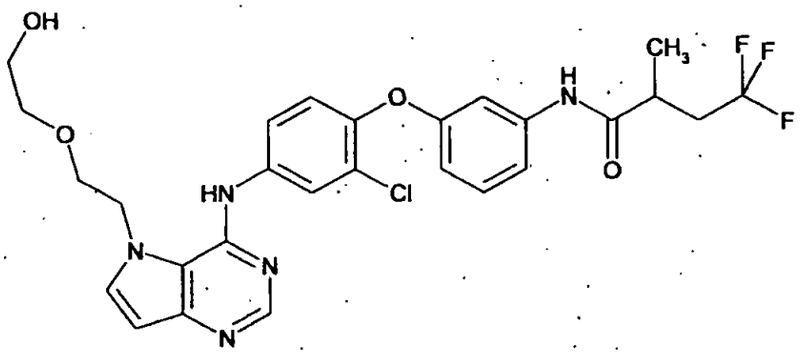
Production of 2-(2-{4-[(3-chloro-4-{3-[(2,2-dimethylpropyl)amino]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol

2-[2-(4-{[4-(3-Aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (220 mg) was suspended in dichloromethane (7.0 mL), and acetic acid (0.7 mL), molecular sieves 4A (300 mg) and pivalaldehyde (120 mg) were added, and the mixture was stirred for 30 min. Sodium triacetoxyborohydride (470 mg) was added, and the mixture was further stirred for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was dissolved in methanol (6.0 mL) and tetrahydrofuran (6.0 mL). 1N Aqueous sodium hydroxide solution (2.0 mL) was added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (67 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.93 (9H, s), 2.77 (2H, d, J= 6.0 Hz), 3.49 (4H, s), 3.83 (2H, t, J= 4.7 Hz), 4.63-4.72 (3H, m), 5.63 (1H, t, J= 6.0 Hz), 6.02-6.05 (1H, m), 6.24 (1H, t, J= 3.0 Hz), 6.34-6.36 (1H, m), 6.51 (1H, d, J= 3.0 Hz), 7.00 (1H, t, J= 6.0 Hz), 7.08 (1H, d, J= 9.0 Hz), 7.56-7.60 (1H, m), 7.68 (1H, d, J= 3.0 Hz), 7.95 (1H, d, J= 3.0 Hz), 8.33 (1H, s), 8.91 (1H, s).

Example C-40



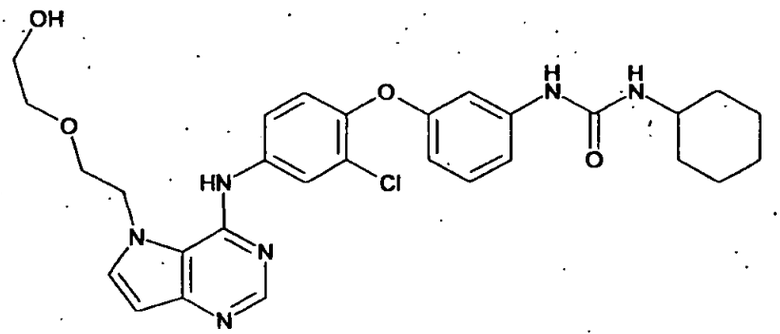
Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-4,4,4-trifluoro-2-methylbutanamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (50 mg), 4,4,4-trifluoro-2-methylbutanoic acid (47 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (125 mg), 1-hydroxybenzotriazole (5 mg), triethylamine (0.7 mL), tetrahydrofuran (7.0 mL), 1N aqueous sodium hydroxide solution (1.5 mL), tetrahydrofuran (3.0 mL) and methanol (2.0 mL) and in the same manner as in Example C-37, the

title compound (25 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, d, J= 6.0 Hz), 2.26-2.85 (3H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.68-6.70 (1H, m), 7.14-7.38 (4H, m), 7.62-7.70 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.95 (1H, s), 10.14 (1H, s).

Example C-41



Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-N'-cyclohexylurea

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (240 mg), toluene (15 mL), triethylamine (2.0 mL), cyclohexylisocyanate (137 mg), 1N aqueous sodium hydroxide solution (3.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-35(ii), the title compound (56 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.82 (10H, m), 3.34-3.51 (1H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.00 (1H, d, J= 9.0 Hz), 6.46-6.52 (2H, m), 6.96-7.21 (4H, m), 7.61-7.69 (2H, m), 7.98 (1H, d, J= 2.7 Hz), 8.34 (1H, s), 8.41 (1H, s), 8.93 (1H, s).

Example C-42

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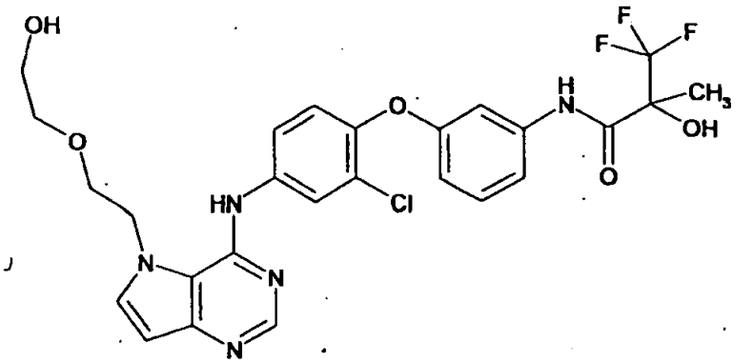
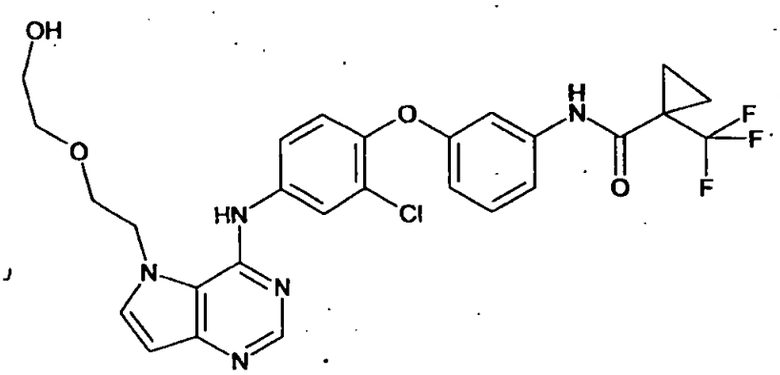


Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-3,3,3-trifluoro-2-hydroxy-2-methylpropanamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (201 mg), 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (175 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (415 mg), 1-hydroxybenzotriazole (47 mg), triethylamine (1.8 mL), tetrahydrofuran (28 mL), 1N aqueous sodium hydroxide solution (4.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-37, the title compound (47 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.01 (3H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.65 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.60-6.70 (1H, m), 7.14 (1H, d, J= 6.0 Hz), 7.22-7.45 (3H, m), 7.60-7.65 (1H, m), 7.71 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.36 (1H, s), 8.98 (1H, s), 9.22 (1H, s).

Example C-43

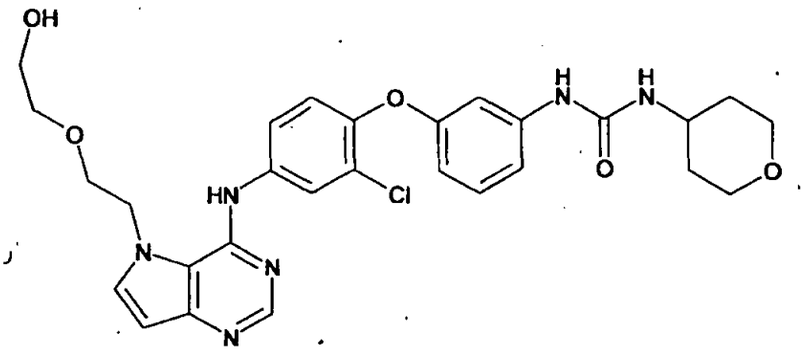


Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-1-(trifluoromethyl)cyclopropanecarboxamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (220 mg), 1-(trifluoromethyl)cyclopropanecarboxylic acid (300 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (450 mg), 1-hydroxybenzotriazole (110 mg), triethylamine (2.6 mL), tetrahydrofuran (15 mL), 1N aqueous sodium hydroxide solution (4.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-37, the title compound (23 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.31 (2H, m), 1.42-1.45 (2H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.51 (1H, d, J= 3.0 Hz), 6.70-6.73 (1H, m), 7.15-7.41 (4H, m), 7.60-7.69 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.95 (1H, s), 9.84 (1H, s).

Example C-44



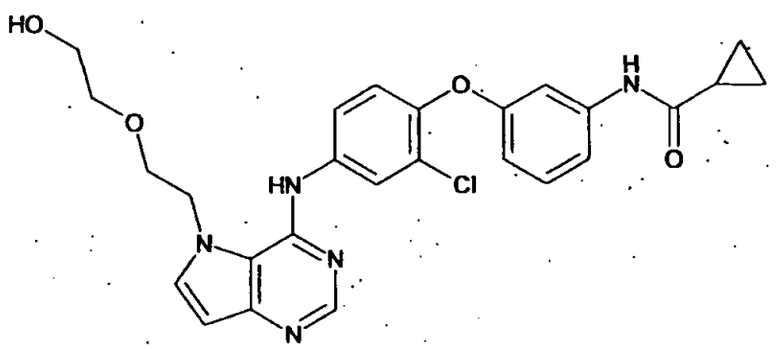
Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-N'-(tetrahydro-2H-pyran-4-yl)urea

To a solution of 1,1'-carbonylbis(1H-imidazole) (401 mg) in toluene (10 mL) was added tetrahydro-2H-pyran-4-amine (250 mg) and the mixture was stirred at room temperature for 1 hr. 2-[2-(4-{[4-(3-Aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (220 mg) and triethylamine (2.0 mL) were added, and the mixture was stirred at 70°C for 30 min. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was dissolved in methanol (8.0 mL) and tetrahydrofuran (2.0 mL). 1N Aqueous sodium hydroxide solution (3.0 mL) was added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective

fractions were concentrated under reduced pressure. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate-hexane to give the title compound (12 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.82 (4H, m), 3.20-3.63 (4H, m), 3.33-3.55 (1H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.00 (1H, d, J= 9.0 Hz), 6.45-6.52 (2H, m), 6.97-7.21 (4H, m), 7.59-7.71 (2H, m), 7.99 (1H, d, J= 2.7 Hz), 8.34 (1H, s), 8.41 (1H, s), 8.94 (1H, s).

Example C-45



Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}cyclopropanecarboxamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (200 mg), cyclopropanecarboxylic acid (200 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (470 mg), 1-hydroxybenzotriazole (42 mg), triethylamine (2.0 mL), tetrahydrofuran (29 mL), 1N aqueous sodium hydroxide solution (3.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-37, the title compound (98 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.76-0.78 (2H, m), 1.04 (2H, d, J= 6.0 Hz), 1.71-1.75 (1H, m), 3.49 (4H, s), 3.84 (2H, t,

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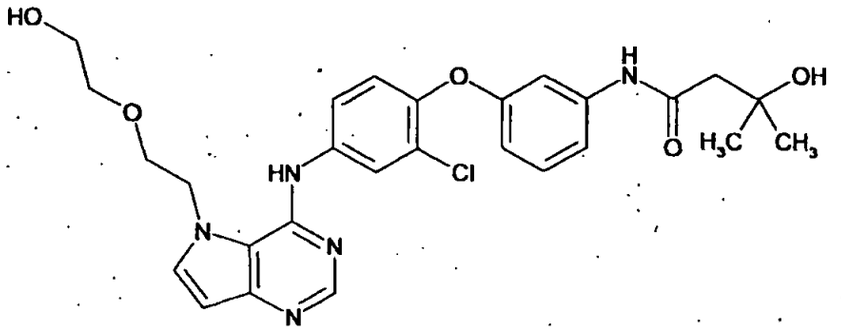
J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.62-6.66 (1H, m), 7.17 (1H, d, J= 9.0 Hz), 7.23-7.31 (3H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.94 (1H, s), 10.25 (1H, s).

Example C-46

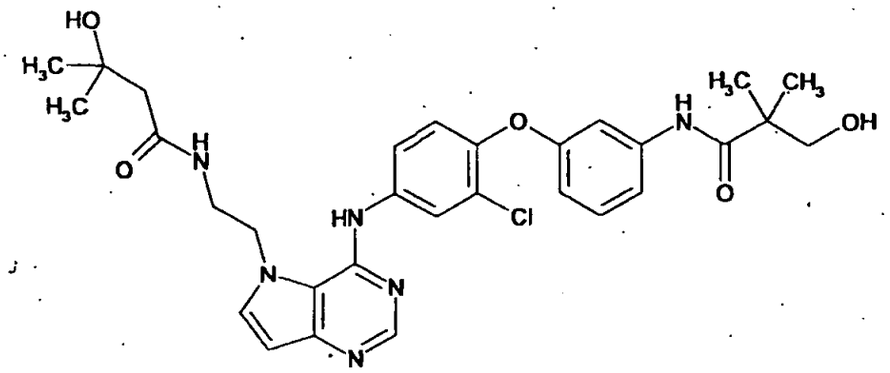


Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-3-hydroxy-3-methylbutanamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (200 mg), 3-hydroxy-3-methylbutanoic acid (200 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (470 mg), 1-hydroxybenzotriazole (41 mg), triethylamine (1.8 mL), tetrahydrofuran(28 mL), 1N aqueous sodium hydroxide solution (2.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-37, the title compound (53 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, s), 2.38 (2H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, s), 4.73 (1H, m), 6.51 (1H, d, J= 3.2 Hz), 6.63 (1H, d, J= 7.7 Hz), 7.15-7.37 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.87 (1H, s).

Example C-47

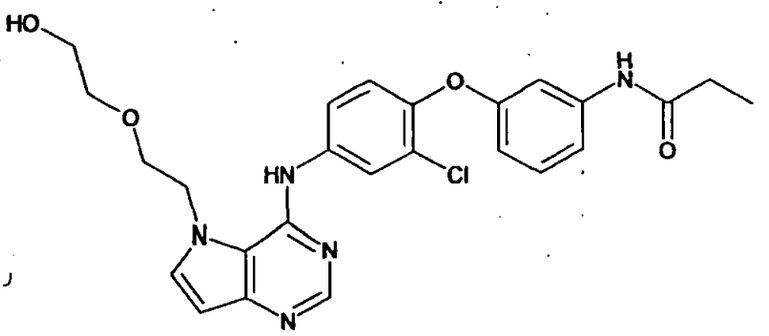


Production of N-(2-{4-[(3-chloro-4-{3-[(3-hydroxy-2,2-dimethylpropanoyl)amino]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide

Using 5-(2-aminoethyl)-N-[4-(3-aminophenoxy)-3-chlorophenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (150 mg), 3-hydroxy-3-methylbutanoic acid (42 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (357 mg), 1-hydroxybenzotriazole (18 mg) and triethylamine (0.9 mL) in tetrahydrofuran (4.0 mL) and in the same manner as in Example C-31, the reaction was carried out. Using the obtained crude product and 3-hydroxy-2,2-dimethylpropanoic acid (200 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (460 mg), 1-hydroxybenzotriazole (150 mg), triethylamine (2.0 mL) in tetrahydrofuran (7.0 mL) and in the same manner as in Example C-31, the title compound (90 mg) was obtained as crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, s), 1.32 (6H, s), 2.48 (2H, s), 2.80 (2H, br s), 3.59 (2H, s), 3.57-3.65 (2H, m), 4.45-4.51 (2H, m), 6.62 (1H, d, J= 3.0 Hz), 7.05-7.44(8H, m), 7.73 (1H, dd, J= 8.7 Hz, 2.7 Hz), 8.03 (1H, d, J= 2.7 Hz), 8.30 (1H, s), 8.50 (1H, s).

Example C-48

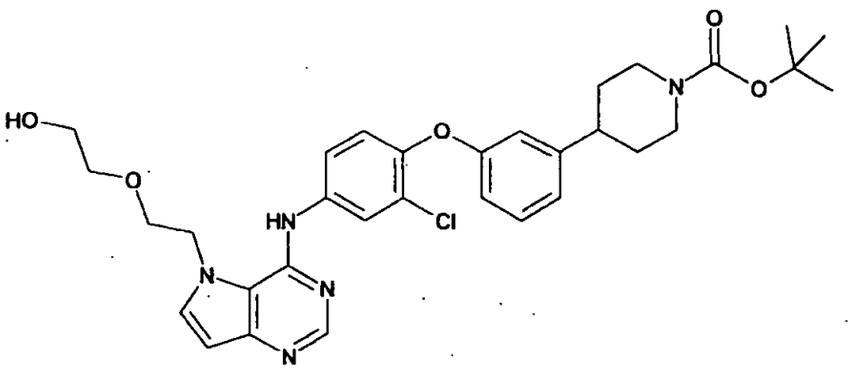


Production of N-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}propanamide

Using 2-[2-(4-{[4-(3-aminophenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate dihydrochloride (200 mg), propionic acid (0.5 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (560 mg), 1-hydroxybenzotriazole (67 mg), triethylamine (2.1 mL), tetrahydrofuran (10 mL), 1N aqueous sodium hydroxide solution (2.0 mL), tetrahydrofuran (6.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-37, the title compound (70 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J= 7.5 Hz), 2.28 (2H, dd, J= 7.5 Hz), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.73 (1H, m), 6.51 (1H, d, J= 3.2 Hz), 6.63 (1H, d, J= 7.7 Hz), 7.15-7.32 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.92 (1H, s).

Example C-49



Production of tert-butyl 4-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}piperidine-1-carboxylate

(i) Production of tert-butyl 4-[3-(2-chloro-4-nitrophenoxy)phenyl]piperidine-1-carboxylate

2-Chloro-1-fluoro-4-nitrobenzene (7.27 g) and tert-butyl 4-(3-hydroxyphenyl)piperidine-1-carboxylate (11.5 g) were dissolved in N,N-dimethylformamide (42 mL), potassium carbonate (8.28 g) was added and the mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with water (300 mL). The organic layer was dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate=100/0→60/40) to give the title compound (17.6 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.50-1.70 (2H, m), 1.84 (2H, d, J= 13 Hz), 2.60-2.90 (3H,m), 4.23 (2H, m), 6.87 (1H, d, J= 9 Hz), 6.92 (2H, m), 7.12 (1H, d, J= 8 Hz), 7.37 (1H, m), 8.04 (1H, dd, J= 3 Hz, 9 Hz), 8.38 (1H, d, J= 3 Hz).

(ii) Production of tert-butyl 4-[3-(4-amino-2-chlorophenoxy)phenyl]piperidine-1-carboxylate

tert-Butyl 4-[3-(2-chloro-4-nitrophenoxy)phenyl]piperidine-1-carboxylate (1.9 g) was suspended in ethanol (43 mL)/water (4.81 mL), calcium chloride (270 mg) was added thereto and the mixture was dissolved by heating with stirring at 90°C for 10 min. Reduced iron (1.63 g) was added thereto, and the mixture was stirred with heating at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residual solid was diluted with ethyl acetate (150 mL) and washed with

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saturated brine (80 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate=80/20→60/40) to give the title compound (1.71 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.50-1.70 (2H, m), 1.80 (2H, d, J= 13 Hz), 2.58 (1H, m), 2.77 (2H, t, J= 13 Hz), 3.69 (2H, br s), 4.22 (2H, m), 6.57 (1H, dd, J= 3 Hz, 9 Hz), 6.60-6.90 (5H, m), 7.20 (1H, t, J= 8 Hz).

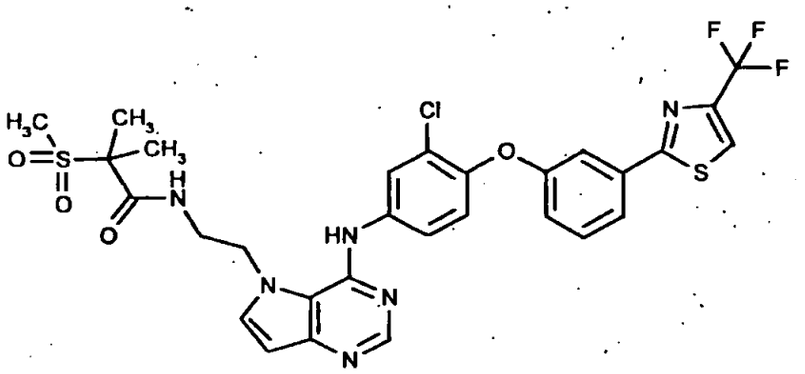
(iii) Production of tert-butyl 4-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}piperidine-1-carboxylate

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (150 mg), tert-butyl 4-[3-(4-amino-2-chlorophenoxy)phenyl]piperidine-1-carboxylate (260 mg) and isopropyl alcohol (1.5 mL) was stirred with heating at 80°C for 16 hr. The reaction mixture was diluted with ethyl acetate (80 mL), and washed with aqueous sodium bicarbonate (40 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=90/10→0/100), and the objective fractions were concentrated under reduced pressure. The obtained residue was dissolved in methanol (1.89 mL), 1N aqueous sodium hydroxide solution (0.433 mL) was added thereto and the mixture was stirred at room temperature for 2 hr. 1N hydrochloric acid (0.433 mL) was added, and the mixture was diluted with ethyl acetate (30 mL), and washed with saturated brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was subjected to basic silica gel column chromatography (ethyl acetate/methanol=100/0→85/15) to give the title compound

(88 mg) as a powder.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.50-1.80 (2H, m), 1.81 (2H, m), 2.61 (1H, m), 2.77 (2H, m), 3.72 (2H, m), 3.79 (2H, m), 4.01 (2H, t, J= 5 Hz), 4.21 (2H, m), 4.55 (2H, t, J= 5 Hz), 6.59 (1H, d, J= 3 Hz), 6.79 (2H, m), 6.90 (1H, d, J= 7.5 Hz), 7.00 (1H, d, J= 9 Hz), 7.18-7.30 (2H, m), 7.55 (1H, dd, J= 3 Hz, 9 Hz), 7.86 (1H, d, J= 3 Hz), 8.49 (1H, s), 8.78 (1H, br s).

Example C-50



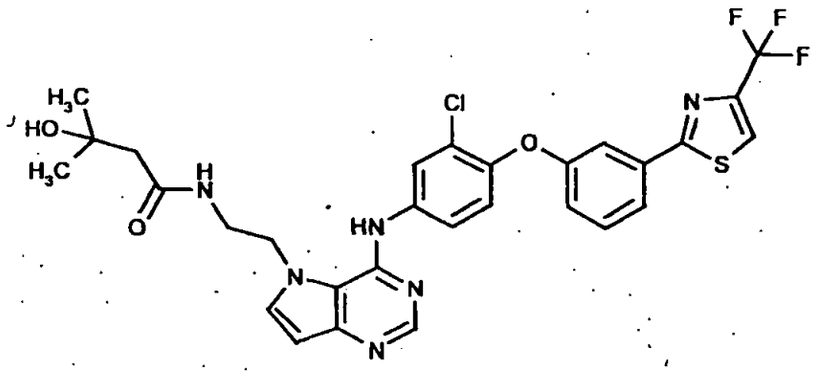
Production of N-(2-{4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-methyl-2-(methylsulfonyl)propanamide

Using 5-(2-aminoethyl)-N-(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (83 mg), 1-hydroxybenzotriazole (75 mg), triethylamine (0.23 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (105 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example C-8(iii), the title compound (171 mg) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.6-3.75 (2H, m), 4.40-4.55 (2H, m), 6.63 (1H, d, J = 3.3 Hz), 7.00-7.10 (1H, m), 7.09 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.25-7.45 (2H, m), 7.60-7.70 (2H, m),

7.75 (1H, s), 7.80-7.95 (1H, m), 8.04 (1H, d, J = 2.4 Hz), 8.36 (1H, s), 8.53 (1H, s).

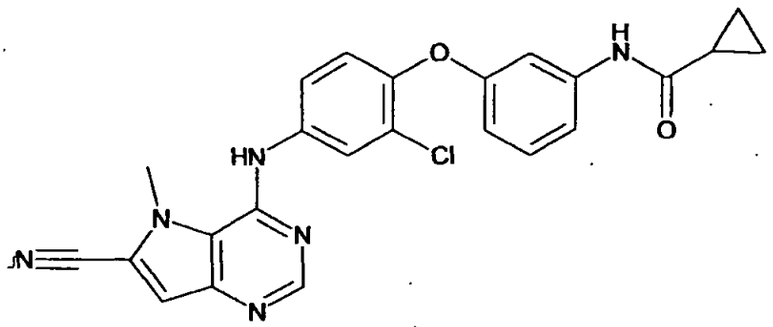
Example C-51



Production of N-(2-{4-[(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide

Using 5-(2-aminoethyl)-N-(3-chloro-4-{3-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 3-hydroxy-3-methylbutanoic acid (59 mg), 1-hydroxybenzotriazole (75 mg), triethylamine (0.23 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (105 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example C-8(iii), the title compound (95.3 mg) was obtained as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 2.48 (2H, s), 3.60-3.70 (2H, m), 4.40-4.50 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 7.00-7.10 (2H, m), 7.18 (1H, d, J = 3.0 Hz), 7.40 (1H, t, J = 9.0 Hz), 7.60-7.80 (4H, m), 8.07 (1H, s), 8.52 (1H, s), 8.63 (1H, s).

Example C-52



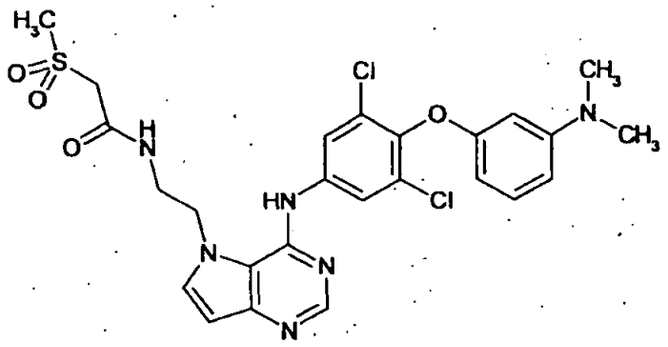
Production of N-{3-[2-chloro-4-[(6-cyano-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide

To a solution of diisopropylamine (545 mg) in tetrahydrofuran (15 mL) was added n-butyllithium (2.9 mL) at 0°C. After stirring for 30 min, the mixture was cooled to -78°C, and 4-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (603 mg) was added thereto. The mixture was stirred for 1 hr, p-toluenesulfonyl cyanide (1300 mg) was added thereto, and the mixture was warmed to -40°C over 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→30:70). After concentration under reduced pressure, resulting crystals were dissolved in isopropyl alcohol (7.0 mL). N-[3-(4-Amino-2-chlorophenoxy)phenyl]cyclopropanecarboxamide (232 mg) was added thereto, and the mixture was stirred at 80°C for 3 hr. After concentration under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were added 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 subjected to silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→0:100). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (103 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 0.77(4H, d, J= 6.1 Hz), 1.73-1.81 (1H, m), 4.31 (3H, s), 6.66-6.70 (1H, m), 7.21-7.40 (4H, m), 7.53 (1H, s), 7.62 (1H, d, J= 8.7 Hz), 7.90 (1H, s), 8.64 (1H, s), 9.87 (1H, br s), 10.25 (1H, s).

Example C-53



Production of N-{2-[4-({3,5-dichloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 3,5-dichloro-4-[3-(dimethylamino)phenoxy]aniline

To a solution of 3-(dimethylamino)phenol (470 mg) and 1,3-dichloro-2-iodo-5-nitrobenzene (1.00 g) in N,N-dimethylformamide (15 mL) was added potassium carbonate (850 mg) and the mixture was stirred at room temperature for 18 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) and the obtained crude

product was dissolved in 15% water-containing ethanol (23 mL). Reduced iron (750 mg) and calcium chloride (120 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (402 mg) as a brown oil.
^{1}H-NMR (DMSO-d_6) δ: 2.85 (6H, s), 5.58 (2H, s), 5.88 (1H, dd, J = 1.9 Hz, 8.0 Hz), 6.19 (1H, t, J = 2.2 Hz), 6.37 (1H, dd, J = 1.9 Hz, 8.0 Hz), 6.69 (2H, s), 7.04 (1H, t, J = 8.3 Hz).

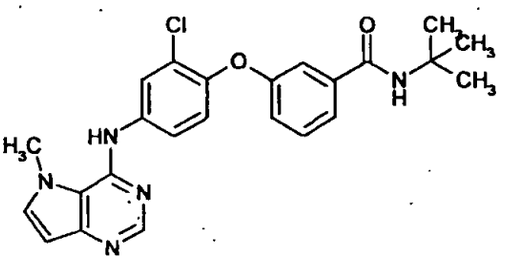
(ii) Production of N-{2-[4-({3,5-dichloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (150 mg), 3,5-dichloro-4-[3-(dimethylamino)phenoxy]aniline (150 mg) and isopropyl alcohol (8.0 mL) was stirred at 80°C for 12 hr. Under ice-cooling, to the reaction mixture was added aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0), the obtained crude product (150 mg) was dissolved in tetrahydrofuran (10 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL) was added, and the mixture was stirred at 70°C for 20 hr. The solvent was evaporated under reduced pressure,

ethanol and diisopropyl ether were added to the residue, and precipitated powder was collected by filtration and dissolved in N,N-dimethylformamide (7.0 mL). Methylsulfonylacetic acid (70 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (160 mg), 1-hydroxybenzotriazole (70 mg) and triethylamine (0.15 mL) were added to the mixture, and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=90:10), and crystallized from diisopropyl ether to give the title compound (74 mg).

^{1}H-NMR (DMSO-d_6) δ: 2.89 (6H, s), 3.11 (3H, s), 3.44-3.49 (2H, m), 4.06 (2H, s), 4.55-4.59 (2H, m), 5.89-7.11 (5H, m), 7.66-8.69 (5H, m), 8.77 (1H, s).

Example C-54



Production of N-(tert-butyl)-3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzamide

(i) Production of methyl 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzoate

A mixture of 4-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (1.01 g), methyl 3-(4-amino-2-chlorophenoxy)benzoate (1.39 g) and isopropyl alcohol (10 mL) was stirred at 80°C overnight. An aqueous sodium

hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The objective fractions were concentrated under reduced pressure. Ethyl acetate-diethyl ether was added to the residue, and the precipitated solid was collected by filtration to give the title compound (1.77 g) as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 4.15 (3H, s), 6.56 (1H, d, J = 3.3 Hz), 6.83 (1H, br s), 7.06 (1H, d, J = 8.8 Hz), 7.16-7.22 (2H, m), 7.40 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.56-7.60 (1H, m), 7.74-7.79 (1H, m), 7.81 (1H, d, J = 2.5 Hz), 8.51 (1H, s).

(ii) Production of 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzoic acid

To methyl 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzoate (1.68 g) were added methanol (20 mL), tetrahydrofuran (5 mL) and 1N aqueous sodium hydroxide solution (8.2 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, 1N hydrochloric acid (8.2 mL), ethyl acetate and diisopropyl ether were added thereto. The precipitated solid was collected by filtration, washed with water and diisopropyl ether to give the title compound (1.62 g) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 4.16 (3H, s), 6.45 (1H, d, J = 3.0 Hz), 7.24-7.32 (3H, m), 7.51 (1H, t, J = 8.0 Hz), 7.60 (1H, d, J = 3.0 Hz), 7.64-7.73 (2H, m), 7.96 (1H, d, J = 2.4 Hz), 8.32 (1H, s), 8.62 (1H, br s).

(iii) Production of N-(tert-butyl)-3-{2-chloro-4-[(5-

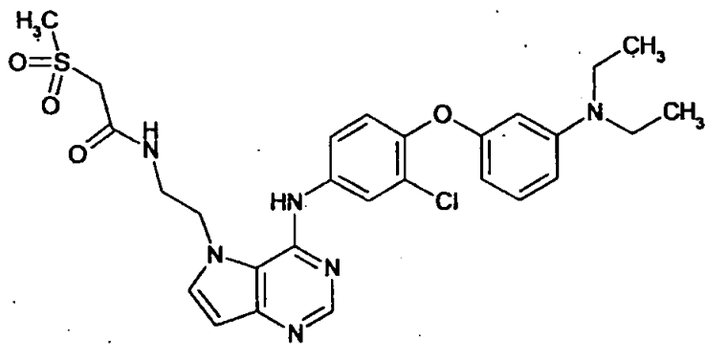
215

methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzamide

A mixture of 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzoic acid (197 mg), tert-butylamine (0.105 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (215 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 4.15 (3H, s), 5.96 (1H, br s), 6.56 (1H, d, J = 3.0 Hz), 6.85 (1H, br s), 7.02 (1H, d, J = 8.5 Hz), 7.05-7.10 (1H, m), 7.18 (1H, d, J = 3.0 Hz), 7.31-7.44 (4H, m), 7.80 (1H, d, J = 2.5 Hz), 8.50 (1H, s).

Example C-55



Production of N-{2-[4-({3-chloro-4-[3-(diethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 3-(4-amino-2-chlorophenoxy)-N,N-diethylaniline

Using 3-(diethylamino)phenol (920 mg), 3-chloro-4-fluoronitrobenzene (1.01 g), potassium carbonate (1.38 g), N,N-dimethylformamide (20 mL), 5% platinum-activated carbon (300 mg), ethyl acetate (10 mL) and methanol (5.0 mL) and in the same manner as in Example C-6(iv) and (v), the title compound (954 mg) was obtained as crystals.

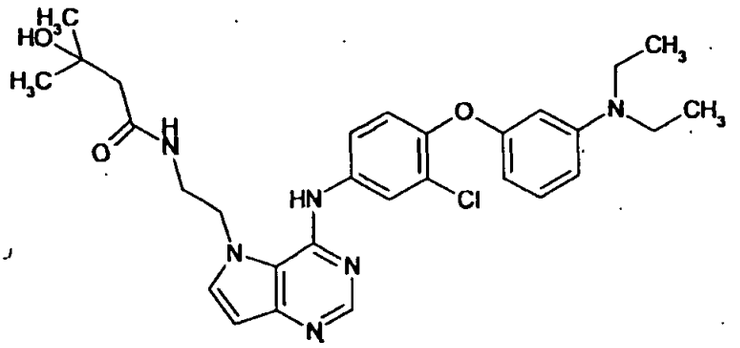
^{1}H-NMR (DMSO-d_6) δ: 1.06-1.12 (6H, m), 3.25-3.34 (4H, m), 5.26 (2H, s), 5.94-6.57 (4H, m), 6.68 (1H, d, J = 2.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.12 (1H, t, J = 8.3 Hz).

(ii) Production of N-{2-[4-({3-chloro-4-[3-(diethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3-(4-amino-2-chlorophenoxy)-N,N-diethylaniline (150 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (150 mg), isopropyl alcohol (10 mL), tetrahydrofuran (15 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL), methylsulfonylacetic acid (190 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (290 mg), 1-hydroxybenzotriazole (10 mg), triethylamine (4.0 mL) and N,N-dimethylformamide (15 mL) and in the same manner as in Example C-53(ii), the title compound (117 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.05-1.10 (6H, m), 3.10 (3H, s), 3.27-3.34 (4H, m), 3.44-3.49 (2H, m), 4.05 (2H, s), 4.53-4.57 (2H, m), 6.00-6.49 (4H, m), 7.07-7.91 (5H, m), 8.32 (1H, s), 8.62-8.68 (2H, m).

Example C-56

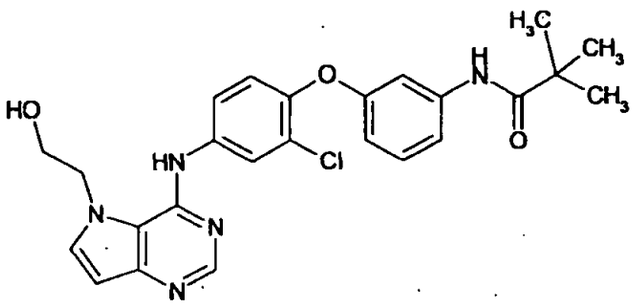


Production of N-{2-[4-({3-chloro-4-[3-(diethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide

Using 3-(4-amino-2-chlorophenoxy)-N,N-diethylaniline (150 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (150 mg), isopropyl alcohol (10 mL), tetrahydrofuran (15 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL), 3-hydroxy-3-methylbutanoic acid (75 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (191 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (0.3 mL) and N,N-dimethylformamide (6 mL) and in the same manner as in Example C-53(ii), the title compound (94 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.05-1.17 (12H, m), 2.20 (2H, s), 3.24-3.34 (4H, m), 3.37-3.44 (2H, m), 4.48-4.53 (2H, m), 4.65 (1H, s), 6.01-6.48 (4H, m), 7.06-7.97 (5H, m), 8.22-8.26 (1H, m), 8.31 (1H, s), 8.80 (1H, s).

Example C-57



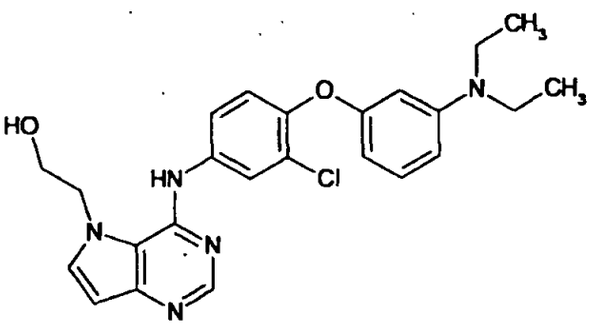
Production of N-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2,2-dimethylpropanamide

A mixture of N-[3-(4-amino-2-chlorophenoxy)phenyl]-2,2-dimethylpropanamide (70 mg) and 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (63 mg) was dissolved in isopropyl alcohol (3 mL), pyridine hydrochloride (5 mg) was added thereto, and the mixture was stirred at 80°C for 16 hr. The reaction mixture was cooled to room temperature, 1N aqueous sodium hydroxide solution (2 mL) was added thereto, and the mixture was stirred at room temperature for 9 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=10:90→0:100→ethyl acetate:methanol=90:10), and crystallized from diisopropyl ether/ethyl acetate to give the title compound (49 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.16 (9H, s), 3.86-3.89 (2H, m), 4.52-4.55 (2H, m), 6.50-6.66 (2H, m), 7.18-7.97 (7H, m), 8.33 (1H, s), 9.22 (1H, s), 9.83 (1H, br s).

Example C-58

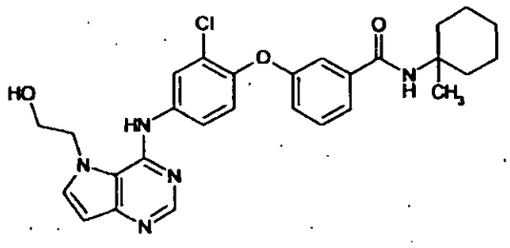


Production of 2-[4-({3-chloro-4-[3-(diethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 3-(4-amino-2-chlorophenoxy)-N,N-diethylaniline (112 mg), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg), isopropyl alcohol (5.0 mL), 1N aqueous sodium hydroxide solution (5.0 mL) and methanol (10 mL) and in the same manner as in Example C-57, the title compound (52 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.05-1.09 (6H, m), 3.26-3.33 (4H, m), 3.85-3.88 (2H, m), 4.51-4.54 (2H, m), 5.99-6.41 (3H, m), 6.49 (1H, d, J = 3.0 Hz), 7.05-7.94 (5H, m), 8.32 (1H, s), 9.76 (1H, br s).

Example C-59

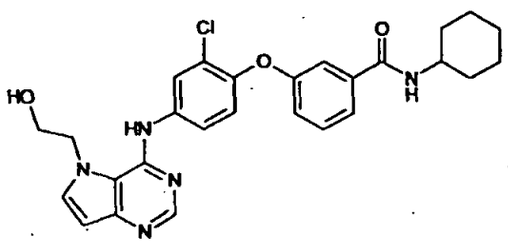


Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-methylcyclohexyl)benzamide

A mixture of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 1-methylcyclohexaneamine hydrochloride (180 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg), triethylamine (0.170 mL) and N,N-dimethylformamide (5 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl

acetate=0:100→20:80) and silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80), and the objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (92 mg) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.70 (13H, m), 2.05-2.20 (2H, m), 4.07-4.17 (2H, m), 4.35-4.42 (2H, m), 5.86 (1H, br s), 6.14 (1H, d, J= 3.3 Hz), 6.68 (1H, br s), 6.97-7.12 (3H, m), 7.30-7.45 (4H, m), 7.81 (1H, d, J= 2.4 Hz), 8.23 (1H, s), 9.69 (1H, br s).

Example C-60

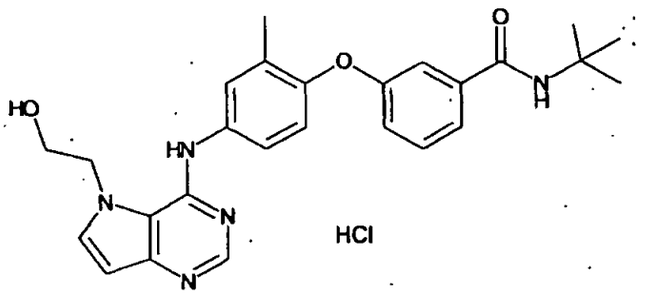


Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-cyclohexylbenzamide

A mixture of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), cyclohexanamine (119 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg) and N,N-dimethylformamide (5 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were

concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (178 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 1.10-1.82 (8H, m), 1.95-2.07 (2H, m), 3.86-4.01 (1H, m), 4.01-4.18 (2H, m), 4.37-4.44 (2H, m), 6.03 (1H, d, J= 8.1 Hz), 6.04-6.12 (1H, m), 6.22 (1H, d, J= 3.0 Hz), 6.98-7.11 (3H, m), 7.32-7.44 (4H, m), 7.79 (1H, d, J= 2.7 Hz), 8.28 (1H, s), 9.57 (1H, br s).

Example C-61



Production of N-(tert-butyl)-3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)benzamide hydrochloride

(i) Production of methyl 3-(2-methyl-4-nitrophenoxy)benzoate

A mixture of methyl 3-hydroxybenzoate (3.04 g), 2-fluoro-5-nitrotoluene (3.10 g), potassium carbonate (4.15 g) and N,N-dimethylformamide (20 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=5:95→15:85). The objective fractions were concentrated under reduced pressure to give the title compound (5.66 g) as a pale-yellow solid.
^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.91 (3H, s), 6.78 (1H,

d, J = 8.9 Hz), 7.21-7.27 (1H, m), 7.49 (1H, t, J = 7.8 Hz), 7.65-7.68 (1H, m), 7.86-7.91 (1H, m), 8.01 (1H, dd, J = 2.8 Hz, 8.9 Hz), 8.17 (1H, d, J = 2.8 Hz).

(ii) Production of 3-(2-methyl-4-nitrophenoxy)benzoic acid

To methyl 3-(2-methyl-4-nitrophenoxy)benzoate (5.66 g) were added isopropyl alcohol (100 mL) and 1N aqueous sodium hydroxide solution (22 mL) and the mixture was stirred at room temperature overnight. To the reaction mixture was added 1N hydrochloric acid (25 mL) and the precipitated solid was collected by filtration, and washed with water to give the title compound (4.54 g) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 6.81 (1H, d, J = 8.9 Hz), 7.26-7.32 (1H, m), 7.52 (1H, t, J = 7.9 Hz), 7.70-7.74 (1H, m), 7.92-7.97 (1H, m), 8.02 (1H, dd, J = 2.9 Hz, 8.9 Hz), 8.17 (1H, d, J = 2.9 Hz).

(iii) Production of N-(tert-butyl)-3-(2-methyl-4-nitrophenoxy)benzamide

A mixture of 3-(2-methyl-4-nitrophenoxy)benzoic acid (820 mg), thionyl chloride (0.438 mL), N,N-dimethylformamide (one drop) and toluene (10 mL) was stirred at 80°C for 2 hr. Thionyl chloride (0.656 mL) was added and the mixture was further stirred for 1 hr. The reaction mixture was concentrated under reduced pressure, toluene was added, and the mixture was concentrated again under reduced pressure. A solution of the residue in tetrahydrofuran (5 mL) was added to a solution of tert-butylamine (439 mg) and triethylamine (0.627 mL) in tetrahydrofuran (10 mL) and the mixture was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=10:90→30:70). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (948 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.40 (3H, s), 5.93 (1H, br s), 6.79 (1H, d, J = 8.9 Hz), 7.14 (1H, ddd, J = 1.2 Hz, 2.5 Hz, 7.8 Hz), 7.40-7.53 (3H, m), 8.00 (1H, dd, J = 2.8 Hz, 8.9 Hz), 8.15 (1H, d, J = 2.8 Hz).

(iv) Production of 3-(4-amino-2-methylphenoxy)-N-(tert-butyl)benzamide

To a solution of N-(tert-butyl)-3-(2-methyl-4-nitrophenoxy)benzamide (948 mg) in ethyl acetate (20 mL) was added 5% platinum-activated carbon (50 mg) and the mixture was stirred under a hydrogen atmosphere at room temperature for 6 hr. The catalyst was filtered off, the filtrate was concentrated and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=25:75→45:55). The objective fractions were concentrated under reduced pressure to give the title compound (892 mg) as a red purple oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.08 (3H, s), 3.56 (2H, br s), 5.89 (1H, br s), 6.51 (1H, dd, J = 2.5 Hz, 8.4 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.77 (1H, d, J = 8.4 Hz), 6.87-6.94 (1H, m), 7.22-7.30 (3H, m).

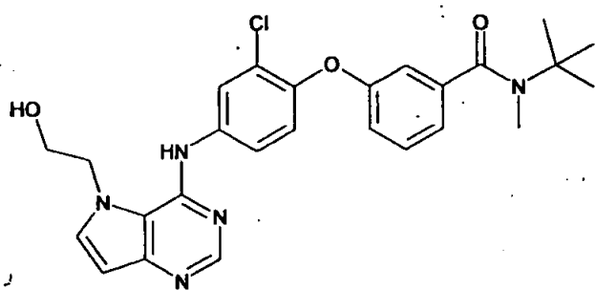
(v) Production of N-(tert-butyl)-3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)benzamide hydrochloride

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (121 mg), 3-(4-amino-2-methylphenoxy)-N-(tert-butyl)benzamide (119 mg) and isopropyl alcohol (5 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether, and collected by filtration. To the obtained powder were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and the mixture was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol and 1N hydrogen chloride/ethyl acetate solution (0.4 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (139 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.20 (3H, s), 3.90 (2H, t, J = 4.4 Hz), 4.69 (2H, t, J = 4.4 Hz), 6.30-6.55 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 7.02-7.12 (2H, m), 7.28-7.32 (1H, m), 7.43 (1H, t, J = 8.0 Hz), 7.48-7.59 (3H, m), 7.81 (1H, br s), 7.99 (1H, d, J = 3.0 Hz), 8.72 (1H, s), 10.77 (1H, br s).

Example C-62



Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-methylbenzamide

(i) Production of methyl 3-(2-chloro-4-nitrophenoxy)benzoate

Using methyl 3-hydroxybenzoate (8.20 g), 2-chloro-1-fluoro-4-nitrobenzene (9.46 g), potassium carbonate (11.2 g) and N,N-dimethylformamide (50 mL) and in the same manner as in Example C-61(i), the title compound (16.0 g) was obtained as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 6.91 (1H, d, J = 9.1 Hz), 7.29 (1H, ddd, J = 0.8 Hz, 2.6 Hz, 8.0 Hz), 7.52 (1H, t, J = 8.0 Hz), 7.70-7.73 (1H, m), 7.91-7.97 (1H, m), 8.07 (1H, dd, J = 2.8 Hz, 9.1 Hz), 8.39 (1H, d, J = 2.8 Hz).

(ii) Production of 3-(2-chloro-4-nitrophenoxy)benzoic acid

Using methyl 3-(2-chloro-4-nitrophenoxy)benzoate (7.08 g), isopropyl alcohol (150 mL), tetrahydrofuran (50 mL) and 1N aqueous sodium hydroxide solution (25.3 mL) and in the same manner as in Example C-61(ii), the title compound (5.31 g) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 6.94 (1H, d, J = 9.0 Hz), 7.31-7.37 (1H, m), 7.56 (1H, t, J = 8.0 Hz), 7.76-7.79 (1H, m), 7.97-8.03 (1H, m), 8.09 (1H, dd, J = 2.6 Hz, 9.0 Hz), 8.40 (1H, d, J = 2.6 Hz).

(iii) Production of N-(tert-butyl)-3-(2-chloro-4-nitrophenoxy)-N-methylbenzamide

Using 3-(2-chloro-4-nitrophenoxy)benzoic acid (881 mg), thionyl chloride (1.09 mL), N,N-dimethylformamide

(one drop), toluene (10 mL), tetrahydrofuran (5 mL), N-methyl-tert-butylamine (523 mg), triethylamine (0.627 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-61(iii), the title compound (1.14 g) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.87 (3H, s), 6.92 (1H, d, J = 9.1 Hz), 7.08-7.16 (2H, m), 7.30-7.35 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.38 (1H, d, J = 2.6 Hz).

(iv) Production of 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)-N-methylbenzamide

Using N-(tert-butyl)-3-(2-chloro-4-nitrophenoxy)-N-methylbenzamide (1.14 g), ethyl acetate (20 mL) and 5% platinum-activated carbon (50 mg) and in the same manner as in Example C-61(iv), the title compound (868 mg) was obtained as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.84 (3H, s), 3.69 (2H, br s), 6.55 (1H, dd, J = 2.8 Hz, 8.7 Hz), 6.76 (1H, d, J = 2.8 Hz), 6.86-6.93 (3H, m), 7.03-7.08 (1H, m), 7.27 (1H, t, J = 7.8 Hz).

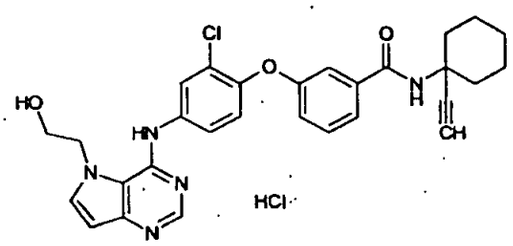
(v) Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-methylbenzamide

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (121 mg), 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)-N-methylbenzamide (133 mg) and isopropyl alcohol (5 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The objective fractions

were concentrated under reduced pressure. To the residue were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (173 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.86 (3H, s), 4.09 (2H, t, J = 4.5 Hz), 4.38 (2H, t, J = 4.5 Hz), 6.19 (1H, d, J = 3.3 Hz), 6.50-6.90 (1H, m), 6.95-7.03 (4H, m), 7.04-7.09 (1H, m), 7.26-7.39 (2H, m), 7.82 (1H, d, J = 2.5 Hz), 8.26 (1H, s), 9.73 (1H, br s).

Example C-63



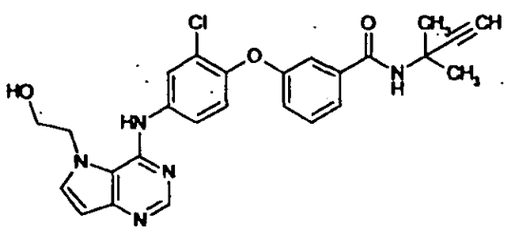
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-ethynylcyclohexyl)benzamide hydrochloride

A mixture of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 1-ethynylcyclohexaneamine (148 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg) and N,N-

dimethylformamide (5 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.4 mL) was added thereto. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (160 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.37 (1H, m), 1.43-1.64 (5H, m), 1.71-1.88 (2H, m), 2.04-2.18 (2H, m), 3.16 (1H, s), 3.85-3.95 (2H, m), 4.64-4.74 (2H, m), 6.20-6.40 (1H, m), 6.70 (1H, d, J = 3.0 Hz), 7.17 (1H, dd, J = 2.3 Hz, 8.1 Hz), 7.27-7.35 (2H, m), 7.48 (1H, t, J = 8.0 Hz), 7.57-7.65 (2H, m), 7.94 (1H, d, J = 2.5 Hz), 7.98-8.03 (1H, m), 8.17 (1H, br s), 8.76 (1H, s), 10.76-10.86 (1H, m).

Example C-64



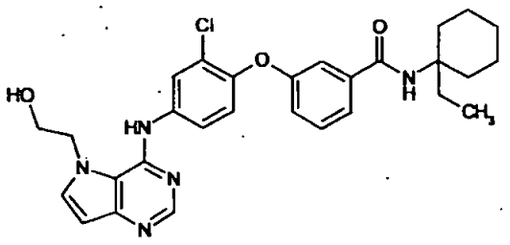
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1,1-dimethylprop-2-yn-1-yl)benzamide

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 3-amino-3-methyl-1-butyne (120 mg), 1-ethyl-3-

(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-59, the title compound (155 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, s), 2.37 (1H, s), 4.13 (2H, t, J = 4.3 Hz), 4.39 (2H, t, J = 4.3 Hz), 6.15 (1H, d, J = 3.3 Hz), 6.25 (1H, br s), 6.45 (1H, br s), 6.98-7.03 (2H, m), 7.08-7.14 (1H, m), 7.31-7.45 (4H, m), 7.78 (1H, d, J = 2.5 Hz), 8.23 (1H, s), 9.62 (1H, br s).

Example C-65

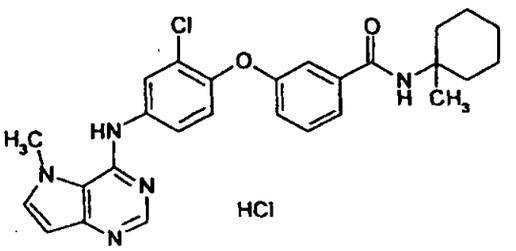


Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-ethylcyclohexyl)benzamide

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 1-ethylcyclohexaneamine (153 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole monohydrate (92 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-59, the title compound (136 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J = 7.4 Hz), 1.20-1.70 (8H, m), 1.88 (2H, q, J = 7.4 Hz), 2.10-2.21 (2H, m), 4.12 (2H, t, J = 4.5 Hz), 4.38 (2H, t, J = 4.5 Hz), 5.70 (1H, br s), 6.15 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.99 (1H, d, J = 3.0 Hz), 7.02 (1H, d, J = 8.8 Hz), 7.04-7.11 (1H, m), 7.30-7.44 (4H, m), 7.80 (1H, d, J = 2.5 Hz), 8.23 (1H, s), 9.64 (1H, br s).

Example C-66

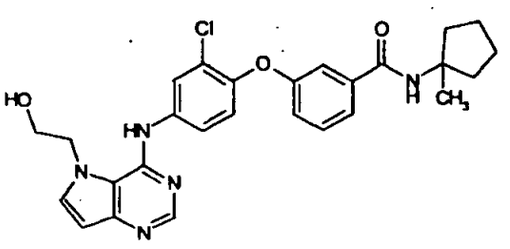


Production of 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}-N-(1-methylcyclohexyl)benzamide hydrochloride

Using 3-{2-chloro-4-[(5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzoic acid (197 mg), 1-methylcyclohexaneamine hydrochloride (150 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg), 1-hydroxybenzotriazole monohydrate (115 mg), triethylamine (0.139 mL) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-63, the title compound (178 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.18-1.57 (8H, m), 1.31 (3H, s), 2.13-2.29 (2H, m), 4.29 (3H, s), 6.62-6.65 (1H, m), 7.16 (1H, dd, J = 2.6 Hz, 8.1 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.33 (1H, m), 7.48 (1H, t, J = 8.0 Hz), 7.55-7.68 (3H, m), 7.91-7.98 (2H, m), 8.71 (1H, s), 9.78-9.94 (1H, m).

Example C-67



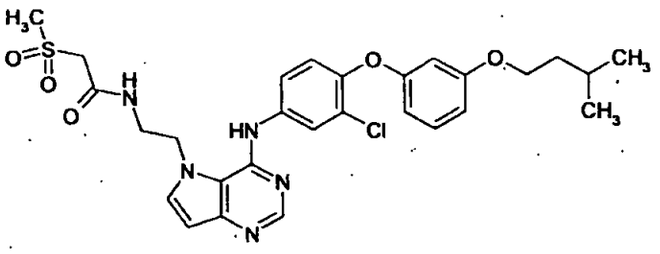
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-methylcyclopentyl)benzamide

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid

(212 mg), 1-methylcyclopentaneamine hydrochloride (136 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg), 1-hydroxybenzotriazole (101 mg), triethylamine (0.139 mL) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-59, the title compound (162 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 1.65-1.82 (6H, m), 1.98-2.13 (2H, m), 4.12 (2H, t, J = 4.4 Hz), 4.39 (2H, t, J = 4.4 Hz), 6.06 (1H, br s), 6.17 (1H, d, J = 3.0 Hz), 6.52 (1H, br s), 7.00 (1H, d, J = 3.0 Hz), 7.01 (1H, d, J = 8.8 Hz), 7.05-7.12 (1H, m), 7.30-7.37 (3H, m), 7.41 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.6 Hz), 8.24 (1H, s), 9.66 (1H, br s).

Example C-68



Production of N-{2-[4-({3-chloro-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 3-chloro-4-[3-(3-methylbutoxy)phenoxy]aniline

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol (1.0 g) and 1-iodo-3-methylbutane (1.0 mL) in N,N-dimethylformamide (20 mL) was added cesium carbonate (1.6 g) and the mixture was stirred at room temperature for 2 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent,

hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (25 mL), reduced iron (1.60 g) and calcium chloride (220 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (806 mg) as a brown oil.

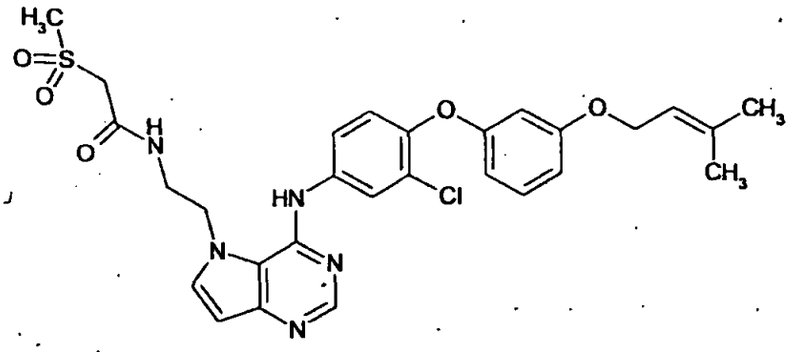
^{1}H-NMR (DMSO-d_6) δ: 0.89-0.92 (6H, m), 1.53-1.60 (2H, m), 1.70-1.79 (1H, m), 3.91-3.95 (2H, m), 5.33 (2H, s), 6.31-6.33 (2H, m), 6.53-6.60 (2H, m), 6.71-6.72 (1H, m), 6.88-6.91 (1H, m), 7.14-7.20 (1H, m).

(ii) Production of N-{2-[4-({3-chloro-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3-chloro-4-[3-(3-methylbutoxy)phenoxy]aniline (250 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (250 mg), isopropyl alcohol (20 mL), ethyl acetate (10 mL), 4N hydrogen chloride/ethyl acetate solution (15 mL), methylsulfonylacetic acid (72 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (187 mg), 1-hydroxybenzotriazole (10 mg), triethylamine (1.5 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-53(ii), the title compound (277 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.91-0.93 (6H, m), 1.56-1.78 (3H, m), 3.10 (3H, s), 3.42-3.49 (2H, m), 3.95-4.05 (4H, m), 4.52-4.60 (2H, m), 6.43-6.70 (4H, m), 7.16-7.94 (5H, m), 8.34 (1H, s), 8.64-8.68 (2H, m).

Example C-69



Production of N-(2-{4-[(3-chloro-4-{3-[(3-methylbut-2-en-1-yl)oxy]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide

(i) Production of 3-chloro-4-{3-[(3-methylbut-2-en-1-yl)oxy]phenoxy}aniline

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol (1.0 g) and 1-bromo-3-methylbut-2-ene (1.5 mL) in N,N-dimethylformamide (20 mL) was added cesium carbonate (1.8 g) and the mixture was stirred at room temperature for 2 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (25 mL), reduced iron (1.60 g) and calcium chloride (220 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column

chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (730 mg) as a brown oil.

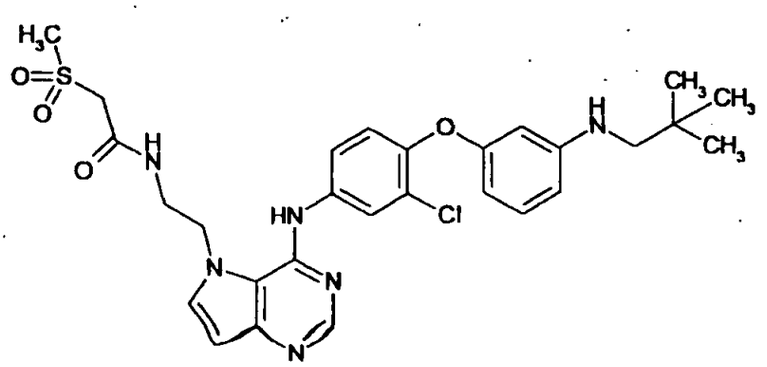
^{1}H-NMR (DMSO-d_6) δ: 1.62-1.71 (6H, m), 4.42-4.47 (2H, m), 5.32-5.36 (1H, m), 6.32-6.35 (2H, m), 6.56-6.59 (2H, m), 6.71-6.72 (1H, m), 6.87-6.90 (1H, m), 7.13-7.19 (1H, m).

(ii) Production of N-(2-{4-[(3-chloro-4-{3-[(3-methylbut-2-en-1-yl)oxy]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide

Using 3-chloro-4-{3-[(3-methylbut-2-en-1-yl)oxy]phenoxy}aniline (150 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (150 mg), isopropyl alcohol (16 mL), ethyl acetate (10 mL), 4N hydrogen chloride/ethyl acetate solution (5 mL), methylsulfonylacetic acid (120 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (470 mg), 1-hydroxybenzotriazole (10 mg), triethylamine (1.5 mL) and N,N-dimethylformamide (15 mL) and in the same manner as in Example C-53(ii), the title compound (108 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.75-1.79 (6H, m), 3.10 (3H, s), 3.40-3.52 (2H, m), 4.03 (2H, s), 4.47-4.60 (4H, m), 5.40-5.51 (1H, m), 6.40-6.70 (4H, m), 7.15-7.95 (5H, m), 8.35 (1H, s), 8.62-8.70 (2H, m).

Example C-70



Production of N-(2-{4-[(3-chloro-4-{3-[(2,2-dimethylpropyl)amino]phenoxy}phenyl)amino]-5H-

pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide

(i) Production of 3-(2-chloro-4-nitrophenoxy)-N-(2,2-dimethylpropyl)aniline

3-(2-Chloro-4-nitrophenoxy)aniline hydrochloride (1.98 g) was suspended in tetrahydrofuran (80 mL), and triethylamine (0.87 mL), acetic acid (6.0 mL) and pivalaldehyde (2.10 g) were added thereto, and the mixture was stirred for 30 min. Sodium triacetoxyborohydride (470 mg) was added, and the mixture was further stirred for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was separated and purified by basic silica gel column chromatography (eluent, hexane:ethyl acetate=95:5→1:1) to give the title compound (1.79 g) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 2.89 (2H, s), 6.31-6.54 (3H, m), 6.89-7.26 (3H, m), 8.01-8.09 (1H, m), 8.37 (1H, s).

(ii) Production of 3-chloro-4-{3-[(2,2-dimethylpropyl)amino]phenoxy}aniline

3-(2-Chloro-4-nitrophenoxy)-N-(2,2-dimethylpropyl)aniline (1.0 g) was dissolved in 15% water-containing ethanol (30 mL), reduced iron (800 mg) and calcium chloride (100 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified

by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (737 mg) as a brown oil.

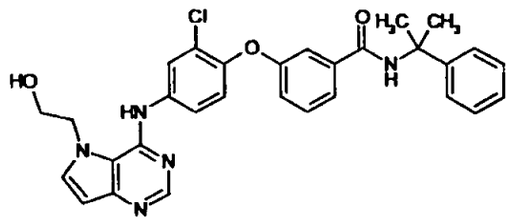
^{1}H-NMR (DMSO-d_6) δ: 0.95 (9H, s), 2.78-2.82 (2H, m), 6.31-6.54 (3H, m), 6.89-7.26 (3H, m), 8.01-8.09 (1H, m), 8.37 (1H, s).

(iii) Production of N-(2-{4-[(3-chloro-4-{3-[(2,2-dimethylpropyl)amino]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide

Using 3-chloro-4-{3-[(2,2-dimethylpropyl)amino]phenoxy}aniline (73 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (71 mg), isopropyl alcohol (5 mL), ethyl acetate (10 mL), 4N hydrogen chloride/ethyl acetate solution (10 mL), methylsulfonylacetic acid (61 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (220 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (1.5 mL) and N,N-dimethylformamide (7.0 mL) and in the same manner as in Example C-53(ii), the title compound (48 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.93 (9H, s), 2.76-2.79 (2H, m), 3.10 (3H, s), 3.42-3.48 (2H, m), 4.05 (2H, s), 4.53-4.59 (2H, m), 5.61-6.50 (5H, m), 6.98-7.12 (2H, m), 7.61-7.91 (3H, m), 8.33 (1H, s), 8.64-8.68 (2H, m).

Example C-71



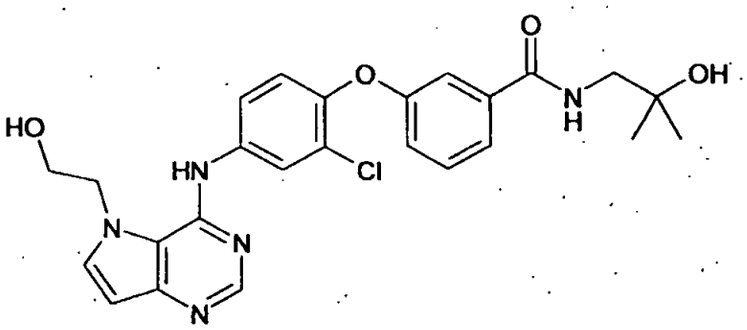
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-methyl-1-phenylethyl)benzamide

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), cumylamine (108 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole (81 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-59, the title compound (139 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.79 (6H, s), 4.02 (2H, t, J = 4.5 Hz), 4.32 (2H, t, J = 4.5 Hz), 6.16 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.95-7.00 (2H, m), 7.07-7.13 (1H, m), 7.17-7.46 (9H, m), 7.77 (1H, d, J = 2.5 Hz), 8.22 (1H, s), 9.66 (1H, br s).

Example C-72



Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(2-hydroxy-2-methylpropyl)benzamide

(i) Production of 3-(2-chloro-4-nitrophenoxy)-N-(2-hydroxy-2-methylpropyl)benzamide

3-(2-Chloro-4-nitrophenoxy)benzoic acid (500 mg) was dissolved in a mixed solvent of tetrahydrofuran (5 mL)/N,N-dimethylformamide (5 mL), and 1-amino-2-methylpropan-2-ol (199 mg), 1-hydroxybenzotriazole (347 mg), triethylamine (0.7 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (496 mg) were added successively, and the mixture was stirred at room temperature for 2.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate

and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=33:67→0:100) to give the title compound (448 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, s), 3.48 (2H, d, J= 5.8 Hz), 6.60 (1H, br s), 6.92 (1H, d, J= 9.1 Hz), 7.19-7.25 (1H, m), 7.47-7.58 (2H, m), 7.61-7.69 (1H, m), 8.07 (1H, dd, J= 2.8 Hz, 9.1 Hz), 8.39 (1H, d, J= 2.8 Hz).

(ii) Production of 3-(4-amino-2-chlorophenoxy)-N-(2-hydroxy-2-methylpropyl)benzamide

3-(2-Chloro-4-nitrophenoxy)-N-(2-hydroxy-2-methylpropyl)benzamide (446 mg) was dissolved in a mixed solvent of ethanol (13.5 mL)/water (1.5 mL), reduced iron (347 mg) and calcium chloride (68 mg) were added, and the mixture was stirred with heating under reflux for 15 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=33:67→0:100) to give the title compound (349 mg) as a colorless oil.

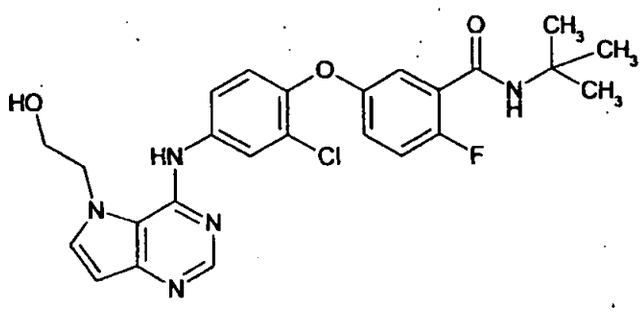
^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, s), 2.38 (1H, br s), 3.44 (2H, d, J= 6.0 Hz), 3.71 (2H, br s), 6.53-6.64 (1H, m), 6.57 (1H, dd, J= 2.8 Hz, 8.7 Hz), 6.78 (1H, d, J= 2.8 Hz), 6.90 (1H, d, J= 8.7 Hz), 6.97-7.03 (1H, m), 7.29-7.37 (2H, m), 7.38-7.44 (1H, m).

(iii) Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(2-hydroxy-2-methylpropyl)benzamide

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (84.3 mg) and 3-(4-amino-2-chlorophenoxy)-N-(2-hydroxy-2-

methylpropyl)benzamide (110 mg) was dissolved in isopropyl alcohol (2 mL), a catalytic amount of pyridine hydrochloride was added thereto, and the mixture was stirred at 70°C for 16 hr. After cooling to room temperature, 1N aqueous sodium hydroxide solution (1 mL) was added thereto, and the mixture was stirred at room temperature for 9 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=10:90→0:100→ethyl acetate:methanol=90:10), and crystallized from diisopropyl ether/ethyl acetate to give the title compound (99.7 mg) as white crystals.
^{1}H-NMR (DMSO-d_6) δ: 1.09 (6H, s), 3.23 (2H, d, J= 6.0 Hz), 3.87 (2H, t, J= 4.5 Hz), 4.47-4.61 (3H, m), 6.30 (1H, br s), 6.51 (1H, d, J= 3.0 Hz), 7.05-7.13 (1H, m), 7.24 (1H, d, J= 8.9 Hz), 7.36-7.42 (1H, m), 7.46 (1H, t, J= 7.9 Hz), 7.56-7.64 (2H, m), 7.66 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 2.6 Hz), 8.31 (1H, t, J= 6.0 Hz), 8.34 (1H, s), 9.87 (1H, br s).

Example C-73



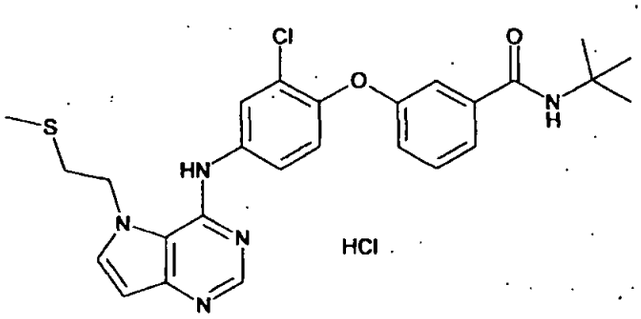
Production of N-(tert-butyl)-5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluorobenzamide

Using 5-(4-amino-2-chlorophenoxy)-N-(tert-butyl)-2-

fluorobenzamide (260 mg), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (150 mg), isopropyl alcohol (7.0 mL), 1N aqueous sodium hydroxide solution (4.0 mL) and methanol (10 mL) and in the same manner as in Example C-57, the title compound (285 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.33 (9H, s), 3.85-3.89 (2H, m), 4.51-4.54 (2H, m), 6.50-7.29 (5H, m), 7.58-7.97 (4H, m), 8.33 (1H, s), 9.76(1H, br s).

Example C-74



Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide hydrochloride

(i) Production of 4-chloro-5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidine

A mixture of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (768 mg), 2-chloroethyl methylsulfide (664 mg), cesium carbonate (1.95 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. 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. To a mixture of the obtained residue, cesium carbonate (3.91 g) and N,N-dimethylformamide (10 mL) was added dropwise a solution of 2-chloroethyl methylsulfide (553 mg) in N,N-dimethylformamide (3 mL) and the mixture was stirred at room temperature overnight. A solution of

2-chloroethyl methylsulfide (553 mg) in N,N-dimethylformamide (3 mL) was again added dropwise and the mixture was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=40:60→60:40). The objective fractions were concentrated under reduced pressure to give the title compound (880 mg) as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s), 2.95 (2H, t, J = 6.9 Hz), 4.67 (2H, t, J = 6.9 Hz), 6.75 (1H, d, J = 3.2 Hz), 7.56 (1H, d, J = 3.2 Hz), 8.71 (1H, s).

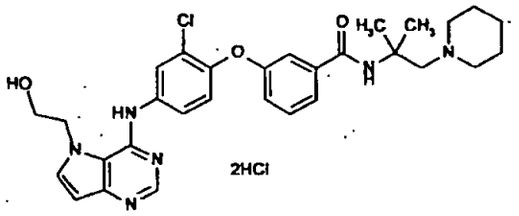
(ii) Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide hydrochloride

A mixture of 4-chloro-5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidine (455 mg), 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)benzamide (638 mg) and isopropyl alcohol (10 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure to give N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide (1.00 g) as an amorphous powder. The obtained N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylthio)ethyl]-5H-

pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide (200 mg) was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.5 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (138 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 1.99 (3H, s), 2.88 (2H, t, J = 6.4 Hz), 4.92 (2H, t, J = 6.4 Hz), 6.69 (1H, d, J = 3.2 Hz), 7.16 (1H, dd, J = 3.0 Hz, 7.7 Hz), 7.24 (1H, d, J = 8.8 Hz), 7.36-7.39 (1H, m), 7.47 (1H, t, J = 8.0 Hz), 7.57-7.65 (2H, m), 7.84 (1H, br s), 7.92 (1H, d, J = 2.5 Hz), 8.06 (1H, d, J = 3.2 Hz), 8.73 (1H, s), 10.06 (1H, br s).

Example C-75



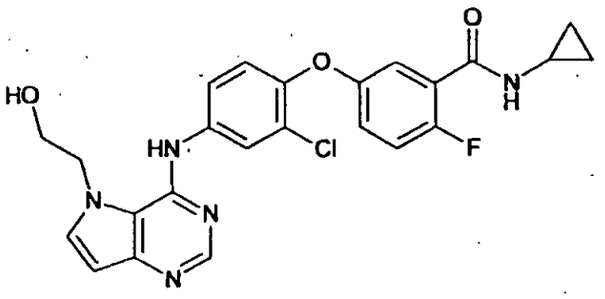
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1,1-dimethyl-2-(piperidin-1-yl)ethyl)benzamide dihydrochloride

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 2-methyl-1-(piperidin-1-yl)propan-2-amine (125 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole (81 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-63, the title compound (136 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.33-2.00 (6H, m), 1.51 (6H, s), 2.91-3.09 (2H, m), 3.27-3.62 (4H, m), 3.90 (2H, t, J = 4.5 Hz), 4.71 (2H, t, J = 4.5 Hz), 6.30-6.65 (1H, m),

6.71 (1H, d, J = 3.0 Hz), 7.15 (1H, dd, J = 2.3, 7.8 Hz), 7.30 (1H, d, J = 8.9 Hz), 7.45-7.53 (2H, m), 7.62 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.73 (1H, d, J = 7.7 Hz), 7.96 (1H, d, J = 2.5 Hz), 8.02 (1H, d, J = 3.0 Hz), 8.17 (1H, br s), 8.76 (1H, s), 9.70 (1H, br s), 10.88 (1H, br s).

Example C-76



Production of 5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-cyclopropyl-2-fluorobenzamide

(i) Production of methyl 5-[4-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-2-fluorobenzoate

Using methyl 5-(4-amino-2-chlorophenoxy)-2-fluorobenzoate (1.50 g), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (1.53 g) and isopropyl alcohol (15 mL) and in the same manner as in Example C-2(v), the title compound (2.12 g) was obtained as crystals.

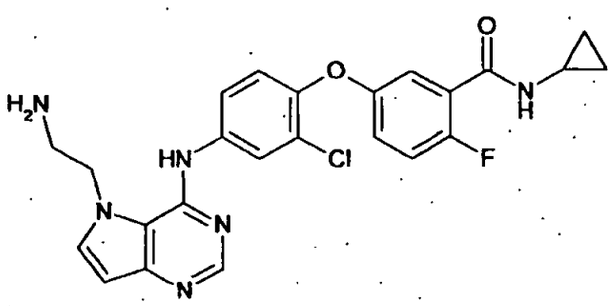
^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s), 4.54-4.57 (2H, m), 4.94-4.97 (2H, m), 6.56 (1H, s), 7.21-7.79 (12H, m), 8.32 (1H, s), 8.78 (1H, br s).

(ii) Production of 5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-cyclopropyl-2-fluorobenzamide

Using methyl 5-[4-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-2-fluorobenzoate (200 mg), 1N aqueous sodium hydroxide

solution (3.0 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-2(v), a compound was obtained. The obtained compound was reacted in the same manner as in Example C-9(v) and using cyclopropaneamine (60 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (200 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (1.5 mL) and N,N-dimethylformamide (5.0 mL) to give the title compound (101 mg) as crystals.
^{1}H-NMR (DMSO-d_6) δ: 0.52-0.71 (4H, m), 2.77-2.83 (1H, m), 3.86-3.89 (2H, m), 4.52-4.55 (2H, m), 6.15-6.51 (2H, m), 7.01-7.97 (7H, m), 8.33 (1H, s), 8.37-8.38 (1H, m), 9.84(1H, br s).

Example C-77



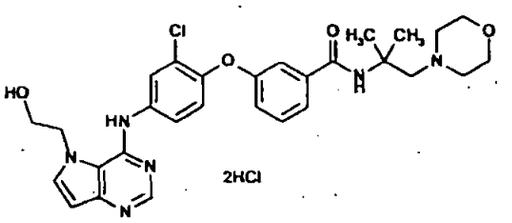
Production of 5-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-cyclopropyl-2-fluorobenzamide

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (286 mg), 5-(4-amino-2-chlorophenoxy)-N-cyclopropyl-2-fluorobenzamide (310 mg) and isopropyl alcohol (5.0 mL) was stirred at 80°C for 12 hr. Under ice-cooling, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The obtained crude product

was dissolved in methanol (10 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL) was added, and the mixture was stirred at 70°C for 20 hr. Ethyl acetate and saturated aqueous sodium hydrogencarbonate were added, and the organic layer was dried over magnesium sulfate. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=10:90→0:100→ethyl acetate:methanol=90:10), and crystallized from diisopropyl ether/ethyl acetate to give the title compound (356 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.53-0.70 (4H, m), 2.77-2.85 (1H, m), 3.06 (2H, br s), 4.36 (2H, br s), 5.95 (2H, br s), 6.48-8.01 (8H, m), 8.31 (1H, s), 8.37-8.38 (1H, m).

Example C-78



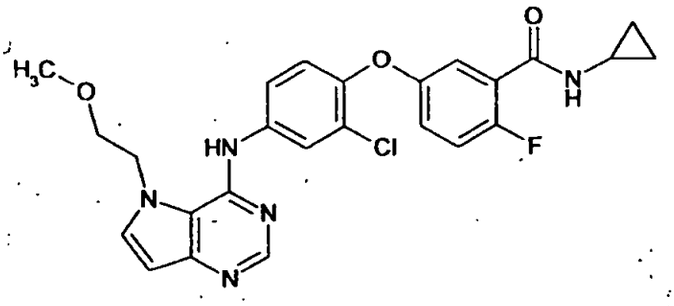
Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1,1-dimethyl-2-(morpholin-4-yl)ethyl)benzamide dihydrochloride

Using 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid (170 mg), 2-methyl-1-(morpholin-4-yl)propan-2-amine (127 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg), 1-hydroxybenzotriazole (81 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-63, the title compound (128 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.52 (6H, s), 3.00-4.20 (12H, m), 4.70 (2H, m), 6.20-6.70 (1H, m), 6.71 (1H, d, J = 3.0 Hz), 7.15 (1H, dd, J = 2.5 Hz, 7.8 Hz), 7.29 (1H, d, J = 8.8 Hz), 7.44-7.54 (2H, m), 7.62 (1H, dd, J = 2.5 Hz,

8.8 Hz), 7.68-7.76 (1H, m), 7.95 (1H, d, J = 2.7 Hz), 8.01 (1H, d, J = 2.7 Hz), 8.15 (1H, br s), 8.75 (1H, s), 10.38 (1H, br s), 10.85 (1H, br s).

Example C-79

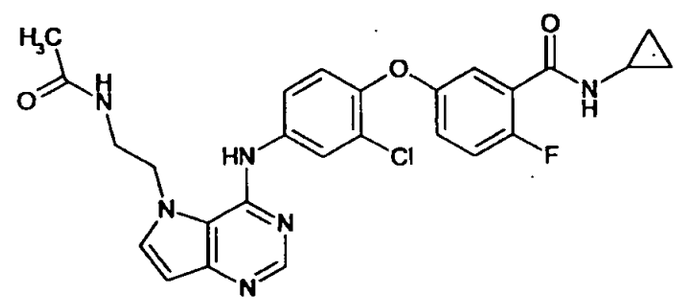


Production of 5-(2-chloro-4-{[5-(2-methoxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-cyclopropyl-2-fluorobenzamide

Using 5-(4-amino-2-chlorophenoxy)-N-cyclopropyl-2-fluorobenzamide (100 mg), 4-chloro-5-(2-methoxyethyl)-5H-pyrrolo[3,2-d]pyrimidine (66 mg) and isopropyl alcohol (5.0 mL) and in the same manner as in Example C-22(i), the title compound (131 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.52-0.71 (4H, m), 2.77-2.83 (1H, m), 3.31 (3H, s), 3.72-3.75 (2H, m), 4.64-4.67 (2H, m), 6.50-7.95 (8H, m), 8.34 (1H, s), 8.37-8.39 (1H, m), 9.97(1H, br s).

Example C-80

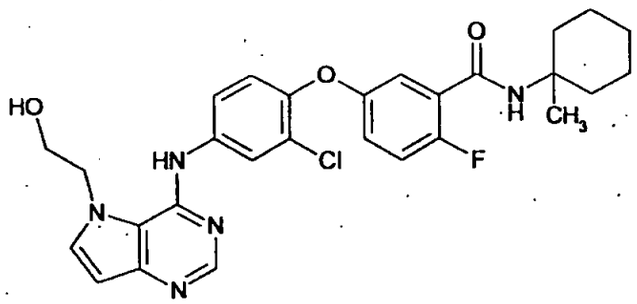


Production of 5-[4-({5-[2-(acetylamino)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-N-cyclopropyl-2-fluorobenzamide

Using 5-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)-N-cyclopropyl-2-fluorobenzamide (100 mg), acetic acid (40 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (120 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (0.5 mL) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example C-23(v), the title compound (71 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.52-0.71 (4H, m), 1.79 (3H, s), 2.79-2.82 (1H, m), 3.33-3.39 (2H, m), 4.48-4.53 (2H, m), 6.49-6.50 (1H, m), 7.02-7.32 (4H, m), 7.63-8.43 (6H, m), 8.79(1H, s).

Example C-81

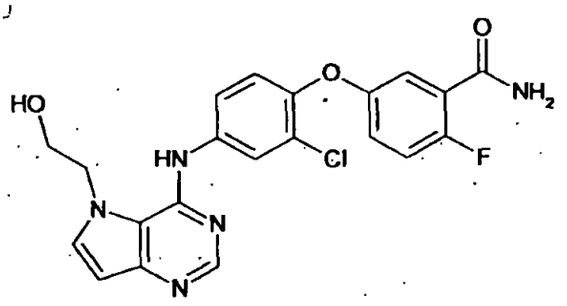


Production of 5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluoro-N-(1-methylcyclohexyl)benzamide

Using methyl 5-[4-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-2-fluorobenzoate (150 mg), 1N aqueous sodium hydroxide solution (3.0 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-2(v), a compound was obtained. The obtained compound was reacted in the same manner as in Example C-9(v) and using 1-methylcyclohexaneamine (110 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (250 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (1.5 mL) and N,N-dimethylformamide (5.0 mL) to give the title compound (82 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.51 (13H, m), 2.14-2.18 (1H, m), 3.86-3.89 (2H, m), 4.52-4.56 (2H, m), 6.49-6.51 (1H, m), 7.17-7.68 (7H, m), 7.98 (1H, s), 8.34(1H, br s), 9.85 (1H, br s).

Example C-82

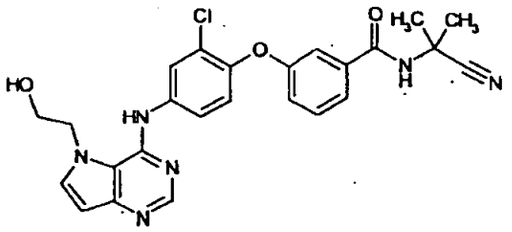


Production of 5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluorobenzamide

Using methyl 5-[4-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-2-fluorobenzoate (150 mg), 1N aqueous sodium hydroxide solution (3.0 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-2(v), a compound was obtained. The obtained compound was reacted in the same manner as in Example C-9(v) and using 30% ammonia/methanol solution (5.0 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (300 mg), 1-hydroxybenzotriazole (30 mg), triethylamine (1.5 mL) and N,N-dimethylformamide (10 mL) to give the title compound (58 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.86-3.89 (2H, m), 4.52-4.56 (2H, m), 6.50-6.51 (1H, m), 7.22-8.04 (9H, m), 8.34(1H, br s), 9.86 (1H, br s).

Example C-83



Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-cyano-1-methylethyl)benzamide

(i) Production of methyl N-[3-(2-chloro-4-nitrophenoxy)benzoyl]-2-methylalaninate

A mixture of 3-(2-chloro-4-nitrophenoxy)benzoic acid (1.47 g), thionyl chloride (1.00 mL), N,N-dimethylformamide (one drop) and toluene (20 mL) was stirred at 80°C for 2 hr. After concentration under reduced pressure, toluene was added, and the mixture was again concentrated under reduced pressure. A solution of the residue in tetrahydrofuran (5 mL) was added to a mixture of methyl 2-aminoisobutyrate hydrochloride (922 mg), triethylamine (1.67 mL) and tetrahydrofuran (10 mL) under ice-cooling, and the mixture was stirred under ice-cooling for 1 hr and at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60). The objective fractions were concentrated under reduced pressure to give the title compound (1.72 g) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.69 (6H, s), 3.79 (3H, s), 6.84 (1H, br s), 6.92 (1H, d, J = 9.2 Hz), 7.20-7.25 (1H, m), 7.48-7.54 (2H, m), 7.61-7.66 (1H, m), 8.08 (1H, dd, J = 2.7 Hz, 9.2 Hz), 8.40 (1H, d, J = 2.7 Hz).

(ii) Production of N-[3-(2-chloro-4-

nitrophenoxy)benzoyl]-2-methylalanine

To methyl N-[3-(2-chloro-4-nitrophenoxy)benzoyl]-2-methylalaninate (1.72 g) were added isopropyl alcohol (20 mL), tetrahydrofuran (5 mL) and 1N aqueous sodium hydroxide solution (6 mL) and the mixture was stirred at room temperature overnight. 1N hydrochloric acid (6.6 mL) was added to the reaction mixture, and the solvent was evaporated under reduced pressure. Water was added and the precipitated solid was collected by filtration, and washed with water to give the title compound (1.53 g) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.45 (6H, s), 7.08 (1H, d, J = 9.1 Hz), 7.39 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.68 (1H, m), 7.83 (1H, d, J = 8.0 Hz), 8.20 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.50 (1H, d, J = 2.7 Hz), 8.55 (1H, br s).

(iii) Production of 3-(2-chloro-4-nitrophenoxy)-N-(1-cyano-1-methylethyl)benzamide

To a solution of N-[3-(2-chloro-4-nitrophenoxy)benzoyl]-2-methylalanine (1.52 g) in N,N-dimethylformamide (20 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (920 mg) and 1-hydroxybenzotriazole (649 mg) under ice-cooling, and the mixture was stirred for 1 hr under ice-cooling. 28% aqueous ammonia (1.4 mL) was added to the reaction mixture, and the mixture was stirred under ice-cooling for 1 hr and at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with aqueous sodium hydroxide solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate. The obtained powder was subjected to basic silica gel column

chromatography (eluent, ethyl acetate). The objective fractions were concentrated under reduced pressure to give N-(2-amino-1,1-dimethyl-2-oxoethyl)-3-(2-chloro-4-nitrophenoxy)benzamide (0.95 g) as a white powder. To a solution of the obtained N-(2-amino-1,1-dimethyl-2-oxoethyl)-3-(2-chloro-4-nitrophenoxy)benzamide (0.95 g) and triethylamine (1.12 mL) in tetrahydrofuran (30 mL) was added dropwise a solution of trifluoroacetic anhydride (0.556 mL) in tetrahydrofuran (5 mL) under ice-cooling, and the mixture was stirred at room temperature overnight. Triethylamine (0.697 mL) and trifluoroacetic anhydride (0.348 mL) were again added to the reaction mixture under ice-cooling, and the mixture was stirred at room temperature overnight. 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=15:85→50:50). The objective fractions were concentrated under reduced pressure to give the title compound (419 mg) as a white amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.82 (6H, s), 6.21 (1H, br s), 6.93 (1H, d, J = 9.1 Hz), 7.22-7.27 (1H, m), 7.48-7.55 (2H, m), 7.58-7.63 (1H, m), 8.08 (1H, dd, J = 2.6, 9.1 Hz), 8.39 (1H, d, J = 2.6 Hz).

(iv) Production of 3-(4-amino-2-chlorophenoxy)-N-(1-cyano-1-methylethyl)benzamide

To a solution of 3-(2-chloro-4-nitrophenoxy)-N-(1-cyano-1-methylethyl)benzamide (419 mg) in ethyl acetate (10 mL) was added 5% platinum-activated carbon (20 mg) under a hydrogen atmosphere and the mixture was stirred at room temperature for 6 hr. The catalyst was filtered off, the filtrate was concentrated and the obtained

residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=30:70→60:40). The objective fractions were concentrated under reduced pressure to give the title compound (283 mg) as a yellow-green amorphous powder.

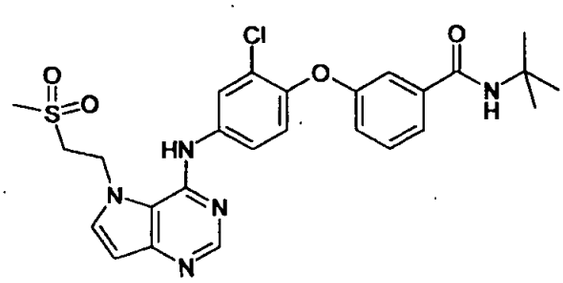
^{1}H-NMR ($CDCl_3$) δ: 1.80 (6H, s), 3.72 (2H, br s), 6.15 (1H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.4 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 8.4 Hz), 7.00-7.10 (1H, m), 7.25-7.40 (3H, m).

(v) Production of 3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-N-(1-cyano-1-methylethyl)benzamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (121 mg), 3-(4-amino-2-chlorophenoxy)-N-(1-cyano-1-methylethyl)benzamide (132 mg), isopropyl alcohol (5 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.8 mL) and in the same manner as in Example C-62(v), the title compound (68 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.80 (6H, s), 4.13 (2H, t, J = 4.3 Hz), 4.38 (2H, t, J = 4.3 Hz), 6.24 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.97 (1H, d, J = 9.1 Hz), 7.06 (1H, d, J = 3.0 Hz), 7.13-7.20 (1H, m), 7.28-7.44 (4H, m), 7.76 (1H, d, J = 2.7 Hz), 8.24 (1H, s), 9.58 (1H, br s).

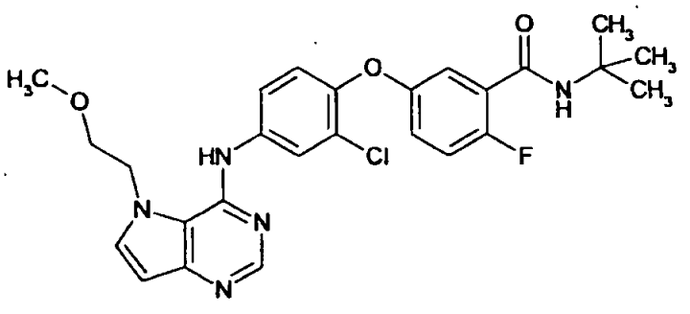
Example C-84



Production of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylsulfonyl)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide

To a solution of N-(tert-butyl)-3-[2-chloro-4-({5-[2-(methylthio)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide (255 mg) in methanol (2 mL) was added a solution of OXONE® monopersulfate compound (615 mg) in water (1 mL) under ice-cooling. Methanol (18 mL) and water (9 mL) were added thereto and the mixture was stirred at room temperature overnight. An aqueous sodium hydrogencarbonate solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with 5% aqueous sodium thiosulfate solution and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0→methanol:ethyl acetate→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (207 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.73 (3H, s), 3.67 (2H, t, J = 6.2 Hz), 4.87 (2H, t, J = 6.2 Hz), 5.95 (1H, br s), 6.74 (1H, d, J = 3.4 Hz), 7.00-7.12 (2H, m), 7.31-7.40 (4H, m), 7.48 (1H, dd, J = 2.7 Hz, 8.7 Hz), 7.86 (1H, d, J = 2.7 Hz), 7.97 (1H, br s), 8.56 (1H, s).

Example C-85



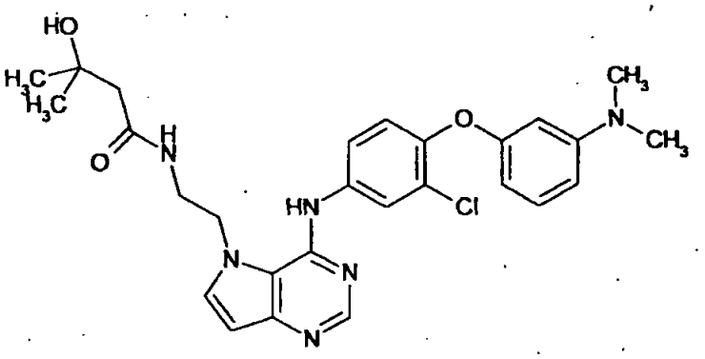
Production of N-(tert-butyl)-5-(2-chloro-4-{[5-(2-methoxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-

yl]amino}phenoxy)-2-fluorobenzamide

Using 5-(4-amino-2-chlorophenoxy)-N-(tert-butyl)-2-fluorobenzamide (60 mg), 4-chloro-5-(2-methoxyethyl)-5H-pyrrolo[3,2-d]pyrimidine (38 mg) and isopropyl alcohol (3.0 mL) and in the same manner as in Example C-22(i), the title compound (84 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.32 (9H, s), 3.72-3.76 (2H, m), 3.80 (3H, s), 4.64-4.68 (2H, m), 6.51-7.99 (8H, m), 8.36 (1H, s), 9.01 (1H, s), 9.97(1H, br s).

Example C-86



Production of N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide

(i) Production of 3-(4-amino-2-chlorophenoxy)-N,N-dimethylaniline

Using 3-(dimethylamino)phenol (5.0 g), 3-chloro-4-fluoronitrobenzene (6.38 g), potassium carbonate (5.38 g), N,N-dimethylformamide (100 mL), 5% platinum-activated carbon (0.73 g) and ethyl acetate (75 mL) and in the same manner as in Example C-1(i) and (ii), the title compound (8.95 g) was obtained.

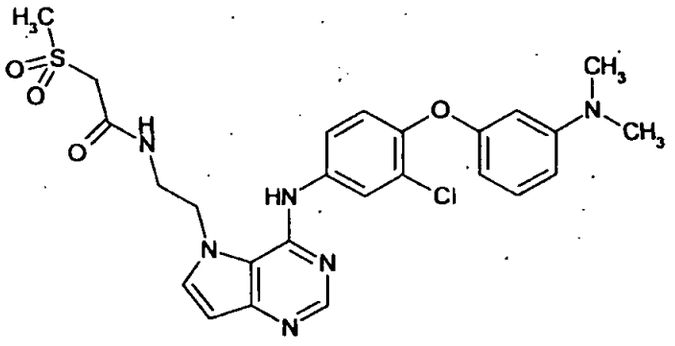
^{1}H-NMR (DMSO-d_6) δ: 2.84 (6H, s), 5.27 (2H, s), 5.95-6.55 (4H, m), 6.69 (1H, d, J = 2.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 8.3 Hz).

(ii) Production of N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide

Using 3-(4-amino-2-chlorophenoxy)-N,N-dimethylaniline (100 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (89 mg), isopropyl alcohol (5.0 mL), ethyl acetate (5.0 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL), 3-hydroxy-3-methylbutanoic acid (54 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (136 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (1.0 mL) and tetrahydrofuran (10 mL) and in the same manner as in Example C-53(ii), the title compound (67 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.13 (6H, s), 2.20 (2H, s), 2.89 (6H, s), 3.38-3.44 (2H, m), 4.49-4.53 (2H, m), 4.66 (1H, s), 6.09-7.15 (6H, m), 7.62-8.26 (4H, m), 8.31 (1H, s), 8.81 (1H, s).

Example C-87



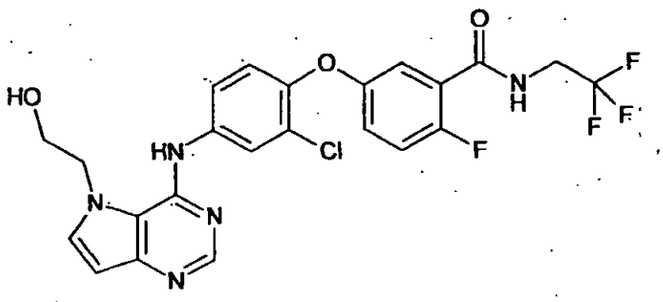
Production of N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3-(4-amino-2-chlorophenoxy)-N,N-dimethylaniline (100 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (89 mg), isopropyl alcohol (5.0 mL), ethyl acetate (5.0 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL), methylsulfonylacetic acid (52 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (141 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (1.0 mL)

and tetrahydrofuran (10 mL) and in the same manner as in Example C-53(ii), the title compound (74 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.89 (6H, s), 3.09 (3H, s), 3.44-3.47 (2H, m), 4.04 (2H, s), 4.51-4.59 (2H, m), 6.08-7.16 (6H, m), 7.60-7.91 (3H, m), 8.32 (1H, s), 8.61-8.69 (2H, m).

Example C-88



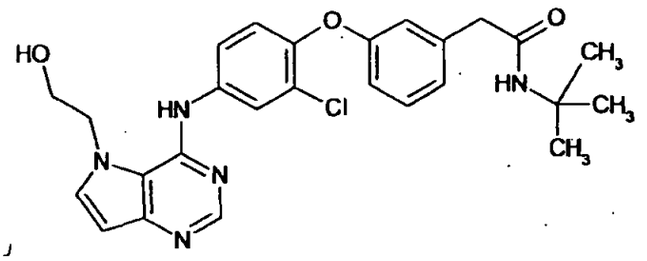
Production of 5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluoro-N-(2,2,2-trifluoroethyl)benzamide

Using methyl 5-[4-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-2-chlorophenoxy]-2-fluorobenzoate (100 mg), 1N aqueous sodium hydroxide solution (2.0 mL) and tetrahydrofuran (5.0 mL) and in the same manner as in Example C-2(v), a compound was obtained. The obtained compound was reacted in the same manner as in Example C-9(v) and using 2,2,2-trifluoroethaneamine (70 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (220 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (0.5 mL) and N,N-dimethylformamide (5.0 mL) to give the title compound (52 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.86-3.90 (2H, m), 3.99-4.10 (2H, m), 4.52-4.56 (2H, m), 6.15-6.52 (1H, m), 7.24-7.99 (7H, m), 8.34 (1H, s), 9.13-9.17 (1H, m), 9.87(1H, br s).

Example C-89

236



Production of N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]acetamide

(i) Production of benzyl [3-(2-chloro-4-nitrophenoxy)phenyl]acetate

Using benzyl (3-hydroxyphenyl)acetate (2.50 g), 3-chloro-4-fluoronitrobenzene (1.83 g), potassium carbonate (1.90 g) and N,N-dimethylformamide (20 mL) and in the same manner as in Example C-1(i), the title compound (1.21 g) was obtained as a brown oil.

^{1}H-NMR (DMSO-d_6) δ: 3.81(2H, s), 5.12 (2H, s), 7.00-7.25 (4H, m), 7.31-7.37 (5H, m), 7.43-7.48 (1H, m), 8.14-8.18 (1H, m), 8.46-8.47 (1H, m).

(ii) Production of 2-[3-(4-amino-2-chlorophenoxy)phenyl]-N-(tert-butyl)acetamide

To benzyl [3-(2-chloro-4-nitrophenoxy)phenyl]acetate (1.00 g) were added 1N aqueous sodium hydroxide solution (5.3 mL) and tetrahydrofuran (4 mL) and the mixture was stirred at room temperature for 21 hr. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue, 2-methylpropan-2-amine (1.1 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.11 g), 1-hydroxybenzotriazole (30 mg), triethylamine (3.5 mL) and N,N-dimethylformamide (10 mL) were reacted in the

same manner as in Example C-9(v), and the obtained compound, 5% platinum-activated carbon (130 mg) and ethyl acetate (10 mL) were reacted in the same manner as in Example C-1(ii) to give the title compound (340 mg) as a pale-yellow oil.

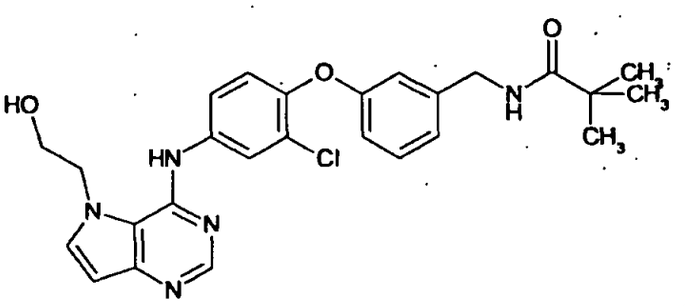
^{1}H-NMR (DMSO-d_6) δ: 1.21 (9H, s), 3.61(2H, s), 5.27 (2H, s), 5.92-6.59 (4H, m), 6.65-6.69 (1H, m), 6.87 (1H, d, J = 8.0 Hz), 7.13 (1H, t, J = 8.3 Hz).

(iii) Production of N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]acetamide

Using 2-[3-(4-amino-2-chlorophenoxy)phenyl]-N-(tert-butyl)acetamide (330 mg), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (270 mg), isopropyl alcohol (20 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and methanol (6.0 mL) and in the same manner as in Example C-57, the title compound (115 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.22 (9H, s), 3.34-3.40 (2H, m), 3.84-3.92 (2H, m), 4.51-4.57 (2H, m), 6.30 (1H, br s), 6.51-7.30 (6H, m), 7.56-7.96 (4H, m), 8.36 (1H, s), 9.91(1H, br s).

Example C-90



Production of N-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzyl]-2,2-dimethylpropanamide

(i) Production of N-[3-(4-amino-2-chlorophenoxy)benzyl]-2,2-dimethylpropanamide

Using N-(3-hydroxybenzyl)-2,2-dimethylpropanamide (2.07 g), 3-chloro-4-fluoronitrobenzene (1.79 g), N,N-dimethylformamide (40 mL), potassium carbonate (1.78 g), 15% water-containing ethanol (23 mL), reduced iron (750 mg) and calcium chloride (120 mg) and in the same manner as in Example C-53(i), the title compound (1.73 g) was obtained as a brown oil.

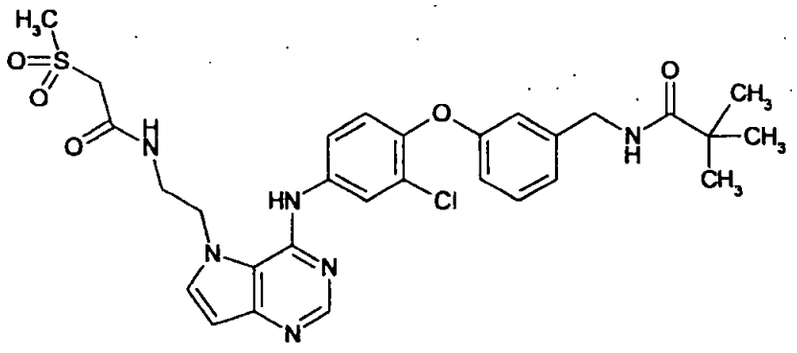
^{1}H-NMR (DMSO-d_6) δ: 1.09 (9H, s), 4.21-4.25 (2H, m), 5.26 (2H, s), 5.90-6.58 (4H, m), 6.64-6.68 (1H, m), 6.85-6.98 (1H, m), 7.13 (1H, t, J = 8.3 Hz).

(ii) Production of N-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzyl]-2,2-dimethylpropanamide

Using N-[3-(4-amino-2-chlorophenoxy)benzyl]-2,2-dimethylpropanamide (190 mg), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (172 mg), isopropyl alcohol (5.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and methanol (5.0 mL) and in the same manner as in Example C-57, the title compound (121 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.07 (9H, s), 3.86-3.89 (2H, m), 4.21-4.23 (2H, m), 4.51-4.55 (2H, m), 6.51-7.32 (6H, m), 7.56-8.06 (4H, m), 8.33 (1H, s), 9.82(1H, br s).

Example C-91



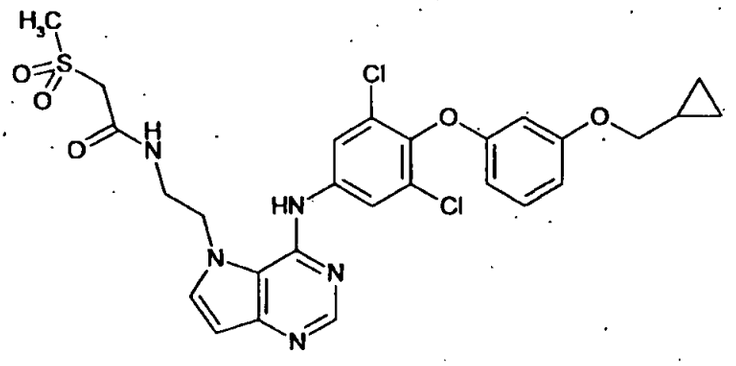
Production of N-[3-(2-chloro-4-{[5-(2-{[(methylsulfonyl)acetyl]amino}ethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzyl]-2,2-

dimethylpropanamide

Using N-[3-(4-amino-2-chlorophenoxy)benzyl]-2,2-dimethylpropanamide (350 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (312 mg), isopropyl alcohol (11 mL), tetrahydrofuran (17 mL), 4N hydrogen chloride/ethyl acetate solution (7.0 mL), methylsulfonylacetic acid (220 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (380 mg), 1-hydroxybenzotriazole (20 mg), triethylamine (4.0 mL) and N,N-dimethylformamide (15 mL) and in the same manner as in Example C-53(ii), the title compound (263 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.08 (9H, s), 3.10 (3H, s), 3.45-3.49 (2H, m), 4.04 (2H, s), 4.22-4.24 (2H, m), 4.54-4.59 (2H, m), 6.48-7.33 (6H, m), 7.62-8.08 (4H, m), 8.34 (1H, s), 8.67(1H, br s).

Example C-92



Production of N-{2-[4-({3,5-dichloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 3-(2,6-dichloro-4-nitrophenoxy)phenyl benzoate

To a solution of 3-hydroxyphenyl benzoate (675 mg) and 1,3-dichloro-2-iodo-5-nitrobenzene (1.0 g) in N,N-dimethylformamide (15 mL) was added potassium carbonate (1.25 g) and the mixture was stirred at room temperature

for 18 hr. Under ice-cooling, to the reaction mixture was added brine, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1) to give the title compound (269 mg) as a brown oil.

^{1}H-NMR (DMSO-d_6) δ: 6.90-6.97 (2H, m), 7.07-7.10 (1H, m), 7.44-7.77 (4H, m), 8.10-8.12 (2H, m), 8.55(2H, s).

(ii) Production of 3,5-dichloro-4-[3-(cyclopropylmethoxy)phenoxy]aniline

To 3-(2,6-dichloro-4-nitrophenoxy)phenyl benzoate (269 mg) were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) and the mixture was stirred at room temperature overnight. 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. To a solution of the obtained residue and 1-(bromomethyl)cyclopropane (0.78 mL) in N,N-dimethylformamide (15 mL) was added potassium carbonate (430 mg) and the mixture was stirred at room temperature for 18 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (10 mL), reduced iron (250 mg) and calcium chloride (70 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by

filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→0:1) to give the title compound (112 mg) as a brown oil.

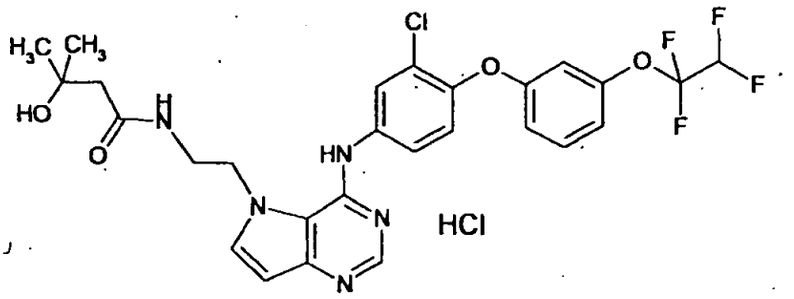
^{1}H-NMR (DMSO-d_6) δ: 0.30-0.57 (4H, m), 1.11-1.35 (1H, m), 3.79-3.81 (2H, m), 5.56 (2H, s), 5.90 (1H, dd, J = 2.0 Hz, 8.0 Hz), 6.22 (1H, t, J = 2.2 Hz), 6.36 (1H, dd, J = 2.0 Hz, 8.0 Hz), 6.71 (2H, s), 7.05 (1H, t, J = 8.3 Hz).

(iii) Production of N-{2-[4-({3,5-dichloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3,5-dichloro-4-[3-(cyclopropylmethoxy)phenoxy]aniline (110 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (101 mg), isopropyl alcohol (5.0 mL), methanol (10 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL), methylsulfonylacetic acid (90 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (120 mg), 1-hydroxybenzotriazole (5.0 mg), triethylamine (0.8 mL) and N,N-dimethylformamide (5 mL) and in the same manner as in Example C-53(ii), the title compound (43 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.30-0.57 (4H, m), 1.11-1.35 (1H, m), 3.11 (3H, s), 3.40-3.50 (2H, m), 3.79-3.81 (2H, m), 4.07 (2H, s), 4.54-4.59 (2H, m), 6.32-6.67 (4H, m), 7.19-7.67 (2H, m), 8.02 (2H, s), 8.41 (1H, s), 8.68(1H, br s), 8.80 (1H, s).

Example C-93



Production of N-{2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide hydrochloride

(i) Production of 2-chloro-4-nitro-1-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]benzene

A mixture of 3-chloro-4-fluoronitrobenzene (5 g) and 3-(1,1,2,2-tetrafluoroethoxy)phenol (6 g) was dissolved in N,N-dimethylformamide (28 mL), potassium carbonate (5.92 g) was added thereto, and the mixture was stirred at room temperature for 15 hr. Water (200 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=90:10→60:40) to give the title compound (10 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 5.91 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.90-7.10 (3H, m), 7.10-7.15 (1H, m), 7.44 (1H, t, J= 8.0 Hz), 8.10 (1H, dd, J= 3.0 Hz, 9.0 Hz), 8.39 (1H, d, J= 3.0 Hz).

(ii) Production of 3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline

A mixture of 2-chloro-4-nitro-1-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]benzene (10 g), reduced iron (10.2 g) and calcium chloride (1.7 g) in ethanol (270 mL)/water (30 mL) was stirred with heating at 90°C for 16

hr. After cooling to room temperature, the mixture was filtered through celite. The filtrate was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (300 mL)/saturated brine (200 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=90:10→60:40) to give the title compound (7.91 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, br s), 5.87 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.58 (1H, dd, J= 3.0 Hz, 8.0 Hz), 6.70-6.85 (3H, m), 6.85-7.00 (2H, m), 7.26 (1H, t, J= 8.0 Hz).

(iii) Production of tert-butyl {2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

tert-Butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.0 g) and 3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline (1.70 g) were dissolved in isopropyl alcohol (10 mL), and the mixture was stirred at 80°C for 20 hr. A saturated aqueous sodium hydrogencarbonate solution (50 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=80:20→0:100) to give the title compound (2.04 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 3.40-3.60 (2H, m), 4.40-4.60 (2H, m), 5.11 (1H, t, J= 6.0 Hz), 5.89 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.60 (1H, d, J= 3.0 Hz), 6.80-7.00 (3H, m), 7.09 (1H, d, J= 9.0 Hz), 7.19 (1H, d, J= 3.0 Hz), 7.31 (1H, t, J= 8.0 Hz), 7.89 (1H, dd, J= 3.0 Hz, 9.0 Hz), 8.03 (1H, d, J= 3.0 Hz), 8.52 (1H, s), 8.64

(1H, br s).

(iv) Production of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

tert-Butyl {2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (1.98 g) was dissolved in tetrahydrofuran (47.2 mL), 2N hydrochloric acid (23.6 mL) was added thereto, and the mixture was stirred at 60°C for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol (50 mL), and the mixture was concentrated again under reduced pressure. This operation was repeated twice. The residual solid was filtrated with isopropyl alcohol and dried to give the title compound (1.65 g) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 3.20-3.40 (2H, m), 5.00-5.10 (2H, m), 6.60-7.00 (4H, m), 7.35 (1H, d, J= 9.0 Hz), 7.51 (1H, t, J= 9.0 Hz), 7.60-7.70 (1H, m), 7.94 (1H, d, J= 2.4 Hz), 8.11 (1H, d, J= 3.0 Hz), 8.40 (3H, br s), 8.75 (1H, s).

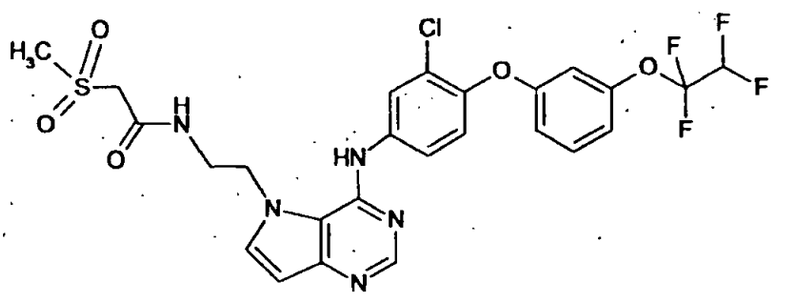
(v) Production of N-{2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide hydrochloride

5-(2-Aminoethyl)-N-{3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (204 mg), 3-hydroxy-3-methylbutanoic acid (63.5 mg), N,N-dimethylformamide (6.9 mL), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg) were stirred at room temperature for 16 hr. The mixture was partitioned between ethyl acetate (80 mL)/water (50 mL), the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The residue was separated and purified by silica gel column chromatography (ethyl acetate:methanol=100:0→85:15) and basic silica gel column chromatography (ethyl acetate:methanol=100:0→85:15). The residue was dissolved in ethyl acetate (5 mL), treated with 4N hydrogen chloride/ethyl acetate solution (0.18 mL), and crystallized from diisopropyl ether/ethyl acetate to give the title compound (134 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.11 (6H, s), 2.20 (2H, s), 3.44-3.56 (2H, m), 4.68 (2H, t, J= 6.0 Hz), 6.60-7.10 (5H, m), 7.35 (1H, d, J= 9.0 Hz), 7.51 (1H, t, J= 8.0 Hz), 7.73 (1H, dd, J= 3.0 Hz, 9.0 Hz), 7.98 (2H, dd, J= 3.0 Hz, 7.0 Hz), 8.43 (1H, m), 8.74 (1H, s).

Example C-94



Production of N-{2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

5-(2-Aminoethyl)-N-{3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (204 mg), methylsulfonylacetic acid (74.2 mg), N,N-dimethylformamide (6.9 mL), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg) were stirred at room temperature for 16 hr. The mixture was partitioned between ethyl acetate (80 mL)/water (50 mL). The organic layer was dried over anhydrous

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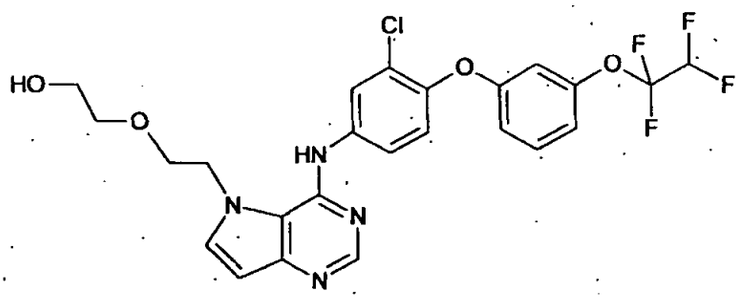
magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (ethyl acetate:methanol=100:0→85:15) and basic silica gel column chromatography (ethyl acetate:methanol=100:0→85:15) to give the title compound (140 mg) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.10 (3H, s), 3.40-3.50 (2H, m), 4.05 (2H, s), 4.56 (2H, t, J= 7.0 Hz), 6.50 (1H, d, J= 3.0 Hz), 6.60-7.10 (4H, m), 7.29 (1H, d, J= 9.0 Hz), 7.47 (1H, t, J= 8.0 Hz), 7.63 (1H, d, J= 3.0 Hz), 7.76 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.35 (1H, s), 8.68 (1H, m), 8.71 (1H, br s).

Example C-95



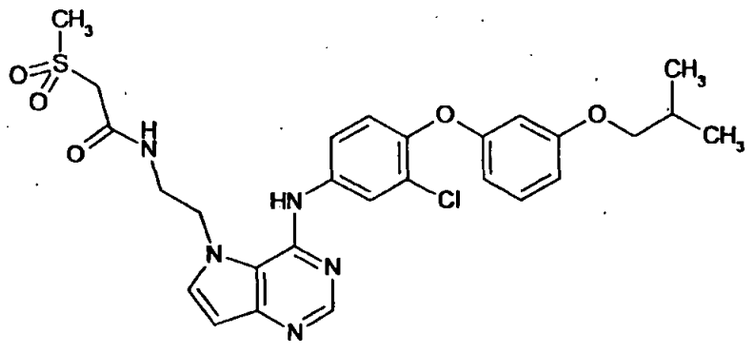
Production of 2-{2-[4-({3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

2-[2-(4-Chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (150 mg) and 3-chloro-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline (217 mg) were stirred in isopropyl alcohol (3 mL) at 80°C for 16 hr. A saturated aqueous sodium hydrogencarbonate solution (40 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (80 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=90:10→0:100). The

obtained oil residue was dissolved in methanol (1.89 mL), 1N aqueous sodium hydroxide solution (0.433 mL) was added and the mixture was stirred at room temperature stirred for 1 hr. 1N hydrochloric acid (0.433 mL) was added to the mixture and the mixture was partitioned between ethyl acetate (50 mL) and saturated brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (ethyl acetate:methanol=100:0→90:10) and basic silica gel column chromatography (ethyl acetate:methanol=100:0→90:10) to give the title compound (136 mg) as white crystals.

^{1}H-NMR (DMSO-d_6)δ: 3.49 (4H, br s), 3.83 (2H, t, J= 4.5 Hz), 4.64 (2H, t, J= 4.5 Hz), 4.73 (1H, t, J= 4.5 Hz), 6.52 (1H, d, J= 3.0 Hz), 6.76 (1H, m), 6.79 (1H, tt, J= 3.0 Hz, 52.0 Hz), 6.91 (1H, dd, J= 2.0 Hz, 8.0 Hz), 7.02 (1H, d, J= 9.0 Hz), 7.27 (1H, d, J= 9.0 Hz), 7.47 (1H, t, J= 8.0 Hz), 7.60-7.70 (2H, m), 8.01 (1H, d, J= 2.0 Hz), 8.34 (1H, s), 8.99 (1H, br s).

Example C-96



Production of N-[2-(4-{[3-chloro-4-(3-isobutoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

(i) Production of 3-chloro-4-(3-isobutoxyphenoxy)aniline

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol

(1.00 g) and 1-iodo-2-methylpropane (1.5 mL) in N,N-dimethylformamide (15 mL) was added potassium carbonate (1.50 g) and the mixture was stirred at room temperature for 12 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (30 mL), reduced iron (750 mg) and calcium chloride (70 mg) were added, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→0:1) to give the title compound (390 mg) as a brown oil.

^{1}H-NMR (DMSO-d_6) δ: 0.94-0.96 (6H, m), 1.90-2.01 (1H, m), 3.67-3.69 (2H, m), 5.33 (2H, s), 6.32-7.34 (2H, m), 6.53-6.59 (2H, m), 6.71-6.72 (1H, m), 6.89-6.91 (1H, m), 7.14-7.20 (1H, m).

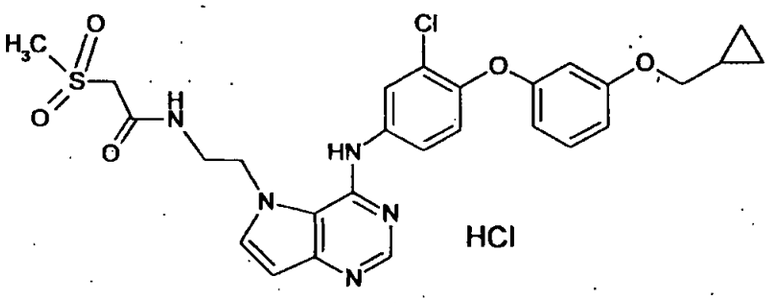
(ii) Production of N-[2-(4-{[3-chloro-4-(3-isobutoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

Using 3-chloro-4-(3-isobutoxyphenoxy)aniline (1.00 g), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.02 g), isopropyl alcohol (25 mL), methanol (35 mL), 4N hydrogen chloride/ethyl acetate solution (10 mL), methylsulfonylacetic acid (870 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (2.50 g), 1-hydroxybenzotriazole (100 mg), triethylamine (4.1 mL) and N,N-dimethylformamide (100 mL) and in the same manner as in Example C-53(ii), the title compound (933 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.95-0.97 (6H, m), 1.95-2.04 (1H, m), 3.09 (3H, s), 3.40-3.50 (2H, m), 3.72-3.74 (2H, m), 4.04 (2H, s), 4.54-4.59 (2H, m), 6.44-7.27 (6H, m), 7.61-7.75 (2H, m), 7.94 (1H, s), 8.33 (1H, s), 8.66 (2H, s).

Example C-97



Production of N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of 2-chloro-1-[3-(cyclopropylmethoxy)phenoxy]-4-nitrobenzene

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol (2.92 g) in N,N-dimethylformamide (10.9 mL) were added cesium carbonate (5.39 g) and 1-(bromomethyl)cyclopropane (1.6 mL) and the mixture was stirred at room temperature for 16 hr. The mixture was partitioned between ethyl acetate (150 mL)/water (80 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=100:0→70:30) to give the title compound (3.17 g) as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.30-0.40 (2H, m), 0.60-0.70 (2H, m), 1.20-1.40 (1H, m), 3.79 (2H, d, J= 7.0 Hz), 6.60-6.70

(2H, m), 6.70-6.82 (1H, m), 6.92(1H, d, J= 9.0 Hz), 7.29 (1H, m), 8.00-8.10 (1H, m), 8.36 (1H, d, J= 3.0 Hz).

(ii) Production of 3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]aniline

2-Chloro-1-[3-(cyclopropylmethoxy)phenoxy]-4-nitrobenzene (3.1 g) was dissolved in ethanol (97 mL)/water (11 mL), reduced iron (3.61 g) and calcium chloride (717 mg) were added thereto, and the mixture was stirred at 90°C for 16 hr. The solid was removed by filtration through celite, and the filtrate was concentrated under reduced pressure. Ethyl acetate (150 mL) was added to the residue, and the mixture was washed with saturated brine (100 mL). The organic layer was dried over magnesium sulfate, concentrated under reduced pressure, and the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=90:10→60:40) to give the title compound (2.50 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 0.20-0.40 (2H, m), 0.50-0.70 (2H, m), 1.10-1.30 (1H, m), 3.66 (2H, br s), 3.74 (2H, d, J= 7.0 Hz), 6.40-6.50 (2H, m), 6.50-6.60 (2H, m), 6.76 (1H, d, J= 3.0 Hz), 6.85 (1H, d, J= 9.0 Hz), 7.10-7.20 (1H, m).

(iii) Production of tert-butyl {2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

tert-Butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (0.5 g) and 3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]aniline (732 mg) were dissolved in isopropyl alcohol (5 mL), and the mixture was stirred at 80°C for 20 hr. A saturated aqueous sodium hydrogencarbonate solution (60 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (80 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified

by silica gel column chromatography (hexane:ethyl acetate=90:10→0:100) to give the title compound (742 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.30-0.40 (2H, m), 0.60-0.70 (2H, m), 1.10-1.30 (1H, m), 1.49 (9H, s), 3.40-3.60 (2H, m), 3.76 (2H, d, J= 7.0 Hz), 4.40-4.50 (2H, m), 5.21 (1H, t, J= 5.0 Hz), 6.50-6.70 (4H, m), 7.04 (1H, d, J= 9.0 Hz), 7.10-7.30 (2H, m), 7.82 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.49 (1H, s), 8.59 (1H, br s).

(iv) Production of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

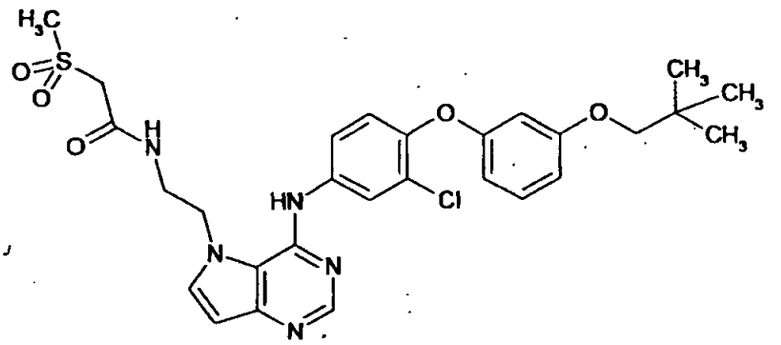
tert-Butyl {2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (700 mg) was dissolved in tetrahydrofuran (18 mL), 2N hydrochloric acid (9.0 mL) was added thereto, and the mixture was stirred at 60°C for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol (50 mL), and the solution was concentrated again under reduced pressure. This operation was repeated twice. The precipitated solid was collected with isopropyl alcohol and dried to give the title compound (599 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 0.20-0.40 (2H, m), 0.50-0.60 (2H, m), 1.10-1.40 (1H, m), 3.20-3.40 (2H, m), 3.80 (2H, d, J= 7.0 Hz), 5.00-5.10 (2H, m), 6.40-6.60 (2H, m), 6.60-6.80 (2H, m), 7.10-7.30 (2H, m), 7.50-7.70 (1H, m), 7.88 (1H, m), 8.08 (1H, m), 8.37 (3H, br s), 8.73 (1H, s), 10.19 (1H, br s).

(v) Production of N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

5-(2-Aminoethyl)-N-{3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (187 mg), methylsulfonylacetic acid (74.2 mg), N,N-dimethylformamide (6.9 mL), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg) were stirred at room temperature for 16 hr. The mixture was partitioned between ethyl acetate (80 mL)/water (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (ethyl acetate:methanol=100:0→85:15) and basic silica gel column chromatography (ethyl acetate:methanol=100:0→85:15). The obtained compound was dissolved in ethyl acetate (4 mL), treated with 4N hydrogen chloride/ethyl acetate solution (0.18 mL), and crystallized from diisopropyl ether/ethyl acetate to give the title compound (167 mg) as white crystals.
^{1}H-NMR (DMSO-d_6) δ: 0.20-0.40 (2H, m), 0.50-0.60 (2H, m), 1.10-1.40 (1H, m), 3.05 (3H, s), 3.50-3.60 (2H, m), 3.80 (2H, d, J= 7.0 Hz), 4.07 (2H, s), 4.73 (1H, t, J= 7.0 Hz), 6.40-6.55 (2H, m), 6.60-6.75 (2H, m), 7.20-7.30 (2H, m), 7.63 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.90 (1H, d, J= 2.0 Hz), 7.96 (1H, d, J= 3.0 Hz), 8.72 (1H, s), 8.87 (1H, m), 10.05 (1H, br s).

Example C-98



Production of N-{2-[4-({3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 2-chloro-1-[3-(2,2-dimethylpropoxy)phenoxy]-4-nitrobenzene

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol (1.0 g) in N,N-dimethylformamide (10 mL) were added potassium hydroxide (423 mg) and tris(dimethylamino)(2,2-dimethylpropoxy)phosphonium hexafluorophosphate (2.99 g) and the mixture was stirred at 180°C for 30 min. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1) to give the title compound (180 mg) as crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s), 3.58(2H, s), 6.63-6.65 (2H, m), 6.80-6.94 (2H, m), 7.30-7.34 (1H, m), 8.04-8.08 (1H, m), 8.37-8.38 (1H, m).

(ii) Production of 3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]aniline

2-Chloro-1-[3-(2,2-dimethylpropoxy)phenoxy]-4-nitrobenzene (210 mg) was dissolved in 15% water-containing ethanol (7 mL), reduced iron (150 mg) and calcium chloride (20 mg) were added, and the mixture was

stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→0:1) to give the title compound (75 mg) as a brown oil.

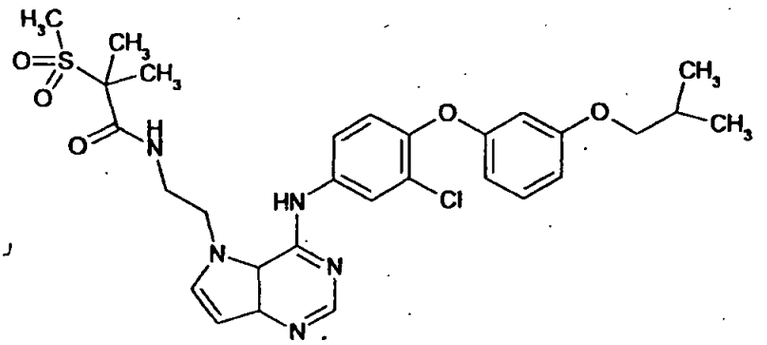
^{1}H-NMR (DMSO-d_6) δ: 0.98 (9H, s), 3.92 (2H, s), 5.34 (2H, s), 6.31-7.33 (2H, m), 6.52-6.58 (2H, m), 6.70-6.72 (1H, m), 6.88-6.92 (1H, m), 7.13-7.20 (1H, m).

(iii) Production of N-{2-[4-({3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]aniline (75 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (73 mg), isopropyl alcohol (10 mL), methanol (10 mL), 4N hydrogen chloride/ethyl acetate solution (5 mL), methylsulfonylacetic acid (50 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (120 mg), 1-hydroxybenzotriazole (10 mg), triethylamine (0.7 mL) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-53(ii), the title compound (62 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.98 (9H, s), 3.09 (3H, s), 3.45-3.49 (2H, m), 3.62 (2H, s), 4.05 (2H, s), 4.54-4.59 (2H, m), 6.44-7.28 (6H, m), 7.66-7.94 (3H, m), 8.39 (1H, s), 8.67 (1H, br s), 8.81 (1H, s).

Example C-99

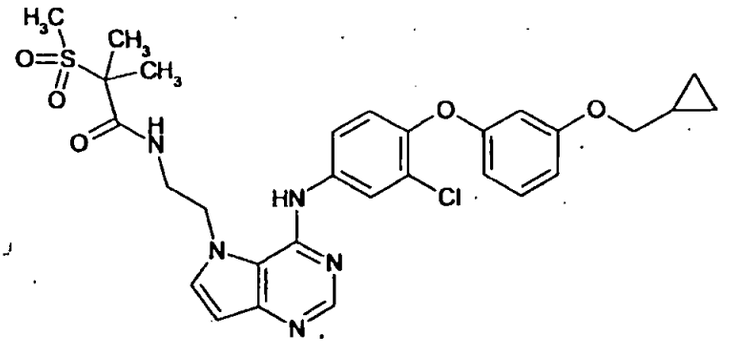


Production of N-[2-(4-{[3-chloro-4-(3-isobutoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

Using 3-chloro-4-(3-isobutoxyphenoxy)aniline (180 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (185 mg), isopropyl alcohol (5.0 mL), methanol (6.0 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL), 2-methyl-2-(methylsulfonyl)propanoic acid (160 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (320 mg), 1-hydroxybenzotriazole (20 mg), triethylamine (1.0 mL) and N,N-dimethylformamide (25 mL) and in the same manner as in Example C-53(ii), the title compound (146 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.95-0.97 (6H, m), 1.41 (6H, s), 1.95-2.04 (1H, m), 2.95 (3H, s), 3.40-3.50 (2H, m), 3.72-3.74 (2H, m), 4.54-4.59 (2H, m), 6.44-7.27 (6H, m), 7.56-7.97 (3H, m), 8.19-8.22 (1H, m), 8.33 (1H, s), 8.65(1H, s).

Example C-100

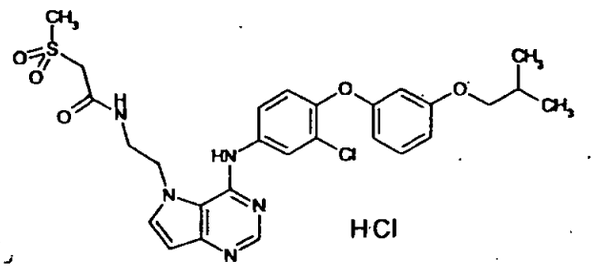


Production of N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-methyl-2-(methylsulfonyl)propanamide

To a solution of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (170 mg) and 1-hydroxybenzotriazole (20 mg) in N,N-dimethylformamide (25 mL) were added triethylamine (0.87 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (320 mg) under ice-cooling and the mixture was stirred at room temperature for 15 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→90:10) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (160 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.29-0.58 (4H, m), 1.11-1.28 (1H, m), 1.41 (6H, s), 2.95 (3H, s), 3.44-3.50 (2H, m), 3.78-3.80 (2H, m), 4.55-4.59 (2H, m), 6.32-6.68 (4H, m), 7.16-7.96 (5H, m), 8.20 (1H, br s), 8.33 (1H, s), 8.65(1H, br s).

Example C-101

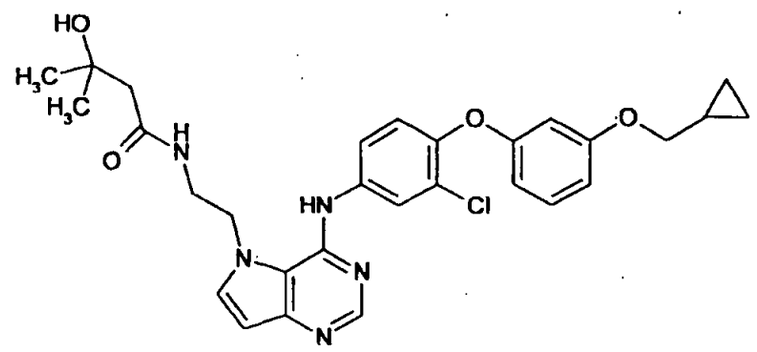


Production of N-[2-(4-{[3-chloro-4-(3-isobutoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide hydrochloride

N-[2-(4-{[3-Chloro-4-(3-isobutoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide (1.00 g) was dissolved in ethyl acetate (10 mL), 4N hydrogen chloride/ethyl acetate solution (5.0 mL) was added thereto , and the precipitated solid was collected by filtration. The solid was washed with diisopropyl ether to give the title compound (1.03 g) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.95-0.98 (6H, m), 1.92-2.04 (1H, m), 3.05 (3H, s), 3.40-3.56 (2H, m), 3.72-3.75 (2H, m), 4.07 (2H, s), 4.71-4.75 (2H, m), 6.47-7.32 (6H, m), 7.62-7.97 (3H, m), 8.73 (1H, s), 8.83-8.88 (1H, m), 10.03 (1H, s).

Example C-102



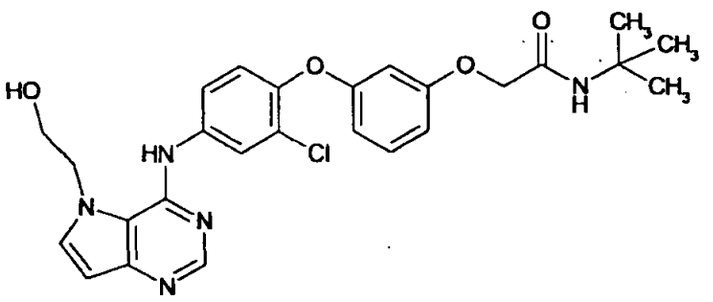
Production of N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-

methylbutanamide

To a solution of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (100 mg), 3-hydroxy-3-methylbutanoic acid (293 mg) and 1-hydroxybenzotriazole (10 mg) in tetrahydrofuran (15 mL) were added triethylamine (0.3 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (216 mg) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→90:10) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (66 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.29-0.58 (4H, m), 1.11-1.28 (1H, m), 1.16 (6H, s), 2.20 (2H, s), 3.35-3.41 (2H, m), 3.78-3.80 (2H, m), 4.49-4.54 (2H, m), 4.66 (1H, s), 6.43-7.26 (6H, m), 7.63-8.00 (3H, m), 8.25 (1H, br s), 8.32 (1H, s), 8.86(1H, br s).

Example C-103



Production of N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenoxy]acetamide

(i) Production of 2-[3-(4-amino-2-chlorophenoxy)phenoxy]-N-(tert-butyl)acetamide

To a solution of 3-(2-chloro-4-nitrophenoxy)phenol (1.0 g) in N,N-dimethylformamide (10 mL) were added ethyl bromoacetate (1.26 g) and potassium carbonate (1.20 g) and the mixture was stirred at room temperature for 18 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (20 mL), 1N aqueous sodium hydroxide solution (5.0 mL) was added thereto and the mixture was stirred at room temperature for 12 hr. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added thereto. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution of the obtained residue, 2-methylpropan-2-amine (1.0 mL) and 1-hydroxybenzotriazole (10 mg) in tetrahydrofuran (15 mL) were added triethylamine (1.3 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.50 g) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (23 mL), reduced iron (550 mg) and calcium chloride (70 mg) were added thereto, and the mixture was stirred at 80°C for 8 hr. The solid was

removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→0:1) to give the title compound (375 mg) as a brown oil.

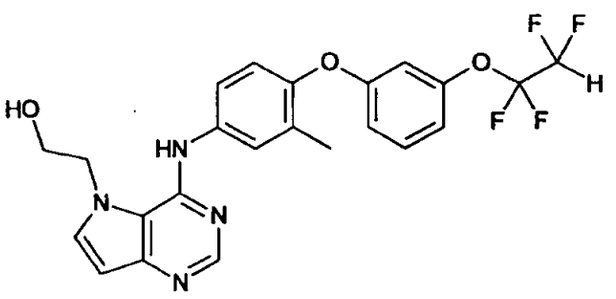
^{1}H-NMR (DMSO-d_6) δ: 1.29 (9H, s), 4.35 (2H, s), 5.35 (2H, s), 6.31-7.34 (2H, m), 6.52-6.58 (2H, m), 6.70-6.72 (1H, m), 6.88-6.93 (1H, m), 7.13-7.20 (1H, m).

(ii) Production of N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenoxy]acetamide

Using 2-[3-(4-amino-2-chlorophenoxy)phenoxy]-N-(tert-butyl)acetamide (100 mg), 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (87 mg), isopropyl alcohol (5.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and methanol (5.0 mL) and in the same manner as in Example C-57, the title compound (73 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.27 (9H, s), 3.86-3.89 (2H, m), 4.37 (2H, s), 4.51-4.55 (2H, m), 6.48-7.66 (9H, m), 7.95-8.97 (1H, m), 8.33 (1H, s), 9.87(1H, br s).

Example C-104



Production of 2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethanol

(i) Production of 2-methyl-4-nitro-1-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]benzene

A mixture of 2-fluoro-5-nitrotoluene (2.10 g) and 3-(1,1,2,2-tetrafluoroethoxy)phenol (3.01 g) was dissolved in N,N-dimethylformamide (13 mL), potassium carbonate (3.04 g) was added thereto, and the mixture was stirred at room temperature for 15 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=100:0→80:20) to give the title compound (4.05 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 5.91 (1H, tt, J= 2.8 Hz, 53.0 Hz), 6.87 (1H, d, J= 9.0 Hz), 6.89-6.98 (2H, m), 7.02-7.14 (1H, m), 7.41 (1H, t, J= 8.2 Hz), 8.04 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.18 (1H, d, J= 2.6 Hz).

(ii) Production of 3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline

Using 2-methyl-4-nitro-1-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]benzene (4.04 g), reduced iron (3.45 g), calcium chloride (691 mg) and ethanol (108 mL)/water (12 mL) and in the same manner as in Example C-72(ii), the title compound (3.45 g) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s), 3.59 (2H, br s), 5.86 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.53 (1H, dd, J= 3.0 Hz, 8.7 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.67 (1H, t, J= 2.2 Hz), 6.72-6.77 (1H, m), 6.80 (1H, d, J= 8.7 Hz), 6.81-6.86 (1H, m), 7.19-7.27 (1H, m).

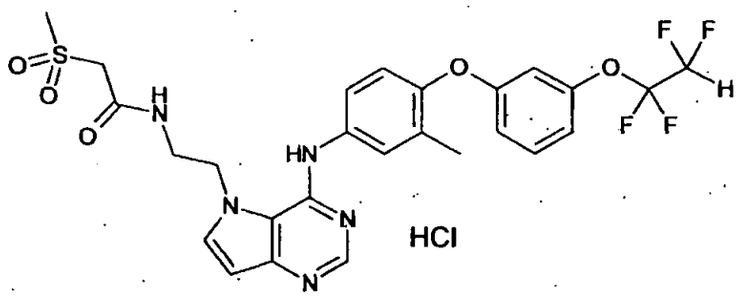
(iii) Production of 2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (102 mg), 3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline (110 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1.5 mL) and in the same manner as in Example C-72(iii), the title compound (114 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 4.14 (2H, t, J= 4.5 Hz), 4.32-4.42 (2H, m), 5.89 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.15 (1H, d, J= 3.4 Hz), 6.75-7.02 (5H, m), 7.20-7.34 (1H, m), 7.40-7.52 (2H, m), 8.24 (1H, s), 9.30 (1H, s).

Example C-105



Production of 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide hydrochloride

(i) Production of tert-butyl {2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

tert-Butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (304 mg) and 3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]aniline (331 mg) were dissolved in isopropyl alcohol (10 mL), and the mixture was stirred at 70°C for 20 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively

with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=67:33→10:90) to give the title compound (540 mg) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.21 (3H, s), 3.43-3.57 (2H, m), 4.40-4.54 (2H, m), 5.00 (1H, t, J= 5.5 Hz), 5.88 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.75-6.80 (1H, m), 6.82-6.93 (2H, m), 6.94-7.02 (1H, m), 7.16 (1H, d, J= 3.0 Hz), 7.27 (1H, t, J= 8.1 Hz), 7.64-7.74 (2H, m), 8.36 (1H, br s), 8.50 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-{3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

tert-Butyl {2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (537 mg) was dissolved in tetrahydrofuran (2 mL), 6N hydrochloric acid (0.8 mL) was added thereto, and the mixture was stirred at 50°C for 15 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and the mixture was concentrated again under reduced pressure. The precipitate was collected by filtration to give the title compound (460 mg) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.22-3.48 (2H, m), 4.99 (2H, t, J= 6.1 Hz), 6.72 (1H, d, J= 3.2 Hz), 6.76 (1H, t, J= 2.3 Hz), 6.80 (1H, tt, J= 3.1 Hz, 52 Hz), 6.90-6.96 (1H, m), 7.00-7.07 (1H, m), 7.11 (1H, d, J= 8.7 Hz), 7.47 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.49 (1H, t, J= 8.3 Hz), 7.54 (1H, d, J= 2.5 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.29 (3H, br s), 8.68 (1H, s), 9.87 (1H, br s).

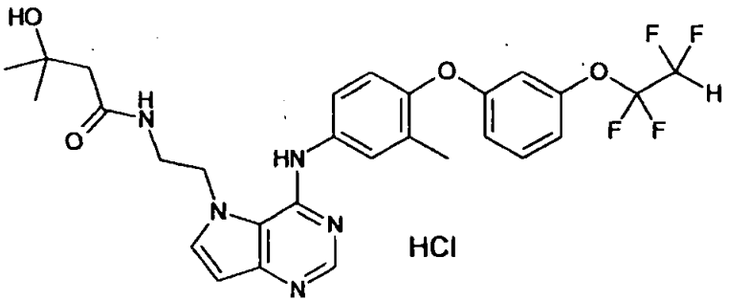
(iii) Production of 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-

d]pyrimidin-5-yl]ethyl}acetamide hydrochloride

Using 5-(2-aminoethyl)-N-{3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (121 mg), methylsulfonylacetic acid (48.8 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (47 mg), triethylamine (0.3 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (64.3 mg) and in the same manner as in Example C-72(i), 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide was obtained. The compound was dissolved in ethyl acetate, treated with 4N hydrogen chloride/ethyl acetate solution, and crystallized from ethyl acetate/ethanol to give the title compound (104 mg) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.07 (2H, m), 4.70 (2H, t, J= 6.4 Hz), 6.61-6.99 (1H, m), 6.64 (1H, d, J= 3.2 Hz), 6.76 (1H, t, J= 2.3 Hz), 6.91-6.96 (1H, m), 6.99-7.07 (1H, m), 7.12 (1H, d, J= 8.5 Hz), 7.44-7.61 (3H, m), 7.91 (1H, d, J= 3.2 Hz), 8.68 (1H, s), 8.78 (1H, t, J= 5.7 Hz), 9.85 (1H, s).

Example C-106



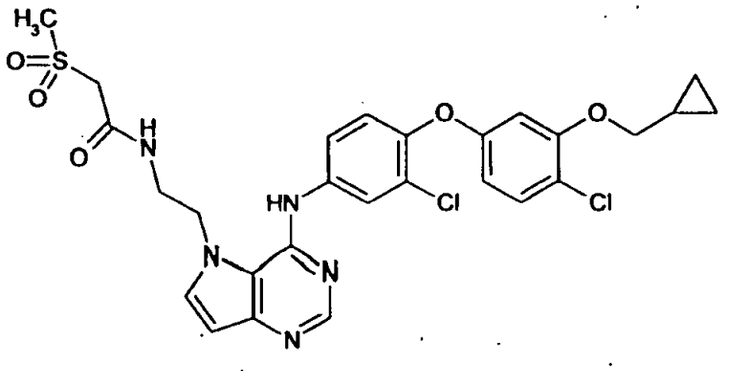
Production of 3-hydroxy-3-methyl-N-{2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}butanamide

hydrochloride

Using 5-(2-aminoethyl)-N-{3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (120 mg), 3-hydroxy-3-methylbutanoic acid (40.5 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (47.6 mg), triethylamine (0.3 mL) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (66.1 mg) and in the same manner as in Example C-72(i), 3-hydroxy-3'-methyl-N-{2-[4-({3-methyl-4-[3-(1,1,2,2-tetrafluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}butanamide was obtained. The compound was dissolved in ethyl acetate, treated with 4N hydrogen chloride/ethyl acetate solution, and crystallized from diisopropyl ether/ethyl acetate to give the title compound (108 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.11 (6H, s), 2.18 (3H, s), 2.20 (2H, s), 3.44-3.56 (2H, m), 4.65 (2H, t, J= 6.8 Hz), 6.60-6.99 (1H, m), 6.65 (1H, d, J= 3.0 Hz), 6.75 (1H, t, J= 2.3 Hz), 6.91-6.96 (1H, m), 6.99-7.06 (1H, m), 7.11 (1H, d, J= 8.7 Hz), 7.49 (1H, t, J= 8.3 Hz), 7.54 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.60 (1H, d, J= 2.5 Hz), 7.95 (1H, d, J= 3.0 Hz), 8.37 (1H, t, J= 5.5 Hz), 8.68 (1H, s), 10.16 (1H, s).

Example C-107



Production of N-{2-[4-({3-chloro-4-[4-chloro-3-

(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 3-chloro-4-[4-chloro-3-(cyclopropylmethoxy)phenoxy]aniline

To a solution of 3-chloro-4-fluoronitrobenzene (5.00 g), 4-chlorobenzene-1,3-diol (4.11 g) in N,N-dimethylformamide (35 mL) was added potassium carbonate (5.50 g) and the mixture was stirred at room temperature for 5 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in N,N-dimethylformamide (15 mL), 1-(bromomethyl)cyclopropane (1.3 mL) and potassium carbonate (1.50 g) were added thereto and the mixture was stirred at room temperature for 12 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=1:0→1:1). The obtained crude product was dissolved in 15% water-containing ethanol (30 mL), reduced iron (550 mg) and calcium chloride (70 mg) were added thereto, and the mixture was stirred at 80°C for 8 hr. The solid was removed by filtration, and the filtrate was concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under

reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=4:1→0:1) to give the title compound (868 mg) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 0.35-0.68 (4H, m), 0.84-0.90 (1H, m), 3.87 (2H, d, J = 6.7 Hz), 5.36 (2H, s), 6.33-7.34 (1H, m), 6.52-6.58 (2H, m), 6.69-6.71 (1H, m), 6.86-6.92 (1H, m), 7.13-7.21 (1H, m).

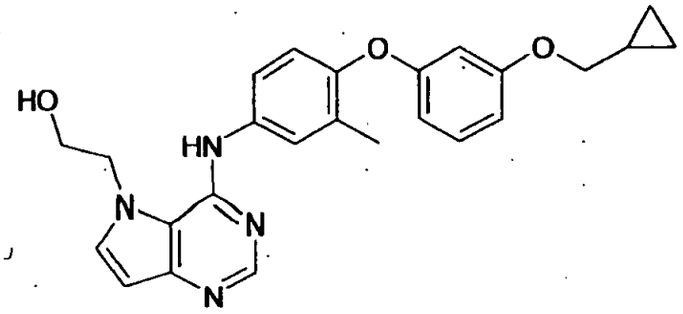
(ii) Production of N-{2-[4-({3-chloro-4-[4-chloro-3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 3-chloro-4-[4-chloro-3-(cyclopropylmethoxy)phenoxy]aniline (200 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (183 mg), isopropyl alcohol (9 mL), methanol (15 mL), 4N hydrogen chloride/ethyl acetate solution (8.0 mL), methylsulfonylacetic acid(170 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (300 mg), 1-hydroxybenzotriazole (50 mg), triethylamine (1.1 mL) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-53(ii), the title compound (61 mg) was obtained as crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.36-0.42 (2H, m), 0.62-0.68 (2H, m), 0.86-0.90 (1H, m), 3.13 (3H, s), 3.68-3.72 (2H, m), 3.86 (2H, d, J = 6.7 Hz), 3.98 (2H, s), 4.45-4.52 (2H, m), 6.43-7.28 (6H, m), 7.50 (1H, br s), 7,68-7.72 (1H, m), 7.92 (1H, s), 8.18 (1H, br s), 8.49 (1H, s).

Example C-108

252



Production of 2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 3-(2-methyl-4-nitrophenoxy)phenol

Using 2-fluoro-5-nitrotoluene (10.0 g), resorcinol (24.8 g), potassium carbonate (31.3 g) and N,N-dimethylformamide (120 mL) and in the same manner as in Example C-104(i), the title compound (7.19 g) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 5.12 (1H, s), 6.52 (1H, t, J= 2.3 Hz), 6.55-6.61 (1H, m), 6.64-6.70 (1H, m), 6.84 (1H, d, J= 9.0 Hz), 7.24 (1H, t, J= 8.1 Hz), 7.99 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.14 (1H, d, J= 2.8 Hz).

(ii) Production of 1-[3-(cyclopropylmethoxy)phenoxy]-2-methyl-4-nitrobenzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (939 mg), 1-(bromomethyl)cyclopropane (0.55 mL), potassium carbonate (963 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (1.02 g) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.28-0.42 (2H, m), 0.58-0.71 (2H, m), 1.17-1.36 (1H, m), 2.39 (3H, s), 3.78 (2H, d, J= 7.2 Hz), 6.53-6.63 (2H, m), 6.71-6.78 (1H, m), 6.82 (1H, d, J= 8.8 Hz), 7.27 (1H, t, J= 8.1 Hz), 7.98 (1H, dd, J= 2.8 Hz, 8.8 Hz), 8.14 (1H, d, 2.8 Hz).

(iii) Production of 4-[3-(cyclopropylmethoxy)phenoxy]-3-methylaniline

Using 1-[3-(cyclopropylmethoxy)phenoxy]-2-methyl-4-

nitrobenzene (1.01 g), reduced iron (964 mg), calcium chloride (196 mg) and ethanol (36 mL)/water (4 mL) and in the same manner as in Example C-72(ii), the title compound (809 mg) was obtained as a black-brown oil.

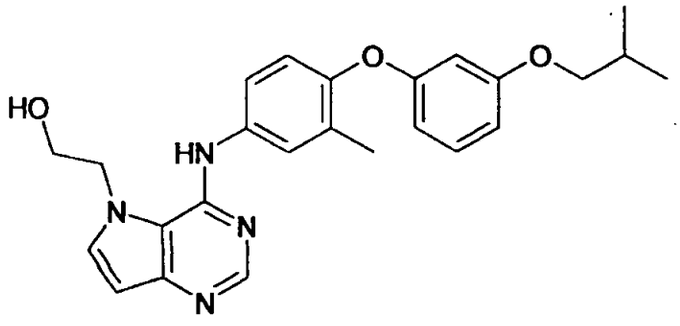
^{1}H-NMR ($CDCl_3$) δ: 0.26-0.38 (2H, m), 0.55-0.68 (2H, m), 1.13-1.34 (1H, m), 2.09 (3H, s), 3.54 (2H, br s), 3.73 (2H, d, J= 6.9 Hz), 6.37-6.45 (2H, m), 6.47-6.54 (2H, m), 6.57 (1H, d, J= 2.5 Hz), 6.78 (1H, d, J= 8.5 Hz), 7.07-7.16 (1H, m).

(iv) Production of 2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (99.7 mg), 4-[3-(cyclopropylmethoxy)phenoxy]-3-methylaniline (98.7 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1.5 mL) and in the same manner as in Example C-72(iii), the title compound (106 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.29-0.39 (2H, m), 0.58-0.70 (2H, m), 1.17-1.33 (1H, m), 2.24 (3H, s), 3.77 (2H, d, J= 7.0 Hz), 4.08-4.17 (2H, m), 4.37 (2H, t, J= 4.4 Hz), 6.13 (1H, d, J= 3.0 Hz), 6.47-6.62 (3H, m), 6.94 (1H, d, J= 3.0 Hz), 6.97 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J= 8.1 Hz), 7.37-7.48 (2H, m), 8.23 (1H, s), 9.28 (1H, s).

Example C-109



Production of 2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-

yl)ethanol

(i) Production of 1-(3-isobutoxyphenoxy)-2-methyl-4-nitrobenzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (822 mg), isobutyl bromide (0.55 mL), potassium carbonate (834 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (884 mg) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J= 6.8 Hz), 1.97-2.18 (1H, m), 2.40 (3H, s), 3.70 (2H, d, J= 6.4 Hz), 6.52-6.64 (2H, m), 6.71-6.78 (1H, m), 6.82 (1H, d, J= 9.1 Hz), 7.22-7.33 (1H, m), 7.99 (1H, dd, J= 3.0 Hz, 9.1 Hz), 8.14 (1H, d, J= 3.0 Hz).

(ii) Production of 4-(3-isobutoxyphenoxy)-3-methylaniline

Using 1-(3-isobutoxyphenoxy)-2-methyl-4-nitrobenzene (879 mg), reduced iron (823 mg), calcium chloride (162 mg) and ethanol (27 mL)/water (3 mL) and in the same manner as in Example C-72(ii), the title compound (756 mg) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, d, J= 6.6 Hz), 1.95-2.10 (1H, m), 2.11 (3H, s), 3.55 (2H, br s), 3.66 (2H, d, J= 6.3 Hz), 6.35-6.44 (2H, m), 6.49-6.52 (1H, m), 6.52-6.55 (1H, m), 6.58 (1H, d, J= 3.0 Hz), 6.80 (1H, d, J= 8.5 Hz), 7.12 (1H, t, J= 8.1 Hz).

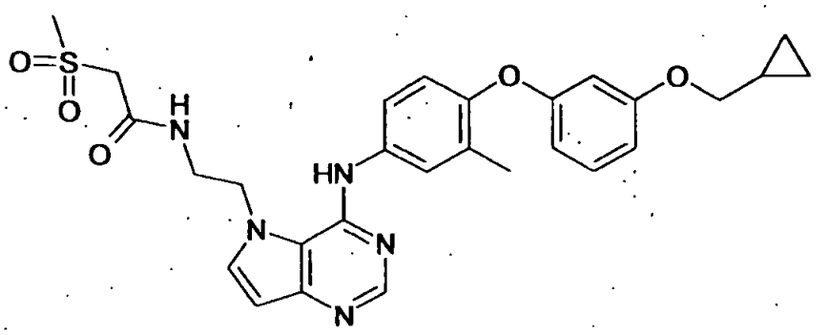
(iii) Production of 2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (110 mg), 4-(3-isobutoxyphenoxy)-3-methylaniline (103 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1.5 mL) and in the same manner as in Example C-72(iii), the title compound (116 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J= 6.8 Hz), 1.97-2.16 (1H,

m), 2.25 (3H,s), 3.70 (2H, d, J= 6.4 Hz), 4.12 (2H, t, J= 4.3 Hz), 4.35 (2H, t, J= 4.3 Hz), 6.10 (1H, d, J= 3.2 Hz), 6.45-6.54 (2H, m), 6.54-6.62 (1H, m), 6.91 (1H, d, J= 3.2 Hz), 6.97 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J=8.3 Hz), 7.37-7.48 (2H, m), 8.21 (1H, s), 9.31 (1H, s).

Example C-110



Production of N-{2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl {2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (402 mg), 4-[3-(cyclopropylmethoxy)phenoxy]-3-methylaniline (395 mg) and isopropyl alcohol (15 mL) and in the same manner as in Example C-105(i), the title compound (710 mg) was obtained as a pale-orange powder.

^{1}H-NMR ($CDCl_3$) δ: 0.27-0.39 (2H, m), 0.54-0.69 (2H, m), 1.16-1.32 (1H, m), 1.46 (9H, s), 2.22 (3H, s), 3.41-3.58 (2H, m), 3.76 (2H, d, J= 6.8 Hz), 4.39-4.53 (2H, m), 4.99 (1H, d, J= 9.5 Hz), 6.46-6.63 (4H, m), 6.95 (1H, d, J= 9.5 Hz), 7.09-7.20 (2H, m), 7.55-7.73 (2H, m), 8.28 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-{4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (707 mg), 6N hydrochloric acid (1 mL) and ethanol (3 mL) and in the same manner as in Example C-105(ii), the title compound (578 mg) was obtained as a yellow powder.

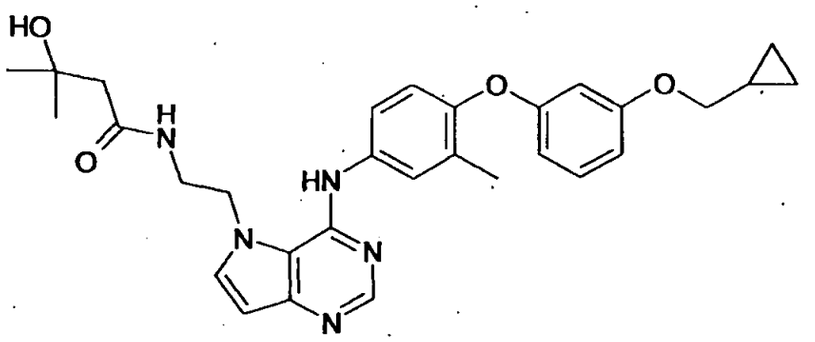
^{1}H-NMR (DMSO-d_6) δ: 0.25-0.36 (2H, m), 0.49-0.62 (2H, m), 1.12-1.27 (1H, m), 2.19 (3H, s), 3.20-3.33 (2H, m), 3.79 (2H, d, J= 6.9 Hz), 5.01 (2H, t, J= 6.1 Hz), 6.40-6.49 (2H, m), 6.62-6.69 (1H, m), 6.71 (1H, d, J= 3.0 Hz), 7.01 (1H, d, J= 8.5 Hz), 7.19-7.29 (1H, m), 7.40 (1H, dd, J= 2.5 Hz, 8.5 Hz), 7.49 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.0 Hz), 8.33 (3H, br s), 8.67 (1H, s), 9.90 (1H, br s).

(iii) Production of N-{2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 5-(2-aminoethyl)-N-{4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (120 mg), methylsulfonylacetic acid (50.5 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (51.5 mg), triethylamine (0.35 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (116 mg) and in the same manner as in Example C-72(i), the title compound (72.4 mg) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 0.28-0.39 (2H, m), 0.57-0.70 (2H, m), 1.17-1.34 (1H, m), 2.24 (3H, s), 3.08 (3H, s), 3.62-3.75 (2H, m), 3.77 (2H, d, J= 7.0 Hz), 3.93 (2H, s), 4.38-4.53 (2H, m), 6.45-6.63 (4H, m), 6.95 (1H, d, J= 8.5 Hz), 7.11-7.23 (2H, m), 7.36-7.50 (2H, m), 7.57 (1H, d, J= 2.1 Hz), 7.83 (1H, s), 8.47 (1H, s).

Example C-111

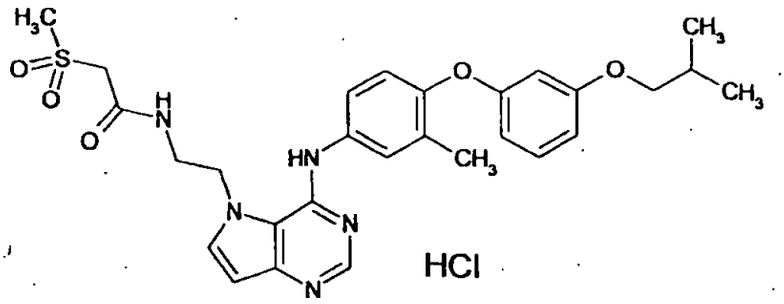


Production of N-{2-[4-({4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide

Using 5-(2-aminoethyl)-N-{4-[3-(cyclopropylmethoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (121 mg), 3-hydroxy-3-methylbutanoic acid (46.2 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (59.8 mg), triethylamine (0.35 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (88.0 mg) and in the same manner as in Example C-72(i), the title compound (60.0 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.29-0.38 (2H, m), 0.58-0.68 (2H, m), 1.17-1.33 (1H, m), 1.30 (6H, s), 2.24 (3H, s), 2.44 (2H, s), 3.56-3.70 (2H, m), 3.77 (2H, d, J= 7.0 Hz), 4.41-4.53 (2H, m), 6.48-6.62 (4H, m), 6.86-6.93 (1H, m), 6.95 (1H, d, J= 8.7 Hz), 7.11-7.22 (2H, m), 7.54 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.62 (1H, d, J= 2.5 Hz), 8.32 (1H, s), 8.47 (1H, s).

Example C-112



Production of N-[2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of tert-butyl [2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (307 mg), 4-(3-isobutoxyphenoxy)-3-methylaniline (304 mg) and isopropyl alcohol (12 mL) and in the same manner as in Example C-105(i), the title compound (504 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, d, J= 6.8 Hz), 1.46 (9H, s), 1.97-2.14 (1H, m), 2.23 (3H, s), 3.41-3.58 (2H, m), 3.68 (2H, d, J= 6.4 Hz), 4.39-4.54 (2H, m), 5.01 (1H, t, J= 5.5 Hz), 6.45-6.63 (4H, m), 6.96 (1H, d, J= 8.7 Hz), 7.09-7.21 (2H, m), 7.58-7.71 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-[4-(3-isobutoxyphenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl [2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (499 mg), 6N hydrochloric acid (1 mL) and ethanol (3 mL) and in the same manner as in Example C-105(ii), the title compound (429 mg) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 0.96 (6H, d, J= 6.6 Hz), 1.91-2.08

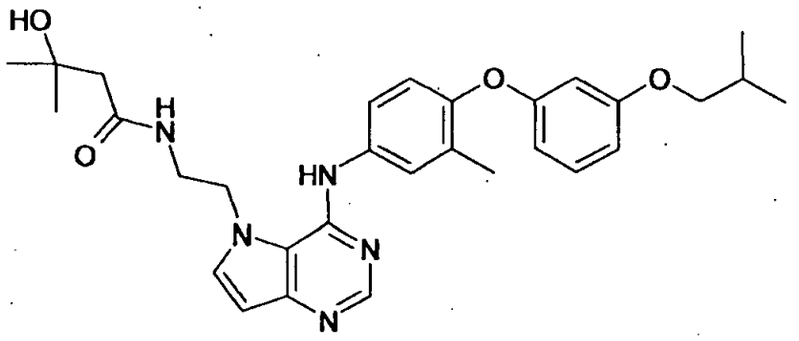
(1H, m), 2.20 (3H, s), 3.21-3.85 (2H, m), 3.73 (2H, d J= 6.4 Hz), 5.02 (2H, t, J= 6.1 Hz), 6.40-6.52 (2H, m), 6.64-6.70 (1H, m), 6.72 (1H, d, J= 3.2 Hz), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.5 Hz), 8.05 (1H, d, J= 3.2 Hz), 8.37 (3H, br s), 8.68 (1H, s), 9.94 (1H, br s).

(iii) Production of N-[2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide hydrochloride

Using 5-(2-aminoethyl)-N-[4-(3-isobutoxyphenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (119 mg), methylsulfonylacetic acid (50.3 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (50.1 mg), triethylamine (0.35 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (82.7 mg) and in the same manner as in Example C-72(i), N-[2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide was obtained. The compound was dissolved in ethyl acetate and treated with 4N hydrogen chloride/ethyl acetate solution, and the precipitate was collected by filtration to give the title compound (104 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.96 (6H, d, J= 6.6 Hz), 1.88-2.09 (1H, m), 2.20 (3H, s), 3.06 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.73 (2H, d, J= 6.6 Hz), 4.06 (2H, s), 4.69 (2H, t, J= 6.0 Hz), 6.39-6.52 (2H, m), 6.64 (1H, d, J= 3.2 Hz), 6.65-6.72 (1H, m), 7.02 (1H, d, J= 8.8 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.45 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.2 Hz), 8.67 (1H, s), 8.77 (1H, t, J= 6.0 Hz), 9.82 (1H, s).

Example C-113

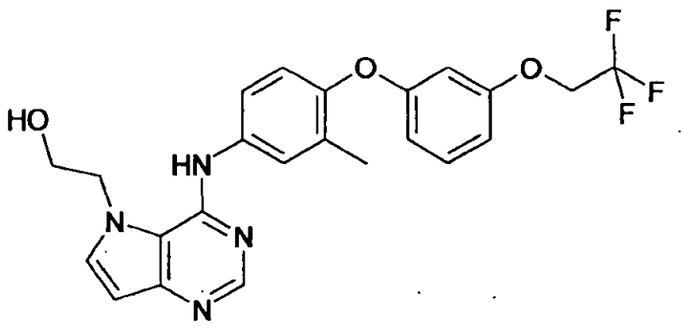


Production of 3-hydroxy-N-[2-(4-{[4-(3-isobutoxyphenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-methylbutanamide

Using 5-(2-aminoethyl)-N-[4-(3-isobutoxyphenoxy)-3-methylphenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (120 mg), 3-hydroxy-3-methylbutanoic acid (46.1 mg), tetrahydrofuran (0.6 mL)/N,N-dimethylformamide (0.6 mL), 1-hydroxybenzotriazole (50.2 mg), triethylamine (0.35 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (82.7 mg) and in the same manner as in Example C-72(i), the title compound (91.0 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, d, J= 6.6 Hz), 1.30 (6H, s), 1.97-2.15 (1H, m), 2.25 (3H, s), 2.44 (2H, s), 3.57-3.67 (2H, m), 3.69 (2H, d, J= 6.6 Hz), 4.41-4.54 (2H, m), 6.44-6.63 (4H, m), 6.84 (1H, t, J= 5.9 Hz), 6.95 (1H, d, J= 8.7 Hz), 7.11-7.21 (2H, m), 7.55 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.63 (1H, d, J= 2.5 Hz), 8.31 (1H, s), 8.48 (1H, s).

Example C-114



Production of 2-[4-({3-methyl-4-[3-(2,2,2-

trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 2-methyl-4-nitro-1-[3-(2,2,2-trifluoroethoxy)phenoxy]benzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (797 mg), 1,1,1-trifluoro-2-iodoethane (0.5 mL), potassium carbonate (903 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (780 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 4.35 (2H, q, J= 8.0 Hz), 6.64 (1H, t, J= 2.4 Hz), 6.67-6.74 (1H, m), 6.74-6.81 (1H, m), 6.84 (1H, d, J= 9.0 Hz), 7.34 (1H, t, J= 8.3 Hz), 8.02 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.16 (1H, d, J= 2.8 Hz).

(ii) Production of 3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]aniline

Using 2-methyl-4-nitro-1-[3-(2,2,2-trifluoroethoxy)phenoxy]benzene (774 mg), reduced iron (685 mg), calcium chloride (138 mg) and ethanol (22.5 mL)/water (2.5 mL) and in the same manner as in Example C-72(ii), the title compound (529 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 3.57 (2H, br s), 4.28 (2H, q, J= 8.0 Hz), 6.43 (1H, t, J= 2.5 Hz), 6.48-6.56 (3H, m), 6.58 (1H, d, J= 2.8 Hz), 6.78 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J= 8.3 Hz).

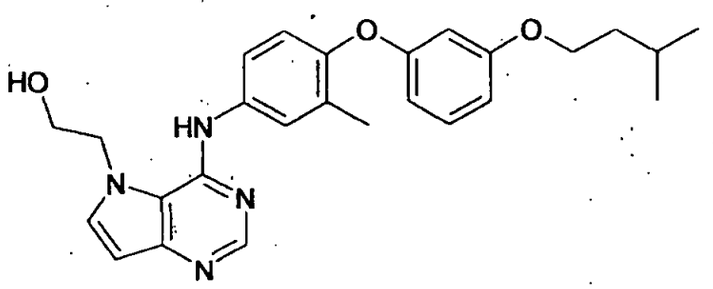
(iii) Production of 2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (101 mg), 3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]aniline (100 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example C-72(iii), the title compound (63.9 mg) was obtained as a white

powder.

^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 4.13 (2H, t, J= 4.4 Hz), 4.25-4.43 (4H, m), 6.13 (1H, d, J= 3.2 Hz), 6.54 (1H, t, J= 2.3 Hz), 6.56-6.68 (2H, m), 6.94 (1H, d, J= 3.2 Hz), 6.98 (1H, d, J= 8.5 Hz), 7.23 (1H, t, J= 8.3 Hz), 7.39-7.49 (2H, m), 8.23 (1H, s), 9.32 (1H, s).

Example C-115



Production of 2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 2-methyl-1-[3-(3-methylbutoxy)phenoxy]-4-nitrobenzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (855 mg), 1-iodo-3-methylbutane (0.8 mL), potassium carbonate (968 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (983 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, J= 6.6 Hz), 1.67 (2H, q, J= 6.6 Hz), 1.74-1.93 (1H, m), 2.40 (3H, s), 3.97 (2H, t, J= 6.6 Hz), 6.55-6.62 (2H, m), 6.71-6.79 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.24-7.33 (1H, m), 8.00 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.6 Hz).

(ii) Production of 3-methyl-4-[3-(3-methylbutoxy)phenoxy]aniline

Using 2-methyl-1-[3-(3-methylbutoxy)phenoxy]-4-nitrobenzene (978 mg), reduced iron (879 mg), calcium chloride (176 mg) and ethanol (27 mL)/water (3 mL) and in the same manner as in Example C-72(ii), the title compound (835 mg) was obtained as a brown oil.

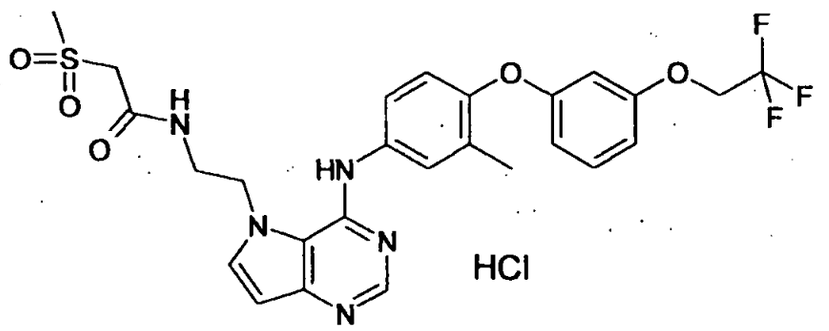
^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, d, J= 6.7 Hz), 1.64 (2H, q, J= 6.7 Hz), 1.72-1.90 (1H, m), 2.10 (3H, s), 3.55 (2H, br s), 3.93 (2H, t, J= 6.7 Hz), 6.36-6.44 (2H, m), 6.48-6.55 (2H, m), 6.58 (1H, d, J= 2.8 Hz), 6.80 (1H, d, J= 8.3 Hz), 7.06-7.18 (1H, m).

(iii) Production of 2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (105 mg), 3-methyl-4-[3-(3-methylbutoxy)phenoxy]aniline (102 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example C-72(iii), the title compound (91.5 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d, J= 6.7 Hz), 1.66 (2H, q, J= 6.7 Hz), 1.75-1.92 (1H, m), 2.25 (3H, s), 3.96 (2H, t, J= 6.7 Hz), 4.12 (2H, t, J= 4.4 Hz), 4.31-4.41 (2H, m), 6.11 (1H, d, J= 3.2 Hz), 6.46-6.54 (2H, m), 6.54-6.62 (1H, m), 6.92 (1H, d, J= 3.2 Hz), 6.97 (1H, d, J= 8.3 Hz), 7.12-7.22 (1H, m), 7.36-7.50 (2H, m), 8.22 (1H, s), 9.29 (1H, s).

Example C-116



Production of 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide hydrochloride

(i) Production of tert-butyl {2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-

pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (305 mg), 3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]aniline (326 mg) and isopropyl alcohol (12 mL) and in the same manner as in Example C-105(i), the title compound (489 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.21 (3H, s), 3.42-3.58 (2H, m), 4.31 (2H, q, J= 8.1 Hz), 4.41-4.55 (2H, m), 5.03 (1H, t, J= 5.0 Hz), 6.53 (1H, t, J= 2.4 Hz), 6.56-6.67 (3H, m), 6.91-7.02 (1H, m), 7.16 (1H, d, J= 3.2 Hz), 7.21 (1H, t, J= 8.2 Hz), 7.56-7.77 (2H, m), 8.38 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-{3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (484 mg), 6N hydrochloric acid (1 mL) and ethanol (3 mL) and in the same manner as in Example C-105(ii), the title compound (423 mg) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 3.21-3.33 (2H, m), 4.78 (2H, q, J= 8.9 Hz), 5.01 (2H, t, J= 6.1 Hz), 6.56 (1H, dd, J= 2.0 Hz, 8.0 Hz), 6.64 (1H, t, J= 2.0 Hz), 6.72 (1H, d, J= 3.2 Hz), 6.81 (1H, dd, J= 2.0 Hz, 8.0 Hz), 7.04 (1H, d, J= 8.7 Hz), 7.33 (1H, t, J= 8.0 Hz), 7.43 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.52 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.2 Hz), 8.34 (3H, br s), 8.68 (1H, s), 9.92 (1H, br s).

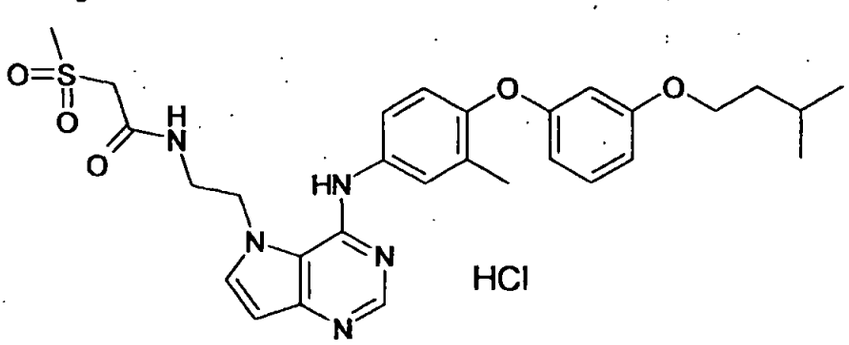
(iii) Production of 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide hydrochloride

Using 5-(2-aminoethyl)-N-{3-methyl-4-[3-(2,2,2-

trifluoroethoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (152 mg), methylsulfonylacetic acid (64.5 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (70.6 mg), triethylamine (0.4 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (93.8 mg) and in the same manner as in Example C-72(i), 2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide was obtained. The compound was dissolved in ethyl acetate and treated with 4N hydrogen chloride/ethyl acetate solution, and the precipitate was collected by filtration to give the title compound (132 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.07 (2H, s), 4.69 (2H, t, J= 6.5 Hz), 4.77 (2H, q, J= 8.9 Hz), 6.52-6.59 (1H, m), 6.61-6.68 (2H, m), 6.81 (1H, dd, J= 2.3 Hz, 8.1 Hz), 7.04 (1H, d, J= 8.7 Hz), 7.33 (1H, t, J= 8.1 Hz), 7.47 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.54 (1H, d, J= 2.5 Hz), 7.91 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.79 (1H, t, J= 5.5 Hz), 9.85 (1H, s).

Example C-117



Production of N-{2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

265.

(i) Production of tert-butyl {2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (400 mg), 3-methyl-4-[3-(3-methylbutoxy)phenoxy]aniline (408 mg) and isopropyl alcohol (15 mL) and in the same manner as in Example C-105(i), the title compound (692 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95 (6H, d, J= 6.6 Hz), 1.46 (9H, s), 1.61-1.71 (2H, m), 1.74-1.91 (1H, m), 2.23 (3H, s), 3.42-3.58 (2H, m), 3.95 (2H, t, J= 6.6 Hz), 4.39-4.54 (2H, m), 5.01 (1H, t, J= 6.1 Hz), 6.45-6.62 (4H, m), 6.96 (1H, d, J= 8.9 Hz), 7.10-7.22 (2H, m), 7.57-7.74 (2H, m), 8.33 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-{3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (685 mg), 6N hydrochloric acid (1 mL) and ethanol (3 mL) and in the same manner as in Example C-105(ii), the title compound (602 mg) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 0.92 (6H, d, J= 6.6 Hz), 1.59 (2H, q, J= 6.6 Hz), 1.67-1.86 (1H, m), 2.20 (3H, s), 3.20-3.33 (2H, m), 3.97 (2H, t, J= 6.6 Hz), 5.01 (2H, t, J= 6.2 Hz), 6.40-6.52 (2H, m), 6.68 (1H, dd, J= 2.0 Hz, 8.3 Hz), 6.72 (1H, d, J= 3.0 Hz), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.3 Hz), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.0 Hz), 8.05 (1H, d, J= 3.0 Hz), 8.35 (3H, br s), 8.67 (1H, s), 9.91 (1H, br s).

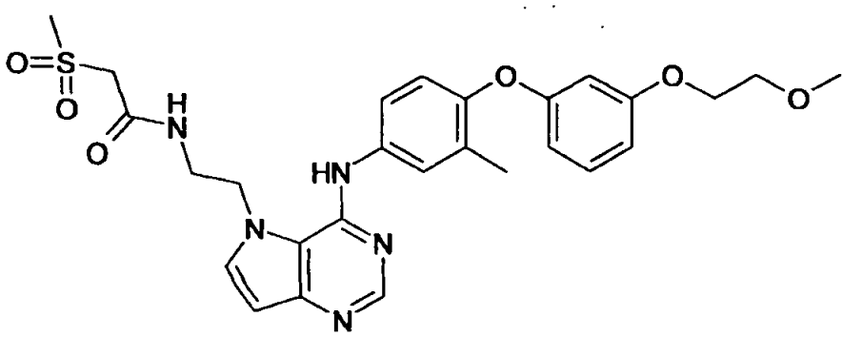
(iii) Production of N-{2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

hydrochloride

Using 5-(2-aminoethyl)-N-{3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (150 mg), methylsulfonylacetic acid (60.9 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (68.1 mg), triethylamine (0.4 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (92.2 mg) and in the same manner as in Example C-72(i), N-{2-[4-({3-methyl-4-[3-(3-methylbutoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide was obtained. The compound was dissolved in ethyl acetate and treated with 4N hydrogen chloride/ethyl acetate solution, and the precipitate was collected by filtration to give the title compound (116 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 0.92 (6H, d, J= 6.6 Hz), 1.59 (2H, q, J= 6.6 Hz), 1.67-1.84 (1H, m), 2.20 (3H, s), 3.05 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.97 (2H, t, J= 6.6 Hz), 4.06 (2H, s), 4.69 (2H, t, J= 6.0 Hz), 6.40-6.52 (2H, m), 6.64 (1H, d, J= 3.2 Hz), 6.66-6.72 (1H, m), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.45 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.2 Hz), 8.67 (1H, s), 8.78 (1H, t, J= 6.0 Hz), 9.83 (1H, s).

Example C-118



Production of N-{2-[4-({4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-

266

yl]ethyl}-2-(methylsulfonyl)acetamide

(i) Production of 1-[3-(2-methoxyethoxy)phenoxy]-2-methyl-4-nitrobenzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (806 mg), 1-bromo-2-methoxyethane (0.5 mL), potassium carbonate (910 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (855 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.45 (3H, s), 3.69-3.80 (2H, m), 4.06-4.15 (2H, m), 6.57-6.65 (2H, m), 6.75-6.80 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.24-7.33 (1H, m), 7.99 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.8 Hz).

(ii) Production of 4-[3-(2-methoxyethoxy)phenoxy]-3-methylaniline

Using 1-[3-(2-methoxyethoxy)phenoxy]-2-methyl-4-nitrobenzene (850 mg), reduced iron (825 mg), calcium chloride (167 mg) and ethanol (27 mL)/water (3 mL) and in the same manner as in Example C-72(ii), the title compound (707 mg) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s), 3.43 (3H, s), 3.56 (2H, br s), 3.67-3.76 (2H, m), 4.02-4.09 (2H, m), 6.35-6.63 (5H, m), 6.79 (1H, d, J= 8.3 Hz), 7.13 (1H, t, J= 8.3 Hz).

(iii) Production of tert-butyl {2-[4-({4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (358 mg), 4-[3-(2-methoxyethoxy)phenoxy]-3-methylaniline (364 mg) and isopropyl alcohol (15 mL) and in the same manner as in Example C-105(i), the title compound (563 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.22 (3H, s), 3.44 (3H, s), 3.45-3.56 (2H, m), 3.69-3.77 (2H, m), 4.04-4.10 (2H,

m), 4.40-4.52 (2H, m), 5.01 (1H, t, J= 5.7 Hz), 6.49-6.65 (4H, m), 6.91-6.99 (1H, m), 7.12-7.23 (2H, m), 7.53-7.73 (2H, m), 8.31 (1H, br s), 8.49 (1H, s).

(iv) Production of 5-(2-aminoethyl)-N-{4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (558 mg), 6N hydrochloric acid (1 mL) and ethanol (4 mL) and in the same manner as in Example C-105(ii), the title compound (471 mg) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 3.21-3.38 (2H, m), 3.29 (3H, s), 3.58-3.69 (2H, m), 4.00-4.13 (2H, m), 5.00 (2H, t, J= 6.0 Hz), 6.44-6.54 (2H, m), 6.65-6.71 (1H, m), 6.72 (1H, d, J= 3.2 Hz), 7.03 (1H, d, J= 8.7 Hz), 7.20-7.33 (1H, m), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.2 Hz), 8.32 (3H, br s), 8.68 (1H, s), 9.88 (1H, br s).

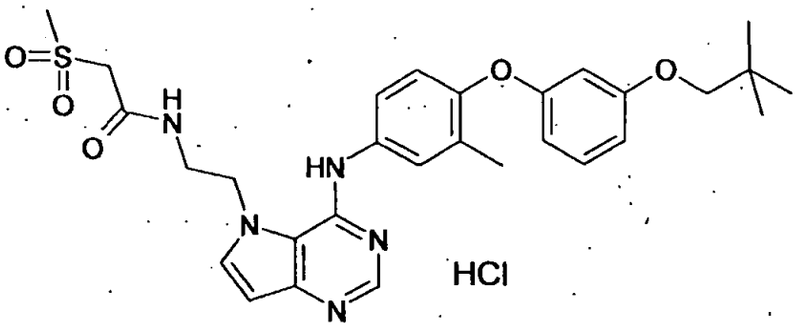
(v) Production of N-{2-[4-({4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

Using 5-(2-aminoethyl)-N-{4-[3-(2-methoxyethoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (151 mg), methylsulfonylacetic acid (67.3 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (94.2 mg), triethylamine (0.4 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (122 mg) and in the same manner as in Example C-72(i), the title compound (98.4 mg) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 3.08 (3H, s), 3.44 (3H, s), 3.63-3.78 (4H, m), 3.93 (2H, s), 4.04-4.13 (2H, m),

4.38-4.54 (2H, m), 6.51 (1H, t, J= 2.4 Hz), 6.53-6.66 (3H, m), 6.94 (1H, d, J= 8.7 Hz), 7.13-7.23 (2H, m), 7.44 (1H, dd, J= 2.0 Hz, 8.7 Hz), 7.51 (1H, t, J= 5.7 Hz), 7.56 (1H, d, J= 2.0 Hz), 7.83 (1H, s), 8.46 (1H, s).

Example C-119



Production of N-{2-[4-({4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of 1-[3-(2,2-dimethylpropoxy)phenoxy]-2-methyl-4-nitrobenzene

Using 3-(2-methyl-4-nitrophenoxy)phenol (803 mg), 1-iodo-2,2-dimethylpropane (0.75 mL), potassium carbonate (911 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example C-104(i), the title compound (826 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (9H, s), 2.40 (3H, s), 3.57 (2H, s), 6.55-6.62 (2H, m), 6.73-6.79 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.28 (1H, t, J= 8.5 Hz), 8.00 (1H, dd, J= 2.5 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.5 Hz).

(ii) Production of 4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylaniline

Using 1-[3-(2,2-dimethylpropoxy)phenoxy]-2-methyl-4-nitrobenzene (821 mg), reduced iron (876 mg), calcium chloride (147 mg) and ethanol (27 mL)/water (3 mL) and in the same manner as in Example C-72(ii), the title compound (745 mg) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (9H, s), 2.11 (3H, s), 3.53 (2H, s), 3.54 (2H, br s), 6.35-6.41 (1H, m), 6.43 (1H, t, J= 2.4 Hz), 6.48-6.56 (2H, m), 6.59 (1H, d, J= 2.8 Hz), 6.80 (1H, d, J= 8.0 Hz), 7.12 (1H, t, J= 8.0 Hz).

(iii) Production of tert-butyl {2-[4-({4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (351 mg), 4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylaniline (357 mg) and isopropyl alcohol (15 mL) and in the same manner as in Example C-105(i), the title compound (592 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (9H, s), 1.46 (9H, s), 2.24 (3H, s), 3.42-3.55 (2H, m), 3.56 (2H, s), 4.39-4.55 (2H, m), 5.02 (1H, t, J= 5.8 Hz), 6.44-6.65 (4H, m), 6.96 (1H, d, J= 8.5 Hz), 7.09-7.22 (2H, m), 7.56-7.72 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(iv) Production of 5-(2-aminoethyl)-N-{4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (586 mg), 6N hydrochloric acid (1 mL) and ethanol (4 mL) and in the same manner as in Example C-105(ii), the title compound (369 mg) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 0.98 (9H, s), 2.20 (3H, s), 3.18-3.36 (2H, m), 3.62 (2H, s), 4.99 (2H, t, J= 6.2 Hz), 6.40-6.55 (2H, m), 6.63-6.77 (2H, m), 7.02 (1H, d, J= 8.5 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.41 (1H, dd, J= 2.3 Hz, 8.5 Hz), 7.50 (1H, d, J= 2.3 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.29 (3H, br s), 8.67 (1H, s), 9.86 (1H, br s).

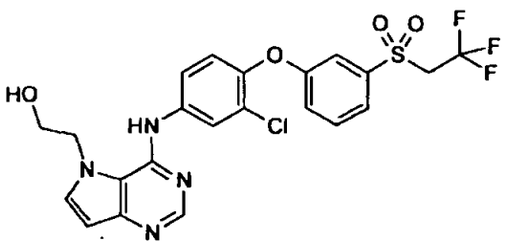
(v) Production of N-{2-[4-({4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}amino)-5H-

pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

Using 5-(2-aminoethyl)-N-{4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (152 mg), methylsulfonylacetic acid (63.0 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (86.5 mg), triethylamine (0.4 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (125 mg) and in the same manner as in Example C-72(i), N-{2-[4-({4-[3-(2,2-dimethylpropoxy)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide was obtained. The compound was dissolved in ethyl acetate and treated with 4N hydrogen chloride/ethyl acetate solution, and the precipitate was collected by filtration to give the title compound (126 mg) as yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.98 (9H, s), 2.20 (3H, s), 3.05 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.61 (2H, s), 4.07 (2H, s), 4.70 (2H, t, J= 6.0 Hz), 6.40-6.53 (2H, m), 6.64 (1H, d, J= 3.0 Hz), 6.69 (1H, dd, J= 1.7 Hz, 8.0 Hz), 7.02 (1H, d, J= 8.5 Hz), 7.26 (1H, t, J= 8.0 Hz), 7.45 (1H, dd, J= 2.0 Hz, 8.5 Hz), 7.53 (1H, d, J= 2.0 Hz), 7.91 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.80 (1H, t, J= 6.0 Hz), 9.86 (1H, s).

Example C-120



Production of 2-{4-[(3-chloro-4-{3-[(2,2,2-trifluoroethyl)sulfonyl]phenoxy}phenyl)amino]-5H-

pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

(i) Production of 2-chloro-4-nitro-1-{3-[(2,2,2-trifluoroethyl)thio]phenoxy}benzene

To a solution of 3-mercaptophenol (2.0 g) and triethylamine (2.70 mL) in N,N-dimethylformamide (20 mL) was added 2,2,2-trifluoro-1-iodoethane (1.72 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 hr, 3-chloro-4-fluoronitrobenzene (2.77 g) and potassium carbonate (2.18 g) were added thereto. The reaction mixture was stirred at room temperature for 20 hr, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=19:1→3:1) to give the title compound (4.27 g) as a yellow oil.

^{1}H-NMR ($CDCl_6$) δ: 3.48 (2H, q, J = 9.6 Hz), 6.91 (1H, d, J = 9.0 Hz), 6.98-7.02 (1H, m), 7.19-7.21 (1H, m), 7.34-7.44 (2H, m), 8.09 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.40 (1H, d, J = 2.7 Hz).

(ii) Production of 2-chloro-4-nitro-1-{3-[(2,2,2-trifluoroethyl)sulfonyl]phenoxy}benzene

To a solution of 2-chloro-4-nitro-1-{3-[(2,2,2-trifluoroethyl)thio]phenoxy}benzene (2.0 g) in ethyl acetate (20 mL) was added 70% 3-chloroperbenzoic acid (2.80 g) at 0°C. The reaction mixture was stirred at 0°C for 2 hr and at room temperature for 4 days, aqueous sodium thiosulfate solution was added to the reaction mixture, and the mixture was stirred for 1 hr. The mixture was extracted with ethyl acetate, and the organic layer was washed successively with aqueous sodium bicarbonate and saturated brine, and dried over magnesium sulfate. After concentration under reduced

pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=9:1→2:3) to give the title compound (2.34 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.94 (2H, q, J = 8.7 Hz), 7.01 (1H, d, J = 9.0 Hz), 7.38-7.43 (1H, m), 7.60-7.62 (1H, m), 7.66-7.71 (1H, m), 7.81-7.85 (1H, m), 8.15 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.43 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-{3-[(2,2,2-trifluoroethyl)sulfonyl]phenoxy}aniline

A mixture of 2-chloro-4-nitro-1-{3-[(2,2,2-trifluoroethyl)sulfonyl]phenoxy}benzene (2.34 g), reduced iron (1.54 g) and calcium chloride (0.31 g) in 15% water-containing ethanol (70 mL) was heated under reflux for 10 hr. The insoluble material was filtered off, and the filtrate was concentrated under reduced pressure. Aqueous sodium bicarbonate was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=3:1→3:7) to give the title compound (892 mg) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.77 (2H, br s), 3.87 (2H, q, J = 9.0 Hz), 6.60 (1H, dd, J = 2.7, 8.7 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.85 (1H, d, J = 8.7 Hz), 7.20-7.25 (1H, m), 7.35-7.37 (1H, m), 7.51 (1H, t, J = 8.1 Hz), 7.61 (1H, d, J = 8.1 Hz).

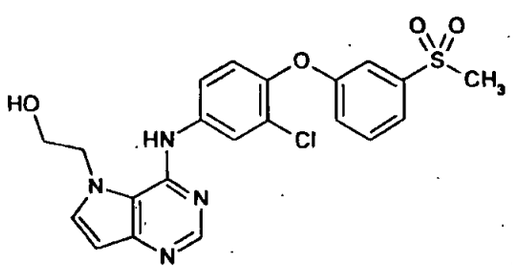
(iv) Production of 2-{4-[(3-chloro-4-{3-[(2,2,2-trifluoroethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

A solution of 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (100 mg) and 3-chloro-4-{3-[(2,2,2-

trifluoroethyl)sulfonyl]phenoxy}aniline (117 mg) in isopropyl alcohol (3.0 mL) was stirred at 80°C for 4 days. After concentration under reduced pressure, methanol (5.0 mL) and 6N hydrochloric acid (1.0 mL) were added to the residue. The mixture was stirred at room temperature for 4 hr, and aqueous sodium bicarbonate 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 magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=9:1) to give the title compound (99 mg) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.90 (2H, q, J = 9.0 Hz), 4.16-4.25 (2H, m), 4.43-4.50 (2H, m), 4.91-5.02 (1H, m), 6.32 (1H, d, J = 3.0 Hz), 7.08 (1H, d, J = 3.0 Hz), 7.11 (1H, d, J = 8.7 Hz), 7.27-7.33 (1H, m), 7.42-7.47 (1H, m), 7.52-7.58 (2H, m), 7.64-7.67 (1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.35 (1H, s), 9.45 (1H, s).

Example C-121



Production of 2-[4-({3-chloro-4-[3-(methylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 2-chloro-1-[3-(methylthio)phenoxy]-4-nitrobenzene

To a solution of 3-mercaptophenol (3.0 g) and triethylamine (3.64 mL) in N,N-dimethylformamide (30 mL) was added methyl iodide (1.48 mL) at 0°C. The reaction

mixture was stirred at 0°C for 1 hr and at room temperature for 30 min, 3-chloro-4-fluoronitrobenzene (4.18 g) and potassium carbonate (3.29 g) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 14 hr, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=19:1→3:1) to give the title compound (2.84 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s), 6.80-6.84 (1H, m), 6.91 (1H, d, J = 9.3 Hz), 6.96-6.97 (1H, m), 7.11-7.15 (1H, m), 7.32-7.37 (1H, m), 8.07 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.39 (1H, d, J = 2.7 Hz).

(ii) Production of 2-chloro-1-[3-(methylsulfonyl)phenoxy]-4-nitrobenzene

To a solution of 2-chloro-1-[3-(methylthio)phenoxy]-4-nitrobenzene (2.84 g) in ethyl acetate (50 mL) was added 70% 3-chloroperbenzoic acid (5.21 g) at 0°C. The reaction mixture was stirred at 0°C for 1 hr, aqueous sodium thiosulfate solution was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. The mixture was extracted with ethyl acetate, the organic layer was washed successively with aqueous sodium bicarbonate and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=4:1→2:3) to give the title compound (2.79 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.09 (3H, s), 7.02 (1H, d, J = 8.7 Hz), 7.32-7.36 (1H, m), 7.61-7.67 (2H, m), 7.79-7.83 (1H, m), 8.13 (1H, dd, J = 2.4 Hz, 8.7 Hz), 8.42 (1H, d, J = 2.7

Hz).

(iii) Production of 3-chloro-4-[3-(methylsulfonyl)phenoxy]aniline

Using 2-chloro-1-[3-(methylsulfonyl)phenoxy]-4-nitrobenzene (2.90 g), reduced iron (2.50 g), calcium chloride (0.50 g) and 15% water-containing ethanol (90 mL) and in the same manner as in Example C-120(iii), the title compound (2.29 g) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s), 3.74 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.4 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.4 Hz), 7.13-7.17 (1H, m), 7.36-7.38 (1H, m), 7.44-7.50 (1H, m), 7.56-7.60 (1H, m).

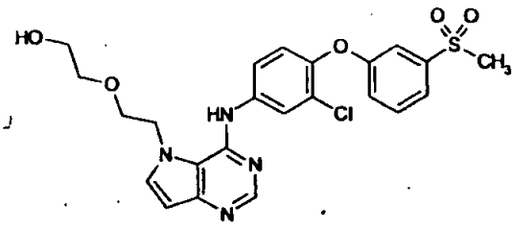
(iv) Production of 2-[4-({3-chloro-4-[3-(methylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

A solution of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg) and 3-chloro-4-[3-(methylsulfonyl)phenoxy]aniline (98.3 mg) in isopropyl alcohol (2.0 mL) was stirred at 80°C for 3 days. The reaction mixture was cooled to room temperature, 1N aqueous sodium hydroxide solution (1.0 mL) was added thereto. The reaction mixture was stirred at room temperature for 2 hr, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=9:1) to give the title compound (116 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.06 (3H, s), 4.18 (2H, t, J = 4.7 Hz), 4.44 (2H, t, J = 4.7 Hz), 6.27 (1H, d, J = 3.0 Hz), 7.05 (1H, d, J = 3.0 Hz), 7.11 (1H, d, J = 9.0 Hz), 7.22-7.28 (1H, m), 7.43-7.45 (1H, m), 7.50-7.55 (2H, m), 7.61-7.64

(1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.31 (1H, s), 9.50 (1H, s).

Example C-122

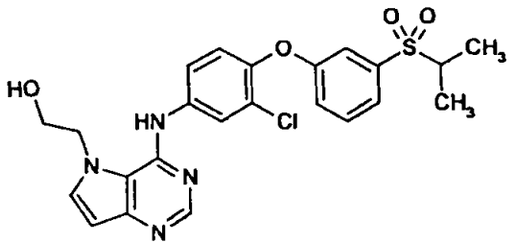


Production of 2-{2-[4-({3-chloro-4-[3-(methylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (100 mg), 3-chloro-4-[3-(methylsulfonyl)phenoxy]aniline (86.1 mg), isopropyl alcohol (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example C-121(iv), the title compound (117 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.78-1.85 (1H, m), 3.05 (3H, s), 3.78-3.84 (4H, m), 4.03 (2H, t, J = 4.4 Hz), 4.59 (2H, t, J = 4.4 Hz), 6.64 (1H, d, J = 3.3 Hz), 7.09 (1H, d, J = 9.0 Hz), 7.22-7.27 (2H, m), 7.39-7.41 (1H, m), 7.48-7.53 (1H, m), 7.61 (1H, s), 7.63 (1H, dd, J = 2.7 Hz, 9.0 Hz), 7.94 (1H, d, J = 2.7 Hz), 8.53 (1H, s), 8.85 (1H, s).

Example C-123



Production of 2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 2-chloro-1-[3-(isopropylthio)phenoxy]-4-nitrobenzene

To a solution of 3-mercaptophenol (1.5 g) and sodium tert-butoxide (1.37 g) in N,N-dimethylformamide (25 mL) was added 2-bromopropane (1.23 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr, sodium tert-butoxide (1.37 g) and 3-chloro-4-fluoronitrobenzene (1.88 g) were added to the reaction mixture, and the mixture was stirred for 4 hr. 3-Chloro-4-fluoronitrobenzene (0.17 g) was further added to the reaction mixture and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=19:1→4:1) to give the title compound (3.36 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, d, J = 6.9 Hz), 3.42 (1H, quintet, J = 6.9 Hz), 6.88-6.92 (2H, m), 7.07-7.08 (1H, m), 7.21-7.27 (1H, m), 7.32-7.37 (1H, m), 8.06 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.38 (1H, d, J = 2.7 Hz).

(ii) Production of 2-chloro-1-[3-(isopropylsulfonyl)phenoxy]-4-nitrobenzene

Using 2-chloro-1-[3-(isopropylthio)phenoxy]-4-nitrobenzene (3.36 g), 70% 3-chloroperbenzoic acid (5.63 g) and ethyl acetate (50 mL) and in the same manner as in Example C-121(ii), the title compound (3.36 g) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, d, J = 6.9 Hz), 3.22 (1H, quintet, J = 6.9 Hz), 6.99 (1H, d, J = 9.0 Hz), 7.33-7.37 (1H, m), 7.54-7.55 (1H, m), 7.61-7.66 (1H, m), 7.74-7.77 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-[3-(isopropylsulfonyl)phenoxy]aniline

Using 2-chloro-1-[3-(isopropylsulfonyl)phenoxy]-4-nitrobenzene (3.30 g), reduced iron (2.59 g), calcium chloride (0.52 g) and 15% water-containing ethanol (100 mL) and in the same manner as in Example C-120(iii), the title compound (3.00 g) was obtained as a yellow oil.

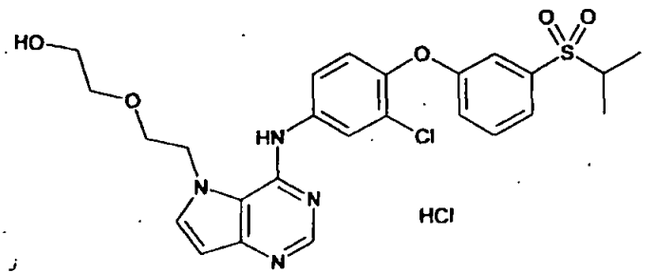
^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, d, J = 6.9 Hz), 3.16 (1H, quintet, J = 6.9 Hz), 3.73 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.14-7.19 (1H, m), 7.28-7.30 (1H, m), 7.44-7.54 (2H, m).

(iv) Production of 2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg), 3-chloro-4-[3-(isopropylsulfonyl)phenoxy]aniline (140 mg), isopropyl alcohol (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example C-121(iv), the title compound (127 mg) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J = 6.9 Hz), 3.19 (1H, quintet, J = 6.9 Hz), 4.16 (2H, t, J = 4.5 Hz), 4.43 (2H, t, J = 4.5 Hz), 5.30-5.71 (1H, m), 6.26 (1H, d, J = 3.0 Hz), 7.05 (1H, d, J = 3.0 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.23-7.30 (1H, m), 7.35-7.37 (1H, m), 7.48-7.61 (3H, m), 7.84 (1H, d, J = 2.4 Hz), 8.31 (1H, s), 9.53 (1H, s).

Example C-124

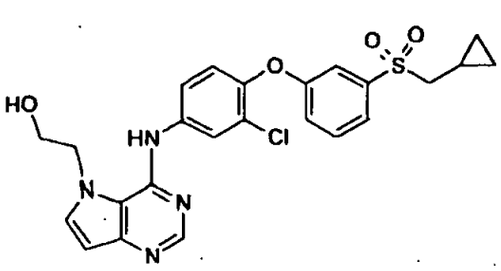


Production of 2-{2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol hydrochloride

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (100 mg), 3-chloro-4-[3-(isopropylsulfonyl)phenoxy]aniline (113 mg), isopropyl alcohol (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example C-121(iv), a pale-yellow oil was obtained. To a solution of the obtained oil in ethanol (5.0 mL) was added 4N hydrogen chloride/ethyl acetate solution (0.50 mL) at room temperature. The mixture was concentrated under reduced pressure, and resulting crystals were collected by filtration. The crystals were washed with ethyl acetate to give the title compound (130 mg) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz), 3.38-3.54 (5H, m), 3.82-3.89 (2H, m), 4.75-4.83 (2H, m), 6.69 (1H, d, J = 3.0 Hz), 7.23-7.25 (1H, m), 7.39-7.44 (2H, m), 7.61-7.75 (3H, m), 7.99-8.03 (2H, m), 8.73 (1H, s), 9.84 (1H, br s).

Example C-125



Production of 2-{4-[(3-chloro-4-{3-

[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

(i) Production of 2-chloro-1-{3-[(cyclopropylmethyl)thio]phenoxy}-4-nitrobenzene

To a solution of 3-mercaptophenol (1.5 g) and sodium tert-butoxide (1.26 g) in N,N-dimethylformamide (15 mL) was added 1-(bromomethyl)cyclopropane (1.27 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 hr, sodium tert-butoxide (1.27 g) and 3-chloro-4-fluoronitrobenzene (1.88 g) were added to the reaction mixture, and the mixture was stirred for 3 days. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=19:1→4:1) to give the title compound (2.93 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.25-0.30 (2H, m), 0.58-0.64 (2H, m), 0.99-1.13 (1H, m), 2.89 (2H, d, J = 7.2 Hz), 6.84-6.89 (1H, m), 6.90 (1H, d, J = 9.0 Hz), 7.05 (1H, t, J = 2.1 Hz), 7.20-7.24 (2H, m), 7.31-7.36 (1H, m), 8.06 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.39 (1H, d, J = 2.7 Hz).

(ii) Production of 2-chloro-1-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}-4-nitrobenzene

Using 2-chloro-1-{3-[(cyclopropylmethyl)thio]phenoxy}-4-nitrobenzene (2.93 g), 70% 3-chloroperbenzoic acid (4.73 g) and ethyl acetate (60 mL) and in the same manner as in Example C-121(ii), the title compound (2.90 g) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.14-0.20 (2H, m), 0.57-0.63 (2H, m), 0.95-1.09 (1H, m), 3.05 (2H, d, J = 7.2 Hz), 7.00 (1H, d, J = 9.0 Hz), 7.33-7.36 (1H, m), 7.59-7.66 (2H, m),

7.78-7.82 (1H, m), 8.13 (1H, dd, J= 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}aniline

Using 2-chloro-1-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}-4-nitrobenzene (2.84 g), reduced iron (2.57 g), calcium chloride (0.51 g) and 15% water-containing ethanol (85 mL) and in the same manner as in Example C-120(iii), the title compound (2.60 g) was obtained a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.10-0.16 (2H, m), 0.52-0.58 (2H, m), 0.90-1.06 (1H, m), 2.99 (2H, d, J = 7.5 Hz), 3.74 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.15-7.19 (1H, m), 7.34-7.35 (1H, m), 7.44-7.49 (1H, m), 7.55-7.59 (1H, m).

(iv) Production of 2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg), 3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}aniline (123 mg), isopropyl alcohol (2.0 mL), 1-methyl-2-pyrrolidone (2.0 mL) and 1N aqueous sodium hydroxide solution (1.0 mL) and in the same manner as in Example C-121(iv), the title compound (126 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.11-0.19 (2H, m), 0.53-0.63 (2H, m), 0.94-1.05 (1H, m), 3.01 (2H, d, J = 7.2 Hz), 4.13-4.21 (2H, m), 4.39-4.47 (2H, m), 5.11-5.31 (1H, m), 6.29 (1H, d, J = 3.3 Hz), 7.06 (1H, d, J = 3.3 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.24-7.30 (1H, m), 7.40-7.42 (1H, m), 7.48-7.54 (2H, m), 7.60-7.63 (1H, m), 7.83 (1H, d, J = 2.4 Hz), 8.32 (1H, s), 9.48 (1H, s).

Example C-126

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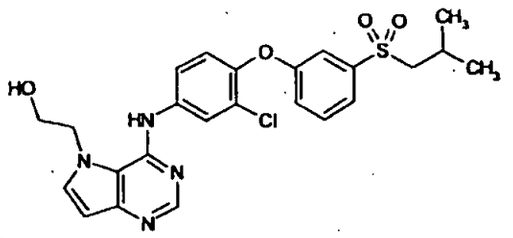


Production of 2-[4-({3-chloro-4-[3-(isobutylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 2-chloro-1-[3-(isobutylthio)phenoxy]-4-nitrobenzene

To a solution of 3-mercaptophenol (1.5 g) and sodium tert-butoxide (1.26 g) in N,N-dimethylformamide (15 mL) was added 1-bromo-2-methylpropane (1.42 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 days, sodium tert-butoxide (1.26 g) and 3-chloro-4-fluoronitrobenzene (2.08 g) were added to the reaction mixture and the mixture was stirred for 6 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=19:1→3:1) to give the title compound (3.63 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J = 6.6 Hz), 1.83-1.96 (1H, m), 2.82 (2H, d, J = 6.3 Hz), 6.81-6.84 (1H, m), 6.89 (1H, d, J = 9.0 Hz), 6.99-7.01 (1H, m), 7.15-7.19 (1H, m), 7.29-7.34 (1H, m), 8.05 (1H, dd, J = 2.4 Hz, 9.0 Hz), 8.37 (1H, d, J = 2.4 Hz).

(ii) Production of 2-chloro-1-[3-(isobutylsulfonyl)phenoxy]-4-nitrobenzene

Using 2-chloro-1-[3-(isobutylthio)phenoxy]-4-nitrobenzene (3.63 g), 70% 3-chloroperbenzoic acid (5.80

g) and ethyl acetate (50 mL) and in the same manner as in Example C-121(ii), the title compound (3.88 g) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.08 (6H, d, J = 6.6 Hz), 2.20-2.23 (1H, m), 3.00 (2H, d, J = 6.6 Hz), 7.00 (1H, d, J = 9.0 Hz), 7.31-7.35 (1H, m), 7.58 (1H, t, J = 2.1 Hz), 7.60-7.66 (1H, m), 7.76-7.80 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-[3-(isobutylsulfonyl)phenoxy]aniline

Using 2-chloro-1-[3-(isobutylsulfonyl)phenoxy]-4-nitrobenzene (3.88 g), reduced iron (2.93 g), calcium chloride (0.58 g) and 15% water-containing ethanol (120 mL) and in the same manner as in Example C-120(iii), the title compound (3.40 g) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, d, J = 6.6 Hz), 2.13-2.28 (1H, m), 2.96 (2H, d, J = 6.6 Hz), 3.74 (2H, br s), 6.60 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.13-7.18 (1H, m), 7.34 (1H, t, J = 2.1 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.54-7.57 (1H, m).

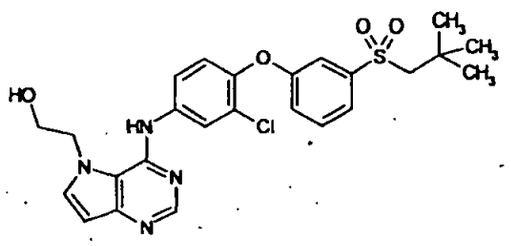
(iv) Production of 2-[4-({3-chloro-4-[3-(isobutylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg), 3-chloro-4-[3-(isobutylsulfonyl)phenoxy]aniline (123 mg), isopropyl alcohol (5.0 mL) and 1N aqueous sodium hydroxide solution (2.0 mL) and in the same manner as in Example C-121(iv), the title compound (112 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d, J =6.9 Hz), 2.18-2.29 (1H, m), 2.98 (2H,d, J = 6.6 Hz), 4.12-4.21 (2H, m), 4.39-4.48 (2H, m), 5.45-5.60 (1H, m), 6.25 (1H, d, J = 3.0 Hz), 7.04 (1H, d, J = 3.0 Hz), 7.09 (1H, d, J = 8.7 Hz),

7.23-7.27 (1H, m), 7.39-7.41 (1H, m), 7.48-7.53 (2H, m), 7.57-7.61 (1H, m), 7.83 (1H, d, J = 2.4 Hz), 8.30 (1H, s), 9.50 (1H, s).

Example C-127



Production of 2-{4-[(3-chloro-4-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

(i) Production of 2-chloro-1-{3-[(2,2-dimethylpropyl)thio]phenoxy}-4-nitrobenzene

To a solution of 3-mercaptophenol (1.5 g) and sodium tert-butoxide (1.26 g) in N,N-dimethylformamide (15 mL) was added 1-bromo-2,2-dimethylpropane (1.64 mL) at room temperature. After stirring at 70°C for 24 hr, the mixture was cooled to room temperature, sodium tert-butoxide (1.26 g) and 3-chloro-4-fluoronitrobenzene (2.08 g) were added thereto, and the mixture was stirred at room temperature for 3 days. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, hexane:ethyl acetate=19:1→7:3) to give the title compound (2.80 g) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 2.89 (2H, s), 6.80-6.84 (1H, m), 6.88 (1H, d, J = 9.0 Hz), 7.02-7.04 (1H, m), 7.18-7.22 (1H, m), 7.28-7.33 (1H, m), 8.05 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.37 (1H, d, J = 3.0 Hz).

(ii) Production of 2-chloro-1-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}-4-nitrobenzene

Using 2-chloro-1-{3-[(2,2-dimethylpropyl)thio]phenoxy}-4-nitrobenzene (2.80 g), 70% 3-chloroperbenzoic acid (4.32 g) and ethyl acetate (56 mL) and in the same manner as in Example C-121(ii), the title compound (3.04 g) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.20 (9H, s), 3.05 (2H, s), 7.00 (1H, d, J = 9.0 Hz), 7.30-7.34 (1H, m), 7.59-7.66 (2H, m), 7.77-7.81 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.42 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}aniline

Using 2-chloro-1-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}-4-nitrobenzene (3.0 g), reduced iron (2.18 g), calcium chloride (0.43 g) and 15% water-containing ethanol (90 mL) and in the same manner as in Example C-120(iii), the title compound (2.34 g) was obtained as a pale-yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (9H, s), 3.01 (2H, s), 3.73 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.92 (1H, d, J = 9.0 Hz), 7.08-7.14 (1H, m), 7.35-7.36 (1H, m), 7.42-7.47 (1H, m), 7.53-7.57 (1H, m).

(iv) Production of 2-{4-[(3-chloro-4-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (100 mg), 3-chloro-4-{3-[(2,2-dimethylpropyl)sulfonyl]phenoxy}aniline (140 mg), isopropyl alcohol (3.0 mL) and 1N aqueous sodium hydroxide solution (1.5 mL) and in the same manner as in Example C-121(iv), the title compound (131 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.19 (9H, s), 3.04 (2H, s), 4.11-4.20

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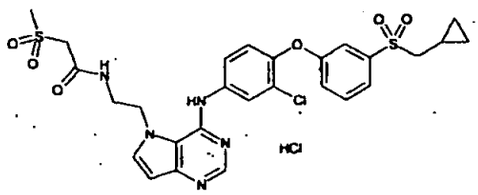
(2H, m), 4.35-5.46 (2H, m), 5.81-5.96 (1H, m), 6.20 (1H, d, J = 3.3 Hz), 7.02 (1H, d, J = 3.3 Hz), 7.08 (1H, d, J = 8.7 Hz), 7.20-7.27 (1H, m), 7.41-7.43 (1H, m), 7.46-7.52 (2H, m), 7.56-7.63 (1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.27 (1H, s), 9.55 (1H, s).

Example C-128



Production of N-(2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of tert-butyl (2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.00 g) and 3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}aniline (1.14 g) in isopropyl alcohol (10 mL) was stirred at 80°C for 14 hr. Aqueous sodium bicarbonate 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 magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by column chromatography (eluent, hexane:ethyl acetate=1:1→ethyl acetate→ethyl acetate:methanol=9:1) to give the title compound (1.86 g) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.10-0.20 (2H, m), 0.54-0.61 (2H, m), 0.92-1.06 (1H, m), 1.50 (9H, s), 3.01 (2H, d, J = 6.9 Hz), 3.43-3.53 (2H, m), 4.43-4.52 (2H, m), 5.02-5.10 (1H, m), 6.61 (1H, d, J = 3.0 Hz), 7.09 (1H, d, J = 9.0

Hz), 7.19 (1H, d, J = 3.0 Hz), 7.21-7.28 (1H, m), 7.46-7.52 (2H, m), 7.60-7.63 (1H, m), 7.91 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.06 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.62 (1H, br s).

(ii) Production of 5-(2-aminoethyl)-N-(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl (2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate (1.86 g), 6N hydrochloric acid (5.0 mL) and ethanol (20 mL) was stirred at 60°C for 3 days. After concentration under reduced pressure, ethanol was added to the residue. The mixture was concentrated under reduced pressure, and the resulting crystals were collected by filtration and washed with diisopropyl ether to give the title compound (1.66 g) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.09-0.14 (2H, m), 0.41-0.48 (2H, m), 0.76-0.88 (1H, m), 3.22-3.38 (4H, m), 4.94-5.05 (2H, m), 6.74 (1H, d, J = 2.7 Hz), 7.30-7.45 (3H, m), 7.61-7.74 (3H, m), 7.92-7.97 (1H, m), 8.00-8.08 (1H, m), 8.23-8.32 (3H, m), 8.72 (1H, s), 9.99 (1H, br s).

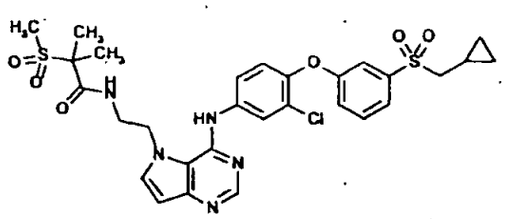
(iii) Production of N-(2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

A mixture of 5-(2-aminoethyl)-N-(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (100 mg), methylsulfonylacetic acid (48.4 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (101 mg), 1-hydroxybenzotriazole monohydrate (80 mg) and triethylamine (0.073 mL) in N,N-dimethylformamide (5.0 mL) was stirred at room temperature for 20 hr. Water was added to the reaction mixture and the mixture was

extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give a pale-yellow amorphous. To a solution of the obtained amorphous in ethanol (5.0 mL) was added 4N hydrogen chloride/ethyl acetate solution (0.5 mL) at room temperature. After stirring at room temperature for 1 hr, the resulting crystals were collected by filtration and washed with ethyl acetate to give the title compound (81 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.06-0.13 (2H, m), 0.40-0.47 (2H, m), 0.75-0.90 (1H, m), 3.06 (3H, s), 3.30 (2H, d, J = 6.9 Hz), 3.49-3.60 (2H, m), 4.06 (2H, s), 4.64-4.73 (2H, m), 6.66 (1H, d, J = 2.7 Hz), 7.30-7.44 (3H, m), 7.65-7,74 (3H, m), 7.91-7.99 (2H, m), 8.68-8.79 (2H, m), 8.86 (1H, br s).

Example C-129



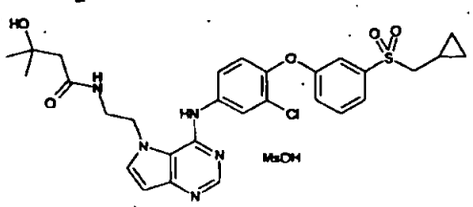
Production of N-(2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-methyl-2-(methylsulfonyl)propanamide

A mixture of 5-(2-aminoethyl)-N-(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (120 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (52 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (90 mg), 1-hydroxybenzotriazole

monohydrate (72 mg) and triethylamine (0.088 mL) in N,N-dimethylformamide (5.0 mL) was stirred at room temperature for 2 days. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) to give the title compound (120 mg) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.11-0.18 (2H, m), 0.54-0.61 (2H, m), 0.92-1.07 (1H, m), 1.70 (6H, s), 2.93 (3H, s), 3.01 (2H, d, J = 7.2 Hz), 3.64-3.74 (2H, m), 4.43-4.52 (2H, m), 6.64 (1H, d, J = 3.3 Hz), 6.99 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 3.3 Hz), 7.22-7.32 (2H, m), 7.42-7.44 (1H, m), 7.51 (1H, t, J = 8.1 Hz), 7.60-7.64 (1H, m), 7.89 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.07 (1H, d, J = 2.7 Hz), 8.37 (1H, s), 8.53 (1H, s).

Example C-130

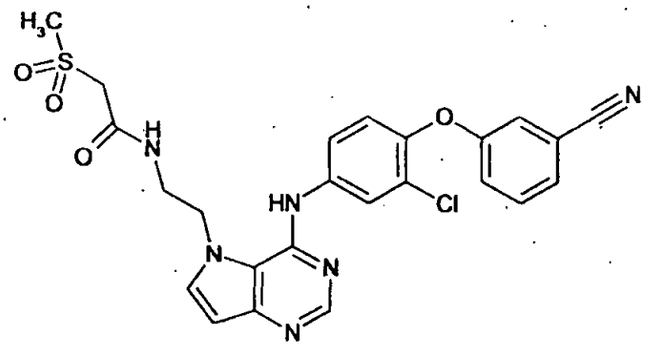


Production of N-(2-{4-[(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide methanesulfonate

A mixture of 5-(2-aminoethyl)-N-(3-chloro-4-{3-[(cyclopropylmethyl)sulfonyl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (120 mg), 3-hydroxy-3-methylbutanoic acid (49.7 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (121 mg), 1-hydroxybenzotriazole monohydrate (97 mg) and triethylamine (0.090 mL) in N,N-dimethylformamide (5.0

mL) was stirred at room temperature for 20 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=4:1) to give a colorless amorphous form. To a solution of the obtained amorphous form in ethyl acetate (5.0 mL) was added methanesulfonic acid (12.4 μL) at room temperature. After stirring at room temperature for 1 hr, the resulting crystals were collected by filtration and washed with ethyl acetate to give the title compound (116 mg) as colorless crystals.
^{1}H-NMR (DMSO-d_6) δ: 0.08-0.14 (2H, m), 0.41-0.47 (2H, m), 0.75-0.88 (1H, m), 1.12 (6H, s), 2.20 (2H, s), 2.30 (3H, s), 3.29 (2H, d, J = 7.2 Hz), 3.43-3.56 (2H, m), 4.62 (2H, t, J = 7.5 Hz), 6.66 (1H, d, J=3.0 Hz), 7.31-7.45 (3H, m), 7.64-7.76 (3H, m), 7.93-8.01 (2H, m), 8.34 (1H, t, J = 5.4 Hz), 8.72 (1H, s), 10.14 (1H, br s).

Example C-131



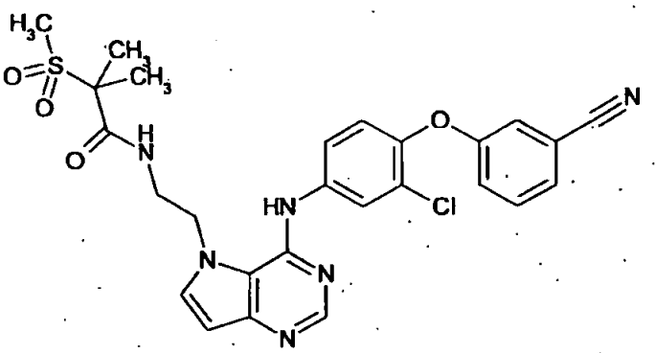
Production of N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

Using 3-(4-amino-2-chlorophenoxy)benzonitrile (115 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (125 mg), isopropyl alcohol (2.0

mL), methanol (2 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL), methylsulfonylacetic acid (170 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (360 mg), 1-hydroxybenzotriazole (15 mg), triethylamine (0.86 mL) and N,N-dimethylformamide (15 mL) and in the same manner as in Example C-53(ii), the title compound (169 mg) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.10 (3H, s), 3.44-3.49 (2H, m), 4.05 (2H, s), 4.55-4.60 (2H, m), 6.51-6.52 (1H, m), 7.24-8.01 (8H, m), 8.38 (1H, s), 8.66-8.69 (1H, m), 8.81 (1H, s).

Example C-132



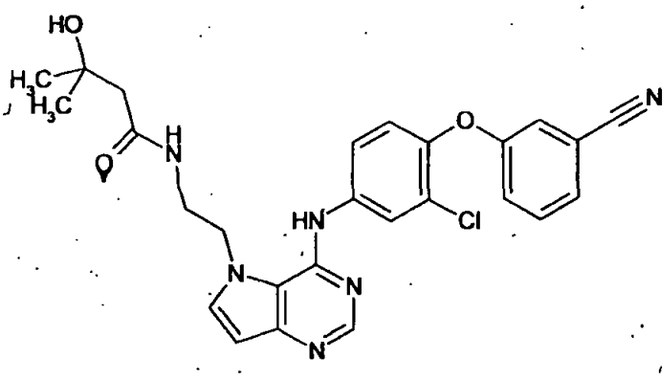
Production of N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide

Using 3-(4-amino-2-chlorophenoxy)benzonitrile (115 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (125 mg), isopropyl alcohol (2.0 mL), methanol (2 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL), 2-methyl-2-(methylsulfonyl)propanoic acid (210 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (370 mg), 1-hydroxybenzotriazole (40 mg), triethylamine (1.0 mL) and N,N-dimethylformamide (20 mL) and in the same manner as in Example C-53(ii), the title compound (173 mg) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.41 (6H, s), 2.95 (3H, s), 3.42-3.49

(2H, m), 4.58-4.62 (2H, m), 6.50-6.51 (1H, m), 7.24-8.00 (8H, m), 8.20 (1H, br s), 8.40 (1H, s), 8.88 (1H, s).

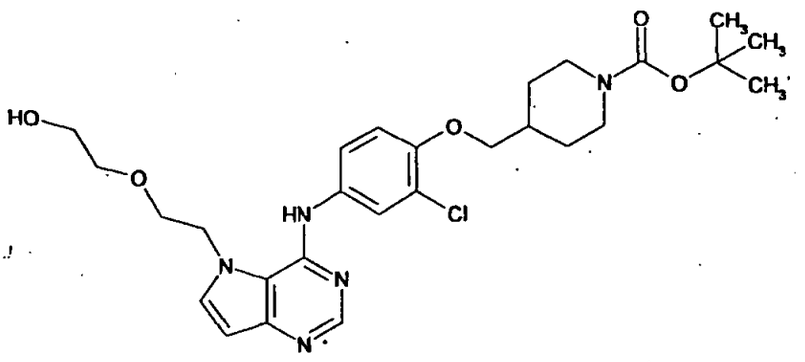
Example C-133



Production of N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide

Using 3-(4-amino-2-chlorophenoxy)benzonitrile (115 mg), tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (125 mg), isopropyl alcohol (2.0 mL), methanol (2 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL), 3-hydroxy-3-methylbutanoic acid (190 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (320 mg), 1-hydroxybenzotriazole (15 mg), triethylamine (0.5 mL) and N,N-dimethylformamide (20 mL) and in the same manner as in Example C-53(ii), the title compound (115 mg) was obtained as pale-yellow crystals.
^{1}H-NMR (DMSO-d_6) δ: 1.13 (6H, s), 2.20 (2H, s), 3.42-3.49 (2H, m), 4.50-4.55 (2H, m), 4.66 (1H, s), 6.50-6.51 (1H, m), 7.24-8.06 (8H, m), 8.24 (1H, br s), 8.35 (1H, s), 8.92 (1H, s).

Example D-1



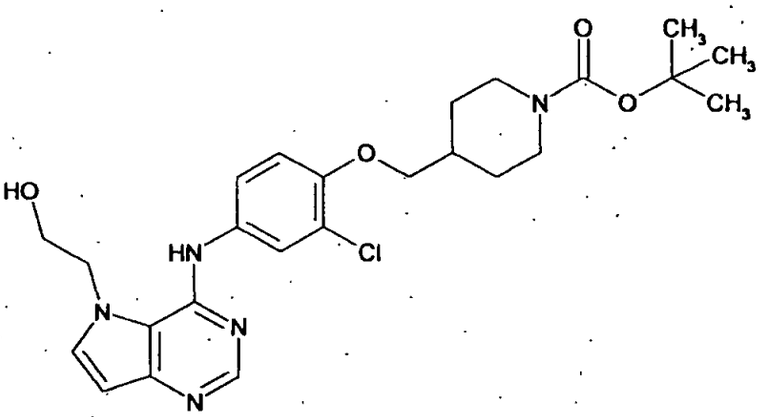
Production of tert-butyl 4-{[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]methyl}piperidine-1-carboxylate

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (156 mg), tert-butyl 4-[(4-amino-2-chlorophenoxy)methyl]piperidine-1-carboxylate (200 mg) and isopropyl alcohol (15 mL) was stirred at 80°C overnight. After concentration under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were 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 subjected to silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20). The objective fractions were concentrated under reduced pressure. The crude product was dissolved in methanol (5.0 mL), tetrahydrofuran (4.0 mL) and 1N aqueous sodium hydroxide solution (3.0 mL) were added and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give the title compound (74 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.27 (2H, m), 1.40 (9H, s), 1.76-1.80 (2H, m), 1.86-2.03 (1H, m), 2.65-2.86 (2H, m), 3.47 (4H, s), 3.78-4.01 (6H, m), 4.60-4.68 (3H, m), 6.47 (1H, d, J= 3.1 Hz), 7.12 (1H, d, J= 9.1 Hz), 7.50 (1H, dd, J= 9.1, 2.7 Hz), 7.63 (1H, d, J= 3.1 Hz), 7.78 (1H, d, J= 2.7 Hz), 8.26 (1H, s), 8.68 (1H, br s).

Example D-2

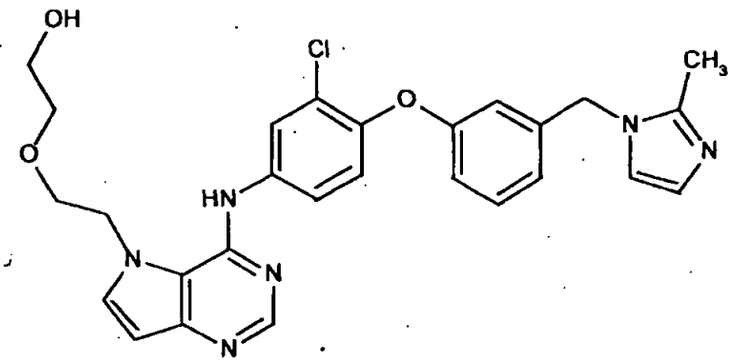


Production of tert-butyl 4-[(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)methyl]piperidine-1-carboxylate

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (200 mg), tert-butyl 4-[(4-amino-2-chlorophenoxy)methyl]piperidine-1-carboxylate (293 mg) and isopropyl alcohol (5.0 mL) was stirred at 80°C overnight. After concentration under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were 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 subjected to silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→80:20). The objective fractions were concentrated under reduced pressure. The crude product was dissolved in methanol (5.0 mL), tetrahydrofuran (4.0 mL) and 1N aqueous sodium hydroxide solution (4.0 mL) were added to the mixture and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give the title compound (147 mg) as a white powder. ^{1}H-NMR (DMSO-d_6) δ: 1.13-1.27 (2H, m), 1.40 (9H, s), 1.76-1.80 (2H, m), 1.86-2.03 (1H, m), 2.65-2.86 (2H, m), 3.83-4.01 (6H, m), 4.50 (2H, t, J= 4.1 Hz), 6.18-6.21 (1H, m), 6.46 (1H, d, J= 3.1 Hz), 7.13 (1H, d, J= 9.1 Hz), 7.46 (1H, dd, J= 9.1, 2.7 Hz), 7.60 (1H, d, J= 3.1 Hz), 7.75 (1H, d, J= 2.7 Hz), 8.26 (1H, s), 9.53 (1H, br s).

Example E-1



Production of 2-(2-{4-[(3-chloro-4-{3-[(2-methyl-1H-imidazol-1-yl)methyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol

(i) Production of [3-(2-chloro-4-nitrophenoxy)phenyl]methanol

To a solution of 3-(hydroxymethyl)phenol (6.21 g) and 3-chloro-4-fluoronitrobenzene (9.24 g) in N,N-dimethylformamide (50 mL) was added potassium carbonate (10.37 g) at room temperature and the mixture was stirred for 4 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60) to give the title compound (5.55 g) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.78 (1H, t, J = 5.7 Hz), 4.74 (2H, d, J = 5.7 Hz), 6.90 (1H, d, J = 9.0 Hz), 6.95-7.05 (1H, m), 7.12 (1H, s), 7.25-7.30 (1H, m), 7.43 (1H, t, J =8.0 Hz), 8.05-8.10 (1H, m), 8.35-8.40 (1H, m).

(ii) Production of 1-[3-(2-chloro-4-nitrophenoxy)benzyl]-2-methyl-1H-imidazole

To a solution of [3-(2-chloro-4-nitrophenoxy)phenyl]methanol (1.12 g) in tetrahydrofuran (30 mL) were added triethylamine (0.67 mL) and methanesulfonyl chloride (0.33 mL) under ice-cooling,

and the mixture was stirred at 0°C for 1 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 2-Methylimidazole (328 mg), potassium carbonate (829 mg) and N,N-dimethylformamide (10 mL) were added to the obtained residue, and the mixture was stirred at room temperature for 15 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate) to give the title compound (0.96 g) as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 5.08 (2H, s), 6.75-6.9 (3H, m), 6.90-7.05 (3H, m), 7.41 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.38 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-{3-[(2-methyl-1H-imidazol-1-yl)methyl]phenoxy}aniline

To a solution of 1-[3-(2-chloro-4-nitrophenoxy)benzyl]-2-methyl-1H-imidazole (0.96 g) in methanol (10 mL) was added 5% platinum-activated carbon (192 mg) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 19 hr, and 5% platinum-activated carbon was filtered off. The filtrate was concentrated under reduced pressure and the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0) to give the title compound (494 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 3.69 (2H, br s), 4.99 (2H, s), 6.56 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.60-6.70

(2H, m), 6.70-6.85 (3H, m), 6.87 (1H, d, J = 9.0 Hz), 6.93 (1H, d, J = 1.2 Hz), 7.22 (1H, t, J = 7.6 Hz).

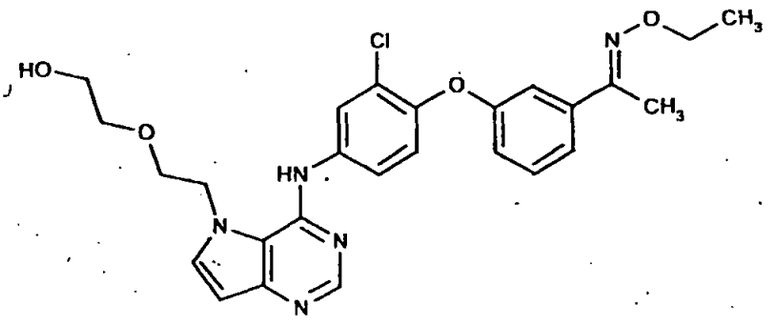
(iv) Production of 2-(2-{4-[(3-chloro-4-{3-[(2-methyl-1H-imidazol-1-yl)methyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (207 mg), 3-chloro-4-{3-[(2-methyl-1H-imidazol-1-yl)methyl]phenoxy}aniline (154 mg), 1-methyl-2-pyrrolidone (5.0 mL) and pyridine hydrochloride (139 mg) was stirred at 120°C for 22 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (2.3 mL) and tetrahydrofuran (4 mL) and the mixture was stirred at room temperature for 21 hr. The reaction mixture was neutralized with 1N hydrochloric acid and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (119 mg) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.70-3.85 (4H, m), 4.02 (2H, t, J = 4.2 Hz), 4.57 (2H, t, J = 4.2 Hz), 5.01 (2H, s), 5.99 (1H, s), 6.63 (1H, d, J = 3.3 Hz), 6.75-6.85 (1H, m), 6.83 (1H, d, J = 8.1 Hz), 6.92 (1H, d, J = 9.0 Hz), 6.95-7.05 (1H, m), 7.21 (1H, d, J = 3.0 Hz), 7.25-7.30 (1H, m), 7.32 (1H, t, J = 8.0 Hz), 7.65 (1H, dd, J

= 2.4 Hz, 9.0 Hz), 8.02 (1H, d, J = 2.4 Hz), 8.54 (1H, s), 8.98 (1H, s).

Example E-2



Production of (1E)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}ethanone O-ethyloxime

(i) Production of (1E)-1-[3-(4-amino-2-chlorophenoxy)phenyl]ethanone O-ethyloxime

To a solution of 1-[3-(4-amino-2-chlorophenoxy)phenyl]ethanone (1.31 g) in ethanol (50 mL) were added O-ethylhydroxylamine hydrochloride (2.44 g) and sodium acetate (2.05 g) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added thereto, 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60). The objective fractions were concentrated under reduced pressure to give the title compound (1.54 g) was obtained as an orange oil.

^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J= 7.0 Hz), 2.19 (3H, s), 3.66 (2H, br s), 4.22 (2H, q, J= 7.0 Hz), 6.56 (1H, dd, J= 2.8 Hz, 8.7 Hz), 6.77-6.83 (2H, m), 6.89 (1H, d, J= 8.7 Hz), 7.21-7.28 (2H, m), 7.29-7.35 (1H, m).

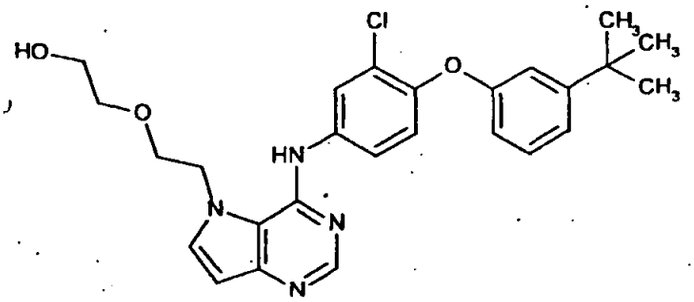
(ii) Production of (1E)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}ethanone O-ethyloxime

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (173 mg), (1E)-1-[3-(4-amino-2-chlorophenoxy)phenyl]ethanone O-ethyloxime (153 mg) and isopropyl alcohol (3 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (134 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J= 7.1 Hz), 1.88-2.04 (1H, m), 2.21 (3H, s), 3.70-3.82 (4H, m), 3.99-4.05 (2H, m), 4.24 (2H, q, J= 7.1 Hz), 4.53-4.59 (2H, m), 6.61 (1H, d, J= 3.0 Hz), 6.86-6.92 (1H, m), 7.01 (1H, d, J= 8.9 Hz), 7.20 (1H, d, J= 3.0 Hz), 7.27-7.40 (3H, m), 7.56 (1H,

dd, J= 2.7 Hz, 8.9 Hz), 7.87 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.75 (1H, br s).

Example E-3

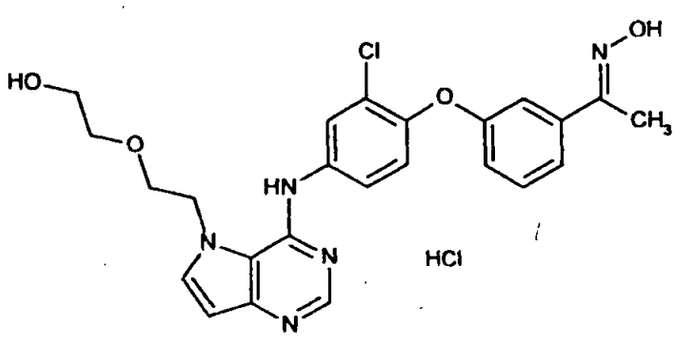


Production of 2-[2-(4-{[4-(3-tert-butylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (173 mg), 4-(3-tert-butylphenoxy)-3-chloroaniline (138 mg), isopropyl alcohol (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-2(ii), the title compound (189 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.32 (9H, s), 1.95-2.30 (1H, m), 3.70-3.82 (4H, m), 3.99-4.05 (2H, m), 4.52-4.59 (2H, m), 6.60 (1H, d, J= 3.0 Hz), 6.68-6.74 (1H, m), 6.99 (1H, d, J= 8.9 Hz), 7.08-7.15 (2H, m), 7.14-7.28 (2H, m), 7.54 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.86 (1H, d, J= 2.5 Hz), 8.49 (1H, s), 8.73 (1H, br s).

Example E-4



Production of (1E)-1-{3-[2-chloro-4-({5-[2-(2-

hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}ethanone oxime hydrochloride

(i) Production of 2-[2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (1.04 g), 1-[3-(4-amino-2-chlorophenoxy)phenyl]ethanone (785 mg) and isopropyl alcohol (10 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure to give the title compound (1.59 g) as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.59 (3H, s), 3.93-3.99 (2H, m), 4.05-4.12 (2H, m), 4.46-4.52 (2H, m), 4.55-4.62 (2H, m), 6.63 (1H, d, J= 3.2 Hz), 6.82 (1H, d, J= 8.8 Hz), 7.07-7.12 (1H, m), 7.22 (1H, d, J= 3.2 Hz), 7.29-7.54 (6H, m), 7.63-7.69 (1H, m), 7.75-7.82 (2H, m), 7.89 (1H, d, J= 2.7 Hz), 8.50 (1H, s), 8.77 (1H, br s).

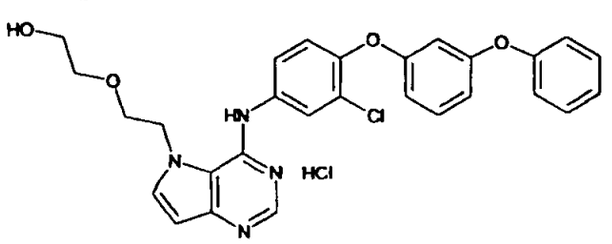
(ii) Production of (1E)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}ethanone oxime hydrochloride

To a solution of 2-[2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (171 mg) in ethanol (5 mL) were added hydroxylamine hydrochloride (104 mg) and sodium acetate (123 mg) and the mixture was stirred at room temperature for 4 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 methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (0.6 mL) were added to the obtained residue. The mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added thereto. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethanol-ethyl acetate to give the title compound (75 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 2.14 (3H, s), 3.40-3.54 (4H, m), 3.81-3.89 (2H, m), 4.76-4.85 (2H, m), 6.69 (1H, d, J= 3.0 Hz), 7.00-7.06 (1H, m), 7.22 (1H, m), 7.27 (1H, d, J= 8.7 Hz), 7.37-7.48 (2H, m), 7.62 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.96 (1H, d, J= 2.5 Hz), 8.01 (1H, m), 8.73 (1H, s), 9.80-9.90 (1H, m), 11.31 (1H, s).

Example E-5



Production of 2-[2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-

5-yl)ethoxy]ethanol hydrochloride

(i) Production of 2-chloro-4-nitro-1-(3-phenoxyphenoxy)benzene

2-Chloro-1-fluoro-4-nitrobenzene (0.943 g) and 3-phenoxyphenol (1 g) were dissolved in N,N-dimethylformamide (5.4 mL), and potassium carbonate (1.07 g) was added thereto. The mixture was stirred at room temperature for 16 hr. The reaction mixture was diluted with ethyl acetate (80 mL), and washed with water (70 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate=100/0→70/30) to give the title compound (1.75 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 6.73 (1H, t, J= 2 Hz), 6.78 (1H, m), 6.89 (1H, m), 6.95 (2H, d, J= 9 Hz), 7.05 (2H,m), 7.16 (1H, m), 7.37 (3H, m), 8.07 (1H, dd, J= 3 Hz, 9 Hz), 8.37 (1H, d, J= 3 Hz).

(ii) Production of 3-chloro-4-(3-phenoxyphenoxy)aniline

2-Chloro-4-nitro-1-(3-phenoxyphenoxy)benzene (1.7 g) was suspended in ethanol (49 mL)/water (5.45 mL), calcium chloride (306 mg) was added thereto and the mixture was dissolved by heating with stirring at 90°C for 10 min. Reduced iron (1.85 g) was added and the mixture was stirred with heating at 90°C for 16 hr. After cooling to room temperature, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residual solid was diluted with ethyl acetate (200 mL), and washed with saturated brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate=80/20→60/40) to give the title compound (1.58 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 3.67 (2H, br s), 6.50-6.70 (4H, m), 6.76 (1H, d, J= 3 Hz), 6.92 (1H, d, J= 9 Hz), 7.01 (2H, m), 7.10 (1H, m), 7.20 (1H, m), 7.33 (2H, m).

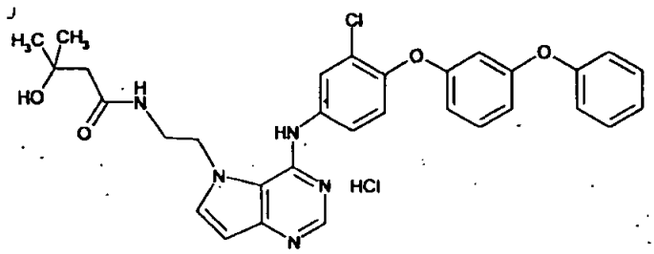
(iii) Production of 2-[2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol hydrochloride

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (150 mg), 3-chloro-4-(3-phenoxyphenoxy)aniline (201 mg) and 1-methyl-2-pyrrolidone (0.863 mL) was stirred with heating at 140°C for 3 hr. The reaction mixture was diluted with ethyl acetate (80 mL), and washed with aqueous sodium bicarbonate (30 mL). The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=90:10→0:100) and the objective fractions were concentrated under reduced pressure. The obtained residue was dissolved in methanol (1.89 mL), 1N aqueous sodium hydroxide solution (0.433 mL) was added thereto, and the mixture was stirred at room temperature for 2 hr. 1N hydrochloric acid (0.433 mL) was added, and the mixture was diluted with ethyl acetate (80 mL), and washed with saturated brine (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate:methanol=100:0→85:15). The fraction containing the title compound was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (4 mL). 4N hydrochloric acid (0.125 mL) was added to the mixture, and the mixture was crystallized from isopropyl ether/ethyl acetate to give the title compound (129 mg).

^{1}H-NMR (DMSO-d_6) δ: 3.46 (4H, d, J= 2 Hz), 3.84 (2H, br s), 4.85 (2H, br s), 6.60 (1H, s), 7.07 (2H, d, J= 8

Hz), 7.18 (2H, t, J= 8 Hz), 7.29 (1H, d, J= 8 Hz), 7.30-7.50 (3H, m), 7.64 (1H, d, J= 9 Hz), 7.96 (1H, d, J= 1 Hz), 8.04 (1H, d, J= 3 Hz), 8.74 (1H, s), 10.02 (1H, br s).

Example E-6



Production of N-[2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide hydrochloride

(i) Production of tert-butyl [2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (0.5 g) and 3-chloro-4-(3-phenoxyphenoxy)aniline (786 mg) in isopropyl alcohol (5 mL) was stirred at 80°C for 12 hr. Aqueous sodium bicarbonate (30 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (80 mL). The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=7:3→ethyl acetate) to give the title compound (713 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.48 (2H, m), 4.46 (2H,m), 5.12 (1H, t, J= 5 Hz), 6.59 (1H, d, J= 3 Hz), 6.69 (3H, m), 7.00-7.40 (8H, m), 7.85 (1H, dd, J= 3 Hz, 9 Hz), 7.98 (1H, d, J= 3 Hz), 8.50 (1H, s), 8.58 (1H, br s).

(ii) Production of 5-(2-aminoethyl)-N-[3-chloro-4-(3-phenoxyphenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (683 mg), 2N hydrochloric acid (8.46 mL) and tetrahydrofuran (16.9 mL) was stirred at 60°C for 20 hr. The solvent was evaporated under reduced pressure, ethanol was added, and the mixture was further concentrated. The precipitated powder was collected by filtration. The powder was washed with isopropyl ether to give the title compound (622 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 3.30 (2H, m), 5.08 (2H, m), 6.60 (1H, t, J= 2 Hz), 6.73 (3H, m), 7.06 (2H, m), 7.18 (1H, m), 7.29 (1H, d, J= 9 Hz), 7.41 (3H, m), 7.64 (1H, dd, J= 3 Hz, 9 Hz), 7.90 (1H, d, J= 3 Hz), 8.10 (1H, d, J= 3 Hz), 8.42 (3H, br s), 8.73 (1H, s).

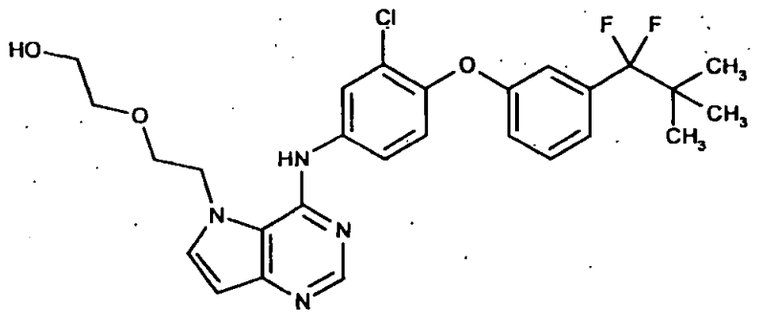
(iii) Production of N-[2-(4-{[3-chloro-4-(3-phenoxyphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide hydrochloride

A mixture of 5-(2-aminoethyl)-N-[3-chloro-4-(3-phenoxyphenoxy)phenyl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (195 mg), 3-hydroxy-3-methylbutanoic acid (0.058 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl

acetate→ethyl acetate:methanol=85:15). The fraction containing the title compound was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (4 mL). 4N hydrochloric acid (0.169 mL) was added, and the mixture was crystallized from ethyl acetate to give the title compound (176 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.10 (6H, s), 2.19 (2H, s), 3.48 (2H, q, J= 6 Hz), 4.66 (2H, t, J= 6 Hz), 6.60 (1H, t, J= 3 Hz), 6.67 (1H, d, J=3 Hz), 6.72 (2H, dt, J= 3 Hz, 9 Hz), 7.06 (2H, d, J= 8 Hz), 7.17 (1H, t, J= 7 Hz), 7.29 (1H, d, J= 9 Hz), 7.40 (3H, m), 7.67 (1H, dd, J= 3 Hz, 9 Hz), 7.92 (1H, d, J= 3 Hz), 7.98 (1H, d, J= 3 Hz), 8.40 (1H, m), 8.71 (1H, s).

Example E-7



Production of 2-{2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2,2-dimethylpropan-1-one

A mixture of 2-chloro-1-fluoro-4-nitrobenzene (2.63 g), 1-(3-hydroxyphenyl)-2,2-dimethylpropan-1-one (2.55 g), potassium carbonate (2.97 g) and N,N-dimethylformamide (20 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, water was added 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=2:98→15:85). The objective fractions were concentrated under reduced pressure to give the title compound (5.17 g) as a pale-yellow-green oil.
^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, s), 6.92 (1H, d, J= 9.1 Hz), 7.18 (1H, ddd, J= 1.1 Hz, 2.6 Hz, 8.1 Hz), 7.37 (1H, m), 7.45-7.52 (1H, m), 7.56-7.60 (1H, m), 8.08 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.7 Hz).

(ii) Production of 2-chloro-1-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]-4-nitrobenzene

A solution of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2,2-dimethylpropan-1-one (3.34 g) and diethylaminosulfur trifluoride (6.85 g) in dichloromethane (100 mL) was stirred with heating under reflux overnight. Ice and aqueous sodium hydrogencarbonate solution were added to the reaction mixture, and the mixture was extracted with dichloromethane. The dichloromethane layer was washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=2:98→15:85). The objective fractions were concentrated under reduced pressure to give the title compound (3.63 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 6.87 (1H, d, J= 9.1 Hz), 7.11-7.18 (2H, m), 7.31-7.37 (1H, m), 7.44-7.52 (1H, m), 8.07 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.7 Hz).

(iii) Production of 3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]aniline

A mixture of 2-chloro-1-[3-(1,1-difluoro-2,2-

dimethylpropyl)phenoxy]-4-nitrobenzene (712 mg), reduced iron (372 mg), calcium chloride (123 mg) and 10% water-containing ethanol (20 mL) was stirred with heating under reflux for 7 hr. Separately, a mixture of 2-chloro-1-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]-4-nitrobenzene (3.00 g), reduced iron (1.57 g), calcium chloride (520 mg) and 10% water-containing ethanol (100 mL) were stirred with heating under reflux overnight. They were combined and the solid was removed by filtration. The filtrate was concentrated and water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=15:85→30:70). The objective fractions were concentrated under reduced pressure to give the title compound (2.40 g) as a pale-brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (9H, s), 3.68 (2H, br s), 6.57 (1H, dd, J= 2.7 Hz, 8.8 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.87-6.95 (3H, m), 7.05-7.11 (1H, m), 7.28-7.33 (1H, m).

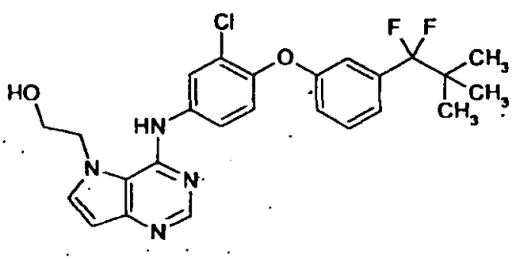
(iv) Production of 2-{2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (173 mg), 3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]aniline (163 mg), isopropyl alcohol (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-2(ii), the title compound (198 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 2.05 (1H, br s), 3.70-3.84 (4H, m), 4.02 (2H, t, J= 4.3 Hz), 4.56 (2H, t, J=

4.3 Hz), 6.61 (1H, d, J= 3.2 Hz), 6.94-7.08 (3H, m), 7.13 (1H, d, J= 7.7 Hz), 7.20 (1H, d, J= 3.2 Hz), 7.32 (1H, t, J= 8.0 Hz), 7.58 (1H, dd, J= 2.6 Hz, 8.9 Hz), 7.89 (1H, d, J= 2.6 Hz), 8.51 (1H, s), 8.78 (1H, br s).

Example E-8



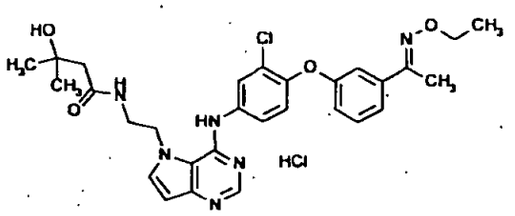
Production of 2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (151 mg), 3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]aniline (163 mg) and isopropyl alcohol (3 mL) was stirred at 80°C for 9 hr. An aqueous sodium hydrogencarbonate solution 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=60:40→100:0). The objective fractions were concentrated under reduced pressure. To the residue were added methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and the mixture was stirred at room temperature for 4 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 subjected

to silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (191 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s), 4.11-4.18 (2H, m), 4.33-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.50 (1H, br s), 6.95 (1H, d, J = 3.3 Hz), 6.97-7.08 (3H, m), 7.14 (1H, d, J = 7.7 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.82 (1H, d, J = 2.5 Hz), 8.21 (1H, s), 9.56 (1H, br s).

Example E-9



Production of N-(2-{4-[(3-chloro-4-{3-[(1E)-N-ethoxyacetoimidoyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide hydrochloride

(i) Production of tert-butyl [2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (890 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]ethanone (785 mg) and isopropyl alcohol (10 mL) was stirred at 80°C overnight. An aqueous sodium hydrogencarbonate solution 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 subjected

to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0). The objective fractions were concentrated under reduced pressure and the residue was crystallized from acetone-diethyl ether to give the title compound (1.14 g) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.59 (3H, m), 3.44-3.55 (2H, m), 4.44-4.53 (2H, m), 5.08 (1H, t, J = 5.6 Hz), 6.61 (1H, d, J = 3.3 Hz), 7.05 (1H, d, J = 8.9 Hz), 7.15-7.21 (2H, m), 7.41 (1H, t, J = 8.0 Hz), 7.56 (1H, m), 7.66 (1H, d, J = 7.7 Hz), 7.89 (1H, dd, J = 2.7 Hz, 8.9 Hz), 8.03 (1H, d, J = 2.7 Hz), 8.52 (1H, s), 8.60 (1H, br s).

(ii) Production of N-[2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide

To tert-butyl [2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (1.10 g) were added ethanol (2 mL) and 4N hydrogen chloride/ethyl acetate solution (5 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. To a solution of the obtained residue in N,N-dimethylformamide (20 mL) were added 3-hydroxy-3-methylbutanoic acid (374 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (607 mg), 1-hydroxybenzotriazole monohydrate (485 mg) and triethylamine (0.882 mL) and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0→methanol:ethyl

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acetate=20:80) and basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→10:90). The objective fractions were concentrated under reduced pressure to give the title compound (596 mg) as a white amorphous powder.

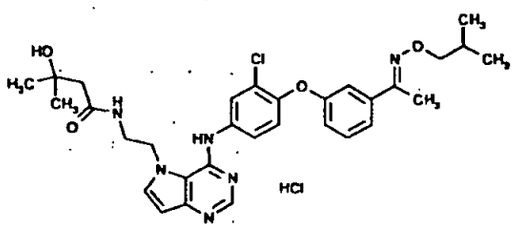
^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 2.48 (2H, s), 2.59 (3H, s), 3.58-3.68 (2H, m), 4.44-4.54 (2H, m), 6.59 (1H, d, J = 3.3 Hz), 7.05 (1H, d, J = 8.8 Hz), 7.09-7.22 (3H, m), 7.42 (1H, t, J = 7.8 Hz), 7.57 (1H, m), 7.64-7.69 (1H, m), 7.74 (1H, dd, J = 2.6 Hz, 8.8 Hz), 8.07 (1H, d, J = 2.6 Hz), 8.50 (1H, s), 8.66 (1H, br s).

(iii) Production of N-(2-{4-[(3-chloro-4-{3-[(1E)-N-ethoxyacetoimidoyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide hydrochloride

To a solution of N-[2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide (157 mg) in ethanol (5 mL) were added O-ethylhydroxylamine hydrochloride (88 mg) and sodium acetate (74 mg) and the mixture was stirred at room temperature overnight. 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 subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→15:85). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate-diethyl ether to give the title compound (91 mg) as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.11 (6H, s), 1.25 (3H, t, J = 7.1 Hz), 2.18 (3H, s), 2.20 (2H, s), 3.43-3.55 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 4.66 (2H, t, J = 6.7 Hz), 6.67 (1H, d, J = 3.2 Hz), 6.95-7.02 (1H, m), 7.22 (1H, d, J = 8.9 Hz), 7.33 (1H, m), 7.40-7.49 (2H, m), 7.67 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 7.98 (1H, d, J = 3.2 Hz), 8.40 (1H, t, J = 5.6 Hz), 8.72 (1H, s), 10.28 (1H, br s).

Example E-10

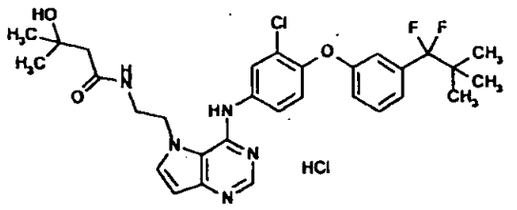


Production of N-(2-{4-[(3-chloro-4-{3-[(1E)-N-isobutoxyacetoimidoyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-3-hydroxy-3-methylbutanamide hydrochloride

Using N-[2-(4-{[4-(3-acetylphenoxy)-3-chlorophenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide (157 mg), ethanol (5 mL), O-isobutylhydroxylamine hydrochloride (113 mg), sodium acetate (74 mg) and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) and in the same manner as in Example E-9(iii), the title compound (87 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 0.92 (6H, d, J = 6.9 Hz), 1.11 (6H, s), 1.90-2.05 (1H, m), 2.20 (5H, s), 3.44-3.54 (2H, m), 3.91 (2H, d, J = 6.6 Hz), 4.66 (2H, t, J = 6.7 Hz), 6.67 (1H, d, J = 3.0 Hz), 6.94-7.02 (1H, m), 7.22 (1H, d, J = 8.9 Hz), 7.32 (1H, m), 7.40-7.48 (2H, m), 7.67 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 7.99 (1H, d, J = 3.0 Hz), 8.40 (1H, t, J = 5.5 Hz), 8.72 (1H, s), 10.29 (1H, br s).

Example E-11



Production of N-{2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide hydrochloride

(i) Production of tert-butyl {2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (594 mg), 3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]aniline (652 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example E-9(i), the title compound (1.15 g) was obtained as a pale-yellow amorphous powder.

^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 1.49 (9H, s), 3.42-3.54 (2H, m), 4.41-4.52 (2H, m), 5.20 (1H, t, J = 5.4 Hz), 6.58 (1H, d, J = 3.3 Hz), 6.96-7.08 (3H, m), 7.12 (1H, d, J = 7.7 Hz), 7.17 (1H, d, J = 3.3 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.84 (1H, dd, J = 2.5 Hz, 8.8 Hz), 8.01 (1H, d, J = 2.5 Hz), 8.50 (1H, s), 8.61 (1H, br s).

(ii) Production of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

To tert-butyl {2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (1.15 g) was added methanol (10 mL) and concentrated hydrochloric acid (2 mL), and the mixture was stirred at room temperature overnight and at 60°C for 3 hr. The reaction mixture was concentrated under reduced pressure, isopropyl alcohol and methanol were added thereto, and the mixture was

concentrated again under reduced pressure. Isopropyl alcohol and diisopropyl ether were added to the residue, and the crystals were collected by filtration to give the title compound (1.09 g) as a white powder.

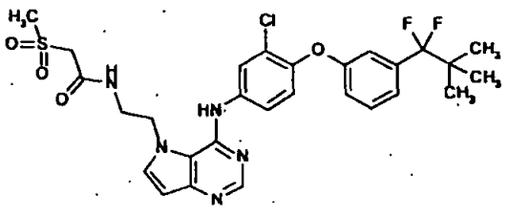
^{1}H-NMR (DMSO-d_6) δ: 0.99 (9H, s), 3.24-3.36 (2H, m), 5.01 (2H, t, J = 6.1 Hz), 6.73 (1H, d, J = 3.1 Hz), 6.93 (1H, m), 7.11 (1H, dd, J = 2.4 Hz, 8.0 Hz), 7.19 (1H, d, J = 8.1 Hz), 7.27 (1H, d, J = 8.9 Hz), 7.51 (1H, t, J = 8.0 Hz), 7.62 (1H, dd, J = 2.4 Hz, 8.9 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.05 (1H, d, J = 3.1 Hz), 8.23-8.33 (3H, m), 8.71 (1H, s), 10.06 (1H, br s).

(iii) Production of N-{2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide hydrochloride

A mixture of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (168 mg), 3-hydroxy-3-methylbutanoic acid (53 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole monohydrate (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were concentrated under reduced pressure. The residue was dissolved in ethyl acetate-ethanol, and 1N hydrogen chloride/ethyl acetate solution (0.3 mL) was added. The solvent was evaporated under reduced pressure and the

obtained residue was crystallized from ethyl acetate to give the title compound (134 mg) as a white powder. ^{1}H-NMR (DMSO-d_6) δ: 0.99 (9H, s), 1.11 (6H, s), 2.20 (2H, s), 3.44-3.54 (2H, m), 4.66 (2H, t, J = 7.0 Hz), 6.67 (1H, d, J = 3.2 Hz), 6.92 (1H, m), 7.13 (1H, dd, J = 2.3 Hz, 8.1 Hz), 7.20 (1H, d, J = 7.7 Hz), 7.29 (1H, d, J = 8.9 Hz), 7.52 (1H, t, J = 8.0 Hz), 7.70 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.96 (1H, d, J = 2.5 Hz), 7.99 (1H, d, J = 3.2 Hz), 8.41 (1H, t, J = 5.1 Hz), 8.73 (1H, s), 10.28 (1H, br s).

Example E-12



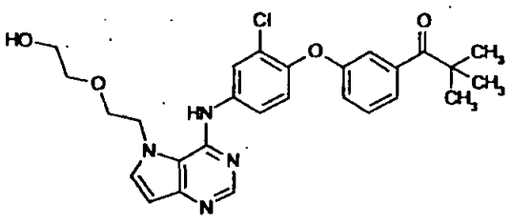
Production of N-{2-[4-({3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-{3-chloro-4-[3-(1,1-difluoro-2,2-dimethylpropyl)phenoxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (168 mg), methylsulfonylacetic acid (62 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg), 1-hydroxybenzotriazole monohydrate (69 mg), triethylamine (0.100 mL) and N,N-dimethylformamide (3 mL) was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. 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 obtained residue was subjected to basic silica gel column chromatography (eluent, methanol:ethyl acetate=0:100→20:80). The objective fractions were

concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (153 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 3.14 (3H, s), 3.65-3.75 (2H, m), 3.98 (2H, s), 4.44-4.53 (2H, m), 6.59 (1H, d, J = 3.0 Hz), 6.98-7.04 (2H, m), 7.07 (1H, m), 7.15 (1H, d, J = 7.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.62 (1H, t, J = 5.5 Hz), 7.72 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 8.18 (1H, br s), 8.50 (1H, s).

Example E-13



Production of 1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one

(i) Production of 1-[3-(4-amino-2-chlorophenoxy)phenyl]-2,2-dimethylpropan-1-one

A mixture of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2,2-dimethylpropan-1-one (1.03 g), reduced iron (575 mg), calcium chloride (190 mg) and 10% water-containing ethanol (30 mL) was stirred with heating under reflux overnight. The reaction mixture was filtered to remove solid, and the filtrate was concentrated. Water was added to the residue, 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 subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60). The objective fractions were concentrated under reduced pressure to give the

title compound (708 mg) as a brown oil.

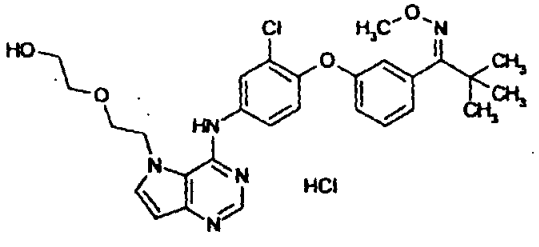
^{1}H-NMR ($CDCl_3$) δ: 1.31 (9H, s), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.5 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.91 (1H, d, J = 8.5 Hz), 6.94-7.00 (1H, m), 7.16 (1H, m), 7.26-7.35 (2H, m).

(ii) Production of 1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one

Using 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (734 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]-2,2-dimethylpropan-1-one (645 mg), isopropyl alcohol (10 mL), methanol (25 mL), tetrahydrofuran (5 mL) and 1N aqueous sodium hydroxide solution (5 mL) and in the same manner as in Example E-2(ii), the title compound (858 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.33 (9H, s), 3.70-3.82 (4H, m), 4.02 (2H, t, J = 4.4 Hz), 4.55 (2H, t, J = 4.4 Hz), 6.58 (1H, d, J = 3.3 Hz), 7.00-7.06 (2H, m), 7.19 (1H, d, J = 3.3 Hz), 7.22 (1H, m), 7.28-7.39 (2H, m), 7.57 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.89 (1H, d, J = 2.6 Hz), 8.48 (1H, s), 8.81 (1H, br s).

Example E-14



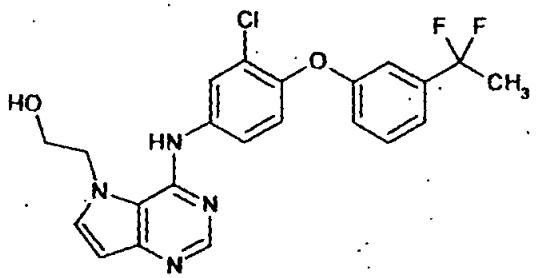
Production of (1Z)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one O-methyloxime hydrochloride

Using 1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one (204

mg), ethanol (5 mL), O-methylhydroxylamine hydrochloride (100 mg), sodium acetate (98 mg) and 1N hydrogen chloride/ethyl acetate solution (0.4 mL) and in the same manner as in Example E-9(iii), the title compound (201 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.10 (9H, s), 3.41-3.51 (4H, m), 3.65 (3H, s), 3.84 (2H, t, J = 4.4 Hz), 4.78-4.85 (2H, m), 6.62 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 6.82 (1H, d, J = 7.7 Hz), 6.94 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.22 (1H, d, J = 8.9 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.61 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.95 (1H, d, J = 2.5 Hz), 8.02 (1H, d, J = 3.0 Hz), 8.73 (1H, s), 9.92 (1H, br s).

Example E-15



Production of 2-[4-({3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]ethanone

Using 2-chloro-1-fluoro-4-nitrobenzene (3.51 g), 3'-hydroxyacetophenone (2.72 g), potassium carbonate (4.15 g) and N,N-dimethylformamide (20 mL) and in the same manner as in Example E-7(i), the title compound (5.60 g) was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s), 6.92 (1H, d, J = 9.1 Hz), 7.28-7.33 (1H, m), 7.56 (1H, t, J = 8.0 Hz), 7.65 (1H, m), 7.82-7.88 (1H, m), 8.09 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.41 (1H, d, J = 2.6 Hz).

(ii) Production of 2-chloro-1-[3-(1,1-difluoroethyl)phenoxy]-4-nitrobenzene

A solution of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]ethanone (2.92 g), diethylaminosulfur trifluoride (8.06 g) in 1,2-dimethoxyethane (10 mL) was stirred at 50°C for 5 days. The reaction mixture was poured into ice, and 8N aqueous sodium hydroxide solution (20 mL) was added thereto. Ethyl acetate was added, and the organic layer was separated, washed with saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=0:100→20:80). The objective fractions were concentrated under reduced pressure to give the title compound (2.75 g) as an orange solid.

^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, t, J = 18.1 Hz), 6.92 (1H, d, J = 9.1 Hz), 7.11-7.17 (1H, m), 7.25 (1H, m), 7.38-7.44 (1H, m), 7.51 (1H, t, J = 7.8 Hz), 8.08 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]aniline

Using 2-chloro-1-[3-(1,1-difluoroethyl)phenoxy]-4-nitrobenzene (2.51 g), reduced iron (1.99 g), calcium chloride (493 mg) and 10% water-containing ethanol (100 mL) and in the same manner as in Example E-13(i), the title compound (1.81 g) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.89 (3H, t, J = 18.1 Hz), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.86-6.92 (1H, m), 6.91 (1H, d, J = 8.6 Hz), 7.04 (1H, m), 7.13-7.18 (1H, m), 7.32 (1H, t, J = 8.0 Hz).

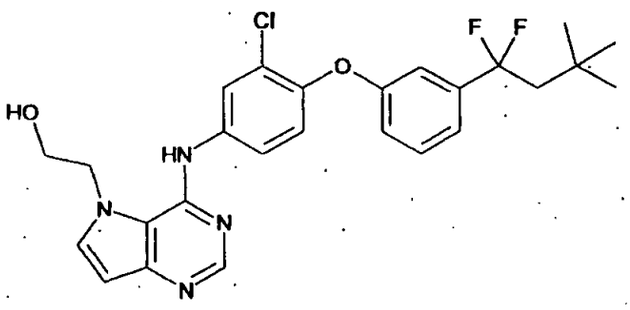
(iv) Production of 2-[4-({3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (151 mg), 3-chloro-4-[3-(1,1-

difluoroethyl)phenoxy]aniline (142 mg), isopropyl alcohol (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-8, the title compound (149 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, t, J = 18.1 Hz), 4.10-4.18 (2H, m), 4.32-4.39 (2H, m), 6.06 (1H, d, J = 3.2 Hz), 6.72 (1H, br s), 6.93 (1H, d, J = 3.2 Hz), 6.97-7.02 (1H, m), 7.05 (1H, d, J = 8.8 Hz), 7.13 (1H, m), 7.20 (1H, d, J = 8.0 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.81 (1H, d, J = 2.5 Hz), 8.18 (1H, s), 9.61 (1H, br s).

Example E-16



Production of 2-[4-({3-chloro-4-[3-(1,1-difluoro-3,3-dimethylbutyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-3,3-dimethylbutan-1-one

Using 2-chloro-1-fluoro-4-nitrobenzene (1.76 g), 1-(3-hydroxyphenyl)-3,3-dimethylbutan-1-one (1.92 g), potassium carbonate (2.07 g) and N,N-dimethylformamide (10 mL) and in the same manner as in Example E-7(i), the title compound (3.24 g) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.07 (9H, s), 2.85 (2H, s), 6.90 (1H, d, J = 9.1 Hz), 7.25-7.30 (1H, m), 7.54 (1H, t, J = 8.0 Hz), 7.63 (1H, m), 7.80-7.86 (1H, m), 8.08 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.41 (1H, d, J = 2.7 Hz).

(ii) Production of 2-chloro-1-[3-(1,1-difluoro-3,3-

295

dimethylbutyl)phenoxy]-4-nitrobenzene

Using 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-3,3-dimethylbutan-1-one (1.90 g), diethylaminosulfur trifluoride (5.0 mL) and 1,2-dimethoxyethane (10 mL) and in the same manner as in Example E-15(ii), the title compound (52 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (9H, s), 2.07 (2H, t, J = 19.1 Hz), 6.88 (1H, d, J = 9.3 Hz), 7.09-7.15 (1H, m), 7.21 (1H, m), 7.38 (1H, d, J = 7.7 Hz), 7.49 (1H, t, J = 7.8 Hz), 8.08 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iii) Production of 3-chloro-4-[3-(1,1-difluoro-3,3-dimethylbutyl)phenoxy]aniline

Using 2-chloro-1-[3-(1,1-difluoro-3,3-dimethylbutyl)phenoxy]-4-nitrobenzene (130 mg), reduced iron (99 mg), calcium chloride (25 mg) and 10% water-containing ethanol (10 mL) and in the same manner as in Example E-13(i), the title compound (100 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s), 2.04 (2H, t, J = 18.9 Hz), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.85-6.90 (1H, m), 6.90 (1H, d, J = 8.6 Hz), 7.00 (1H, m), 7.12 (1H, d, J = 7.7 Hz), 7.30 (1H, t, J = 8.1 Hz).

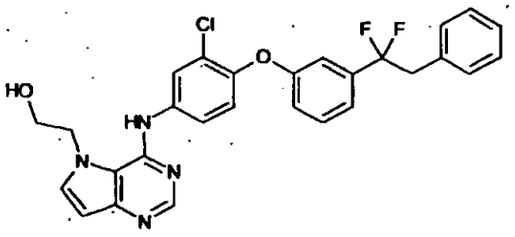
(iv) Production of 2-[4-({3-chloro-4-[3-(1,1-difluoro-3,3-dimethylbutyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (121 mg), 3-chloro-4-[3-(1,1-difluoro-3,3-dimethylbutyl)phenoxy]aniline (100 mg), isopropyl alcohol (5 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-8, the title compound (67 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (9H, s), 2.07 (2H, t, J = 19.0

Hz), 4.11-4.18 (2H, m), 4.33-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.49 (1H, br s), 6.94 (1H, d, J = 3.3 Hz), 6.95-7.01 (1H, m), 7.04 (1H, d, J = 8.7 Hz), 7.10 (1H, m), 7.17 (1H, d, J = 7.7 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.47 (1H, dd, J = 2.6 Hz, 8.7 Hz), 7.81 (1H, d, J = 2.6 Hz), 8.20 (1H, s), 9.55 (1H, br s).

Example E-17



Production of 2-[4-({3-chloro-4-[3-(1,1-difluoro-2-phenylethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2-phenylethanone

Using 2-chloro-1-fluoro-4-nitrobenzene (702 mg), 1-(3-hydroxyphenyl)-2-phenylethanone (849 mg), potassium carbonate (829 mg) and N,N-dimethylformamide (10 mL) and in the same manner as in Example E-7(i), the title compound (725 mg) was obtained as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 4.26 (2H, s), 6.86 (1H, d, J = 9.1 Hz), 7.20-7.36 (6H, m), 7.53 (1H, t, J = 8.0 Hz), 7.65 (1H, m), 7.86-7.92 (1H, m), 8.05 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.39 (1H, d, J = 2.6 Hz).

(ii) Production of 2-chloro-1-[3-(1,1-difluoro-2-phenylethyl)phenoxy]-4-nitrobenzene

Using 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2-phenylethanone (478 mg), diethylaminosulfur trifluoride (2.0 mL) and 1,2-dimethoxyethane (5 mL) and in the same manner as in Example E-15(ii), the title compound (372 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.41 (2H, t, J = 15.4 Hz), 6.59 (1H, d,

J = 9.1 Hz), 6.91 (1H, m), 7.01-7.13 (3H, m), 7.20-7.29 (4H, m), 7.44 (1H, t, J = 8.0 Hz), 7.99 (1H, dd, J = 2.5 Hz, 9.1 Hz), 8.35 (1H, d, J = 2.5 Hz).

(iii) Production of 3-chloro-4-[3-(1,1-difluoro-2-phenylethyl)phenoxy]aniline

Using 2-chloro-1-[3-(1,1-difluoro-2-phenylethyl)phenoxy]-4-nitrobenzene (372 mg), reduced iron (186 mg), calcium chloride (62 mg) and 10% water-containing ethanol (10 mL) and in the same manner as in Example E-13(i), the title compound (200 mg) was obtained as a yellow oil.

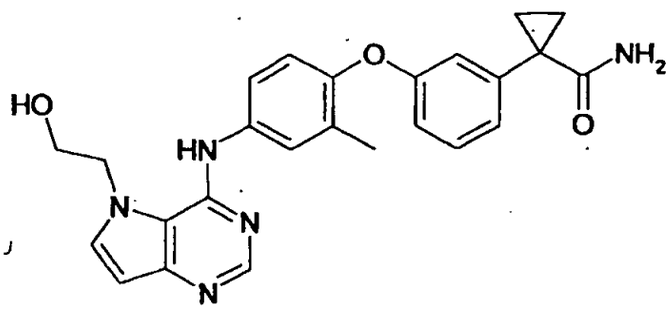
^{1}H-NMR ($CDCl_3$) δ: 3.36 (2H, t, J = 15.9 Hz), 3.67 (2H, br s), 6.54 (1H, dd, J = 2.7 Hz, 8.8 Hz), 6.77 (1H, d, J = 2.7 Hz), 6.78-6.84 (2H, m), 6.85-6.91 (1H, m), 6.98 (1H, d, J = 8.0 Hz), 7.05-7.12 (2H, m), 7.20-7.30 (4H, m).

(iv) Production of 2-[4-({3-chloro-4-[3-(1,1-difluoro-2-phenylethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (169 mg), 3-chloro-4-[3-(1,1-difluoro-2-phenylethyl)phenoxy]aniline (200 mg), isopropyl alcohol (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-8, the title compound (171 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 3.39 (2H, t, J = 15.8 Hz), 4.10-4.19 (2H, m), 4.32-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.53 (1H, br s), 6.90-7.14 (7H, m), 7.20-7.38 (4H, m), 7.45 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.5 Hz), 8.21 (1H, s), 9.57 (1H, br s).

Example E-18



Production of 1-[3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarboxamide

(i) Production of 1-(3-methoxyphenyl)cyclopropanecarbonitrile

60% Sodium hydride (2.72 g) was suspended in N,N-dimethylformamide (80 mL) and the mixture was cooled to 0°C. A solution of (3-methoxyphenyl)acetonitrile (4.00 g) in N,N-dimethylformamide (20 mL) was added dropwise to the mixture and the mixture was stirred at 0°C for 1 hr. 1,2-Dibromoethane (3.5 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 17 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=100:0→80:20) to give the title compound (2.76 g) as a yellow oil.
^{1}H-NMR ($CDCl_3$) δ: 1.36-1.44 (2H, m), 1.67-1.75 (2H, m), 3.81 (3H, s), 6.77-6.89 (3H, m), 7.21-7.29 (1H, m).

(ii) Production of 1-(3-methoxyphenyl)cyclopropanecarboxamide and 1-(3-methoxyphenyl)cyclopropanecarboxylic acid

1-(3-Methoxyphenyl)cyclopropanecarbonitrile (2.75 g) was dissolved in a mixed solvent of ethanol (100

mL)/water (5.0 mL), potassium hydroxide (8.94 g) was added thereto, and the mixture was stirred with heating under reflux for 5 hr. The reaction mixture was concentrated under reduced pressure, the residue was adjusted to pH 1-2 with 6N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=50:50→0:100) to give 1-(3-methoxyphenyl)cyclopropanecarboxamide (762 mg) and 1-(3-methoxyphenyl)cyclopropanecarboxylic acid (1.78 g), each as pale-orange crystals.

1-(3-methoxyphenyl)cyclopropanecarboxamide

^{1}H-NMR (DMSO-d_6) δ: 0.91-0.98 (2H, m), 1.26-1.34 (2H, m), 3.75 (3H, s), 6.11 (1H, br s), 6.79-6.96 (3H, m), 7.02 (1H, br s), 7.25 (1H, t, J= 8.0 Hz).

1-(3-methoxyphenyl)cyclopropanecarboxylic acid

^{1}H-NMR (DMSO-d_6) δ: 1.02-1.20 (2H, m), 1.33-1.50 (2H, m), 3.73 (3H, s), 6.71-7.00 (3H, m), 7.20 (1H, t, J= 7.8 Hz), 12.27 (1H, br s).

(iii) Production of 1-(3-hydroxyphenyl)cyclopropanecarboxamide

1-(3-Methoxyphenyl)cyclopropanecarboxamide (756 mg) was dissolved in benzotrifluoride (20 mL), 1N boron tribromide/dichloromethane solution (10 mL) was added thereto at 0°C, and the mixture was stirred at room temperature for 2 days. The reaction mixture was ice-cooled, saturated aqueous sodium hydrogencarbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column

chromatography (hexane:ethyl acetate=67:33→0:100) to give the title compound (350 mg) as a white powder.
^{1}H-NMR (DMSO-d_6) δ: 0.85-0.95 (2H, m), 1.22-1.32 (2H, m), 6.04 (1H, br s), 6.59-6.71 (1H, m), 6.71-6.82 (2H, m), 7.02 (1H, br s), 7.12 (1H, t, J= 7.8 Hz), 9.40 (1H, s).

(iv) Production of 1-[3-(2-methyl-4-nitrophenoxy)phenyl]cyclopropanecarboxamide

A mixture of 1-(3-hydroxyphenyl)cyclopropanecarboxamide (345 mg) and 2-fluoro-5-nitrotoluene (347 mg) was dissolved in N,N-dimethylformamide (5 mL), potassium carbonate (588 mg) was added thereto, and the mixture was stirred at room temperature for 19 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=67:33→10:90) to give the title compound (561 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 1.11 (2H, q, J=3.9 Hz), 1.58-1.70 (2H, m), 2.41 (3H, s), 5.35 (1H, br s), 5.56 (1H, br s), 6.80 (1H, d, J= 9.0 Hz), 6.93-7.00 (1H, m), 7.13 (1H, t, J= 2.1 Hz), 7.27-7.33 (1H, m), 7.41 (1H, t, J= 7.8 Hz), 8.02 (1H, dd, J= 2.0 Hz, 9.0 Hz), 8.18 (1H, d, J= 2.0 Hz).

(v) Production of 1-[3-(4-amino-2-methylphenoxy)phenyl]cyclopropanecarboxamide

1-[3-(2-Methyl-4-nitrophenoxy)phenyl]cyclopropanecarboxamide (556 mg) was suspended in a mixed solvent of ethanol (18 mL)/water (2 mL), reduced iron (615 mg) and calcium chloride (105 mg) were added thereto, and the mixture was stirred with heating under reflux for 4 hr. The reaction mixture was filtered through celite, and the filtrate was

concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=50:50→0:100) to give the title compound (433 mg) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03-1.11 (2H, m), 1.54-1.63 (2H, m), 2.09 (3H, s), 3.59 (2H, br s), 5.38 (2H, br s), 6.49-6.56 (1H, m), 6.60 (1H, d, J= 2.8 Hz), 6.72-6.82 (2H, m), 6.89-6.94 (1H, m), 7.01-7.07 (1H, m), 7.23 (1H, t, J= 8.4 Hz).

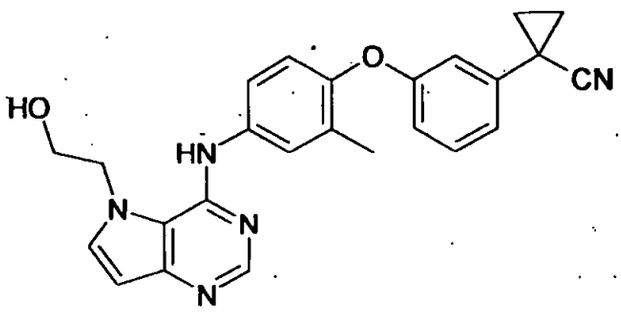
(vi) Production of 1-[3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarboxamide

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (113 mg) and 1-[3-(4-amino-2-methylphenoxy)phenyl]cyclopropanecarboxamide (108 mg) was dissolved in isopropyl alcohol (3 mL), and the mixture was stirred at 70°C for 21 hr. The reaction mixture was cooled to room temperature, 1N aqueous sodium hydroxide solution (1 mL) was added thereto, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=20:80→0:100→ethyl acetate:methanol=90:10) and crystallized from ethyl acetate to give the title compound (110 mg) as white crystals.

^{1}H-NMR (DMSO-d_6) δ:.0.90-0.98 (2H, m), 1.25-1.33 (2H, m),

2.16 (3H, s), 3.87 (2H, t, J= 4.5 Hz), 4.52 (2H, t, J= 4.5 Hz), 6.25 (2H, br s), 6.48 (1H, d, J= 3.0 Hz), 6.74-6.82 (1H, m), 6.82-6.87 (1H, m), 6.96-7.09 (3H, m), 7.30 (1H, t, J= 7.9 Hz), 7.47-7.56 (2H, m), 7.62 (1H, d, J= 3.0 Hz), 8.27 (1H, s), 9.61 (1H, br s).

Example E-19



Production of 1-[3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarbonitrile

(i) Production of 1-(3-hydroxyphenyl)cyclopropanecarbonitrile

Using 1-(3-methoxyphenyl)cyclopropanecarbonitrile (1.28 g), toluene (75 mL) and 1N boron tribromide/dichloromethane solution (25 mL) and in the same manner as in Example E-18(iii), the title compound (1.11 g) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.37-1.46 (2H, m), 1.69-1.77 (2H, m), 5.16 (1H, s), 6.70-6.81 (2H, m), 6.83 (1H, t, J= 2.1 Hz), 7.21 (1H, t, J= 7.8 Hz).

(ii) Production of 1-[3-(2-methyl-4-nitrophenoxy)phenyl]cyclopropanecarbonitrile

Using 2-fluoro-5-nitrotoluene (409 mg), 1-(3-hydroxyphenyl)cyclopropanecarbonitrile (450 mg), potassium carbonate (731 mg) and N,N-dimethylformamide (8 mL) and in the same manner as in Example E-18(iv), the title compound (776 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.38-1.47 (2H, m), 1.72-1.82 (2H, m),

2.40 (3H, s), 6.78 (1H, d, J= 9.0 Hz), 6.88-6.95 (1H, m), 7.01 (1H, t, J= 2.1 Hz), 7.10-7.17 (1H, m), 7.38 (1H, t, J= 8.0 Hz), 8.01 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.12-8.22 (1H, m).

(iii) Production of 1-[3-(4-amino-2-methylphenoxy)phenyl]cyclopropanecarbonitrile

Using 1-[3-(2-methyl-4-nitrophenoxy)phenyl]cyclopropanecarbonitrile (771 mg), reduced iron (847 mg), calcium chloride (151 mg) and ethanol (27 mL)/water (3 mL) and in the same manner as in Example E-18(v), the title compound (665 mg) was obtained as a yellow oil.

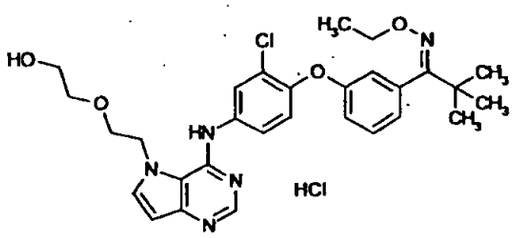
^{1}H-NMR ($CDCl_3$) δ: 1.36-1.39 (2H, m), 1.67-1.71 (2H, m), 2.09 (3H, s), 3.57 (2H, br s), 6.52 (1H, dd, J= 2.7 Hz, 8.7 Hz), 6.59 (1H, d, J=2.7 Hz), 6.67-6.70 (1H, m), 6.75-6.79 (2H, m), 6.93-6.96 (1H, m), 7.21 (1H, t, J= 8.1 Hz).

(iv) Production of 1-[3-(4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarbonitrile

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (127 mg), 1-[3-(4-amino-2-methylphenoxy)phenyl]cyclopropanecarbonitrile (130 mg), isopropyl alcohol (3 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-18(vi), the title compound (115 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.38-1.45 (2H, m), 1.69-1.76 (2H, m), 2.24 (3H, s), 4.08-4.18 (2H, m), 4.31-4.43 (2H, m), 6.12 (1H, d, J= 3.3 Hz), 6.35 (1H, br s), 6.80 (1H, dd, J= 1.9 Hz, 8.0 Hz), 6.88-7.03 (4H, m), 7.25 (1H, t, J= 8.0 Hz), 7.38-7.51 (2H, m), 8.22 (1H, s), 9.31 (1H, m).

Example E-20

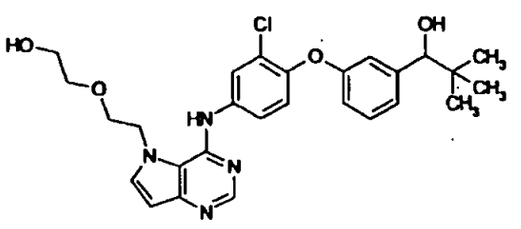


Production of (1Z)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one O-ethyloxime hydrochloride

Using 1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one (255 mg), ethanol (5 mL), O-ethylhydroxylamine hydrochloride (146 mg), sodium acetate (123 mg) and 1N hydrogen chloride/ethyl acetate solution (0.5 mL) and in the same manner as in Example E-9(iii), the title compound (144 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.07 (3H, t, J = 7.0 Hz), 1.10 (9H, s), 3.40-3.50 (4H, m), 3.84 (2H, t, J = 4.5 Hz), 3.92 (2H, q, J = 7.0 Hz), 4.82 (2H, t, J = 4.5 Hz), 6.61 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 6.82 (1H, d, J = 7.4 Hz), 6.93-6.99 (1H, m), 7.19 (1H, d, J = 8.8 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.61 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.95 (1H, d, J = 2.5 Hz), 8.01 (1H, d, J = 3.0 Hz), 8.71 (1H, s), 9.92 (1H, br s).

Example E-21

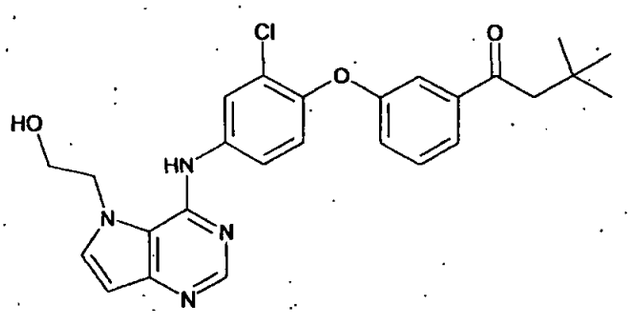


Production of 1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-ol

To a solution of 1-{3-[2-chloro-4-({5-[2-(2-

hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one (255 mg) in methanol (5 mL) was added sodium borohydride (38 mg) and the mixture was stirred at room temperature for 4 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 crystallized from ethyl acetate-diisopropyl ether to give the title compound (206 mg) as a white powder.
^{1}H-NMR ($CDCl_3$) δ: 0.92 (9H, s), 2.02 (1H, br s), 2.12 (1H, br s), 3.69-3.80 (4H, m), 4.01 (2H, t, J = 4.4 Hz), 4.36 (1H, s), 4.55 (2H, t, J = 4.4 Hz), 6.59 (1H, d, J = 3.0 Hz), 6.82-6.88 (1H, m), 6.92 (1H, m), 6.96-7.04 (2H, m), 7.19 (1H, d, J = 3.0 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.54 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.85 (1H, d, J = 2.5 Hz), 8.47 (1H, s), 8.73 (1H, br s).

Example E-22



Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one

(i) Production of 1-[3-(4-amino-2-chlorophenoxy)phenyl]-3,3-dimethylbutan-1-one

To a solution of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-3,3-dimethylbutan-1-one (1.04 g) in ethyl acetate (20 mL) was added 5% platinum-activated carbon (50 mg) and the mixture was stirred under a

hydrogen atmosphere at room temperature for 3 hr. The catalyst was filtered off, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography (eluent, ethyl acetate:hexane=15:85→35:65) and the objective fractions were concentrated under reduced pressure to give the title compound (964 mg) as a brown oil.

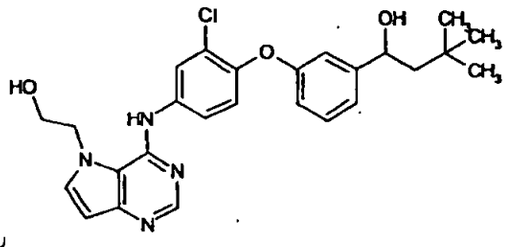
^{1}H-NMR ($CDCl_3$) δ: 1.04 (9H, s), 2.80 (2H, s), 3.69 (2H, br s), 6.57 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 8.7 Hz), 7.05 (1H, ddd, J = 0.9 Hz, 2.6 Hz, 8.1 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.41 (1H, m), 7.55-7.59 (1H, m).

(ii) Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (754 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]-3,3-dimethylbutan-1-one (795 mg), isopropyl alcohol (5 mL), methanol (10 mL), tetrahydrofuran (2 mL) and 1N aqueous sodium hydroxide solution (2.5 mL) and in the same manner as in Example E-8, the title compound (878 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.06 (9H, s), 2.84 (2H, s), 4.13 (2H, t, J = 4.4 Hz), 4.37 (2H, t, J = 4.4 Hz), 6.09 (1H, d, J = 3.2 Hz), 6.58 (1H, br s), 6.95 (1H, d, J = 3.2 Hz), 7.04 (1H, d, J = 8.8 Hz), 7.13-7.18 (1H, m), 7.39 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.50 (1H, m), 7.62 (1H, d, J = 7.7 Hz), 7.81 (1H, d, J = 2.6 Hz), 8.19 (1H, s), 9.59 (1H, br s).

Example E-23

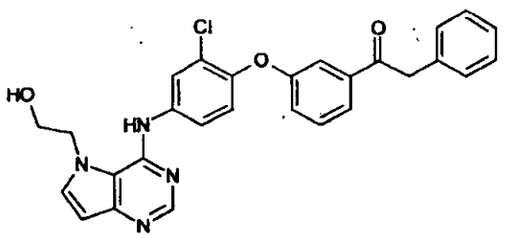


Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-ol

Using 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one (239 mg), methanol (5 mL) and sodium borohydride (38 mg) and in the same manner as in Example E-21, the title compound (234 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s), 1.61 (1H, dd, J = 3.4 Hz, 14.5 Hz), 1.74 (1H, dd, J = 8.3 Hz, 14.5 Hz), 1.91 (1H, br s), 4.13 (2H, t, J = 4.5 Hz), 4.36 (2H, t, J = 4.5 Hz), 4.82 (1H, dd, J = 3.4 Hz, 8.3 Hz), 6.09 (1H, d, J = 3.0 Hz), 6.52 (1H, br s), 6.85 (1H, dd, J = 2.5 Hz, 8.0 Hz), 6.95 (1H, d, J = 3.0 Hz), 7.00-7.08 (3H, m), 7.28 (1H, t, J = 7.8 Hz), 7.45 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.6 Hz), 8.19 (1H, s), 9.56 (1H, br s).

Example E-24



Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2-phenylethanone

(i) Production of 1-[3-(4-amino-2-chlorophenoxy)phenyl]-2-phenylethanone

Using 1-[3-(2-chloro-4-nitrophenoxy)phenyl]-2-phenylethanone (240 mg), ethyl acetate (10 mL) and 5% platinum-activated carbon (12 mg) and in the same manner as in Example E-22(i), the title compound (192 mg) was obtained as a colorless oil.

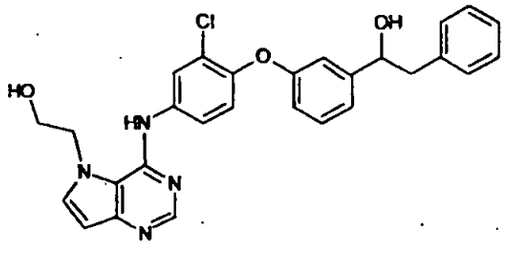
^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, br s), 4.21 (2H, s), 6.57 (1H, dd, J = 2.7 Hz, 8.8 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.89 (1H, d, J = 8.8 Hz), 7.06-7.11 (1H, m), 7.19-7.40 (6H, m), 7.46 (1H, m), 7.64-7.69 (1H, m).

(ii) Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2-phenylethanone

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (166 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]-2-phenylethanone (186 mg), isopropyl alcohol (3 mL), methanol (5 mL), tetrahydrofuran (1 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-8, the title compound (123 mg) was obtained as a pale-brown powder.

^{1}H-NMR ($CDCl_3$) δ: 4.14 (2H, t, J = 4.5 Hz), 4.25 (2H, s), 4.38 (2H, t, J = 4.5 Hz), 6.15 (1H, d, J = 3.2 Hz), 6.19 (1H, br s), 6.97 (1H, d, J = 3.2 Hz), 7.05 (1H, d, J = 8.7 Hz), 7.17-7.37 (6H, m), 7.42 (1H, t, J = 8.0 Hz), 7.49 (1H, dd, J = 2.7 Hz, 8.7 Hz), 7.54 (1H, m), 7.72 (1H, d, J = 7.7 Hz), 7.82 (1H, d, J = 2.7 Hz), 8.24 (1H, s), 9.55 (1H, br s).

Example E-25



Production of 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-

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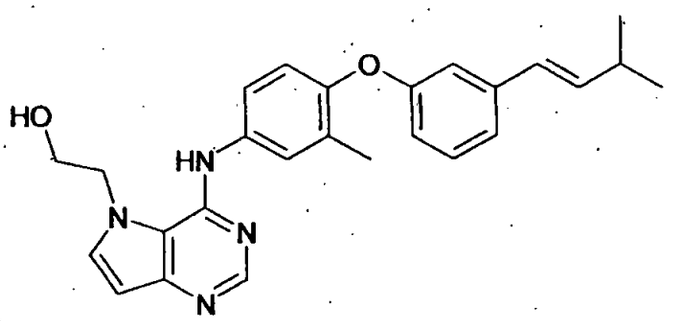
pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2-phenylethanol

Using 1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-2-phenylethanone (60 mg), methanol (2 mL) and sodium borohydride (10 mg) and in the same manner as in Example E-21, the title compound (24 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 2.08 (1H, br s), 2.98 (1H, dd, J = 8.2 Hz, 13.7 Hz), 3.05 (1H, dd, J = 4.9 Hz, 13.7 Hz), 4.14 (2H, t, J = 4.6 Hz), 4.38 (2H, t, J = 4.6 Hz), 4.89 (1H, dd, J = 4.9 Hz, 8.2 Hz), 6.07 (1H, br s), 6.15 (1H, d, J = 3.3 Hz), 6.87-6.93 (1H, m), 6.96-7.02 (3H, m), 7.08 (1H, d, J = 7.7 Hz), 7.17-7.35 (6H, m), 7.45 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.79 (1H, d, J = 2.5 Hz), 8.24 (1H, s), 9.48 (1H, br s).

Example E-26



Production of 2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

(i) Production of 3-(2-methyl-4-nitrophenoxy)benzaldehyde

Using 2-fluoro-5-nitrotoluene (3.00 g), 3-hydroxybenzaldehyde (2.59 g), potassium carbonate (4.58 g) and N,N-dimethylformamide (30 mL) and in the same manner as in Example E-18(iv), the title compound (4.14 g) was obtained was obtained as a pale-yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 6.85 (1H, d, J= 9 Hz),

7.28-7.36 (1H, m), 7.46-7.54 (1H, m), 7.60 (1H, t, J= 7.8 Hz), 7.68-7.76 (1H, m), 8.04 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.19 (1H, d, J= 2.8 Hz), 10.00 (1H, s).

(ii) Production of 2-methyl-1-{3-[3-methylbut-1-en-1-yl]phenoxy}-4-nitrobenzene

Isobutyltriphenylphosphonium bromide (1.86 g) was suspended in tetrahydrofuran (20 mL) and the suspension was cooled to 0°C. 1.6 M n-butyllithium/hexane solution (3.5 mL) was added dropwise, and the mixture was stirred at 0°C for 1 hr. A solution of 3-(2-methyl-4-nitrophenoxy)benzaldehyde (1.00 g) in tetrahydrofuran (10 mL) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 2 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=100:0→90:10) to give the title compound (1.09 g, E/Z= about 1/5) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (5H, d, J= 6.5 Hz), 1.09 (1H, d, J= 6.5 Hz), 2.41 (3H, s), 2.40-2.51 (0.17H, m), 2.77-2.92 (0.83H, m), 5.51 (0.83H, dd, J= 10.3 Hz, 11.6 Hz), 6.15-6.38 (1.17H, m), 6.72-6.96 (2.83H, m), 7.03 (0.17H, t, J= 7.7 Hz), 7.11 (0.83H, d, J= 7.7 Hz), 7.20 (0.17H, d, J= 7.7 Hz), 7.28-7.41 (1H, m), 7.94-8.06 (1H, m), 8.11-8.21 (1H, m).

(iii) Production of 3-methyl-4-{3-[3-methylbut-1-en-1-yl]phenoxy}aniline

Using 2-methyl-1-{3-[3-methylbut-1-en-1-yl]phenoxy}-4-nitrobenzene (1.08 g), reduced iron (1.01 g), calcium chloride (205 mg) and ethanol (36 mL)/water (4 mL) and in the same manner as in Example E-18(v), the

title compound (821 mg, E/Z= about 1/5) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.00 (5H, d, J= 6.6 Hz), 1.07 (1H, d, J= 6.6 Hz), 2.12 (3H, s), 2.36-2.52 (0.17H, m), 2.74-2.96 (0.83H, m), 3.55 (2H, br s), 5.43 (0.83H, dd, J= 10.2 Hz, 11.6 Hz), 6.08-6.33 (1.17H, m), 6.47-6.92 (5.83H, m), 6.95-7.01 (0.17H, m), 7.16 (0.17H, t, J= 8.0 Hz), 7.19 (0.83H, t, J= 8.0 Hz).

(iv) Production of 3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}aniline

3-Methyl-4-{3-[3-methylbut-1-en-1-yl]phenoxy}aniline (815 mg) was dissolved in tetrahydrofuran (15 mL), diphenyl disulfide (133 mg) and 2,2'-azobis(butyronitrile) (103 mg) were added, and the mixture was stirred with heating under reflux 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, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=90:10→50:50) to give the title compound (181 mg) as an orange oil.

^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d, J= 6.9 Hz), 2.11 (3H, s), 2.35-2.53 (1H, m), 3.55 (2H, br s), 6.13 (1H, dd, J= 6.3 Hz, 16.0 Hz), 6.25 (1H, d, J= 16.0 Hz), 6.51 (1H, dd, J= 3.0 Hz, 8.4 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.65 (1H, dd, J= 2.6 Hz, 8.0 Hz), 6.78 (1H, d, J= 8.4 Hz), 6.81-6.86 (1H, m), 6.97 (1H, d, J= 8.0 Hz), 7.15 (1H, t, J= 8.0 Hz).

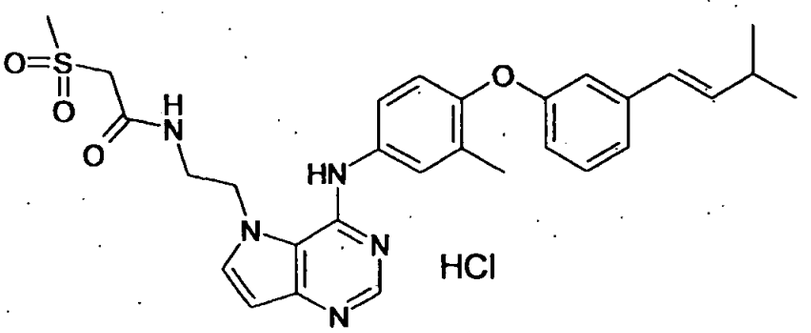
(v) Production of 2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (69.6 mg), 3-methyl-4-{3-[(1E)-3-

methylbut-1-en-1-yl]phenoxy}aniline (65.0 mg), isopropyl alcohol (2 mL) and 1N aqueous sodium hydroxide solution (1 mL) and in the same manner as in Example E-18(vi), the title compound (47.7 mg) was obtained was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.09 (6H, d, J= 6.8 Hz), 2.26 (3H, s), 2.36-2.56 (1H, m), 4.13 (2H, t, J= 4.5 Hz), 4.31-4.42 (2H, m), 6.12 (1H, d, J= 3.2 Hz), 6.19 (1H, dd, J= 6.6 Hz, 16.2 Hz), 6.30 (1H, d, J= 16.2 Hz), 6.72-6.81 (1H, m), 6.90-6.99 (3H, m), 7.04 (1H, d, J= 8.0 Hz), 7.21 (1H, t, J= 8.0 Hz), 7.37-7.48 (2H, m), 8.23 (1H, s), 9.28 (1H, s).

Example E-27



Production of N-(2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of tert-butyl (2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (120 mg) and 3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}aniline (109 mg) was dissolved in isopropyl alcohol (5 mL), and stirred at 70°C for 22 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was

washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=67:33→10:90) to give the title compound (186 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.08 (6H, d, J= 6.6 Hz), 1.46 (9H, s), 2.24 (3H, s), 2.35-2.55 (1H, m), 3.42-3.58 (2H, m), 4.40-4.52 (2H, m), 4.95-5.08 (1H, m), 6.18 (1H, dd, J= 6.6 Hz, 16.2 Hz), 6.29 (1H, d, J= 16.2 Hz), 6.58 (1H, d, J= 3.0 Hz), 6.73-6.81 (1H, m), 6.90-6.98 (2H, m), 7.03 (1H, d, J= 8.0 Hz), 7.16 (1H, d, J= 3.0 Hz), 7.20 (1H, t, J= 8.0 Hz), 7.58-7.70 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

tert-Butyl (2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate (180 mg) was dissolved in ethanol (1 mL), 6N hydrochloric acid (0.3 mL) was added thereto, and the mixture was stirred at 50°C for 12 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ethanol, and the mixture was concentrated again under reduced pressure. The precipitate was collected by filtration to give the title compound (158 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 1.05 (6H, d, J= 6.8 Hz), 2.22 (3H, s), 2.37-2.54 (1H, m), 3.18-3.32 (2H, m), 5.00 (2H, t, J= 6.1 Hz), 6.22-6.41 (2H, m), 6.67-6.79 (2H, m), 6.92-7.04 (2H, m), 7.16 (1H, d, J= 7.9 Hz), 7.31 (1H, t, J= 7.9 Hz), 7.39 (1H, dd, J= 2.0 Hz, 8.6 Hz), 7.49 (1H, d, J= 2.0 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.31 (3H br s), 8.67 (1H, s), 9.87 (1H, br s).

(iii) Production of N-(2-{4-[(3-methyl-4-{3-[(1E)-3-

methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

A mixture of 5-(2-aminoethyl)-N-(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (74.8 mg) and methylsulfonylacetic acid (31.1 mg) was dissolved in tetrahydrofuran (0.4 mL)/N,N-dimethylformamide (0.4 mL), 1-hydroxybenzotriazole (32.5 mg), triethylamine (0.2 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (45.0 mg) were added successively thereto, and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=20:80→0:100→ethyl acetate:methanol=90:10) to give N-(2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide. The compound was dissolved in ethyl acetate and treated with 4N hydrogen chloride/ethyl acetate solution, and the precipitate was collected by filtration to give the title compound (32.5 mg) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 1.05 (6H, d, J= 6.8 Hz), 2.22 (3H, s), 2.36-2.55 (1H, m), 3.06 (3H, s), 3.47-3.62 (2H, m), 4.06 (2H, s), 4.69 (2H, t, J= 6.4 Hz), 6.20-6.42 (2H, m), 6.64 (1H, d, J= 3.0 Hz), 6.69-6.78 (1H, m), 6.93-7.03 (2H, m), 7.16 (1H, d, J= 8.0 Hz), 7.31 (1H, t, J= 8.0 Hz), 7.44 (1H, dd, J= 2.5 Hz, 8.6 Hz), 7.53 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.79 (1H, t, J= 5.6 Hz), 9.85 (1H, s).

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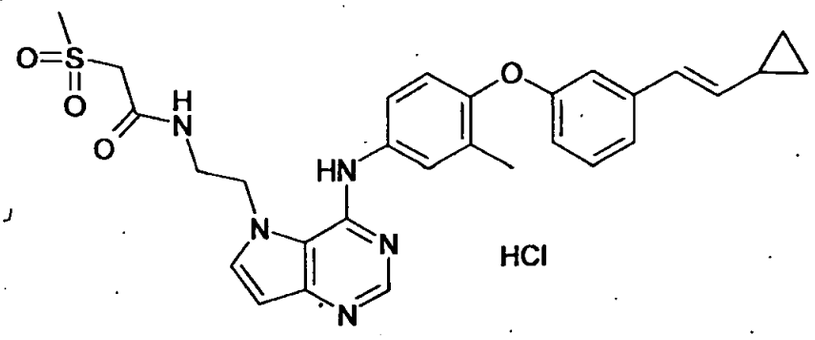
Example E-28



Production of N-(2-{4-[(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of 1-{3-[2-cyclopropylvinyl]phenoxy}-2-methyl-4-nitrobenzene

Using (cyclopropylmethyl)triphenylphosphonium bromide (1.86 g), tetrahydrofuran (30 mL), 1.6M n-butyllithium/hexane solution (3.5 mL) and 3-(2-methyl-4-nitrophenoxy)benzaldehyde (1.00 g) and in the same manner as in Example E-26(ii), the title compound (1.15 g, E/Z = about 1/2) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.43-0.56 (2H, m), 0.76-0.89 (2H, m), 1.50-1.63 (0.33H, m), 1.75-1.91 (0.67H, m), 2.40 (1H, s), 2.41 (2H, s), 5.10 (0.67H, dd, J= 10 Hz, 11.5 Hz), 5.72 (0.33H, dd, J= 8.9 Hz, 15.7 Hz), 6.30 (0.67H, d, J= 11.5 Hz), 6.43 (0.33H, d, J= 15.7 Hz), 6.76 (0.33H, d, J= 9.0 Hz), 6.80 (0.67H, d, J= 9.0 Hz), 6.79-6.84 (0.33H, m), 6.84-6.90 (0.67H, m), 6.96 (0.33H, t, J= 1.9 Hz), 7.09 (0.67H, t, J= 1.9 Hz), 7.13 (0.33H, d, J= 8.0 Hz), 7.27 (0.67H, d, J= 8.0 Hz), 7.30 (0.33H, t, J= 8.0 Hz), 7.36 (0.67H, t, J= 8.0 Hz), 7.93-8.02 (1H, m), 8.09 (1H, m).

(ii) Production of 1-{3-[(E)-2-cyclopropylvinyl]phenoxy}-2-methyl-4-nitrobenzene

Using 1-{3-[2-cyclopropylvinyl]phenoxy}-2-methyl-4-nitrobenzene (1.14 g), tetrahydrofuran (25 mL), diphenyl

disulfide (172 mg) and 2,2'-azobis(butyronitrile) (134 mg) and in the same manner as in Example E-26(iv), the title compound (734 mg) was obtained as an orange oil.
^{1}H-NMR ($CDCl_3$) δ: 0.47-0.55 (2H, m), 0.79-0.89 (2H, m), 1.50-1.63 (1H, m), 2.41 (3H, s), 5.73 (1H, dd, J= 9.0 Hz, 15.7 Hz), 6.44 (1H, d, J= 15.7 Hz), 6.77 (1H, d, J= 9.0 Hz), 6.80-6.85 (1H, m), 6.97 (1H, t, J= 2.0 Hz), 7.14 (1H, d, J= 7.7 Hz), 7.30 (1H, t, J= 7.7 Hz), 7.98 (1H, dd, J= 2.2 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.2 Hz).

(iii) Production of 4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylaniline

Using 1-{3-[(E)-2-cyclopropylvinyl]phenoxy}-2-methyl-4-nitrobenzene (729 mg), reduced iron (712 mg), calcium chloride (156 mg) and ethanol (18 mL)/water (2 mL) and in the same manner as in Example E-18(v), the title compound (352 mg) was obtained as a brown oil.
^{1}H-NMR ($CDCl_3$) δ: 0.44-0.53 (2H, m), 0.75-0.85 (2H, m), 1.44-1.63 (1H, m), 2.10 (3H, s), 3.54 (2H, br s), 5.67 (1H, dd, J= 9.0 Hz, 15.7 Hz), 6.39 (1H, d, J= 15.7 Hz), 6.51 (1H, dd, J= 2.7 Hz, 8.7 Hz), 6.59 (1H, d, J= 2.7 Hz), 6.61-6.67 (1H, m), 6.75-6.82 (2H, m), 6.92 (1H, d, J= 7.8 Hz), 7.14 (1H, t, J= 7.8 Hz).

(iv) Production of tert-butyl (2-{4-[(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (352 mg), 4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylaniline (347 mg) and isopropyl alcohol (15 mL) and in the same manner as in Example E-27(i), the title compound (540 mg) was obtained as a white solid.
^{1}H-NMR ($CDCl_3$) δ: 0.47-0.55 (2H, m), 0.75-0.87 (2H, m), 1.46 (9H, s), 1.50-1.61 (1H, m), 2.23 (3H, s), 3.43-3.56 (2H, m), 4.39-4.54 (2H, m), 4.98 (1H, t, J= 5.9 Hz), 5.71 (1H, dd, J= 9.0 Hz, 15.7 Hz), 6.41 (1H, d, J= 15.7

Hz), 6.59 (1H, d, J= 3.2 Hz), 6.75 (1H, dd, J= 1.6 Hz, 8.2 Hz), 6.87-7.01 (3H, m), 7.12-7.23 (2H, m), 7.57-7.71 (2H, m), 8.31 (1H, br s), 8.50 (1H, s).

(v) Production of 5-(2-aminoethyl)-N-(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl (2-{4-[(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate (536 mg), 6N hydrochloric acid (1 mL) and ethanol (4 mL) and in the same manner as in Example E-27(ii), the title compound (399 mg) was obtained as a yellow solid.

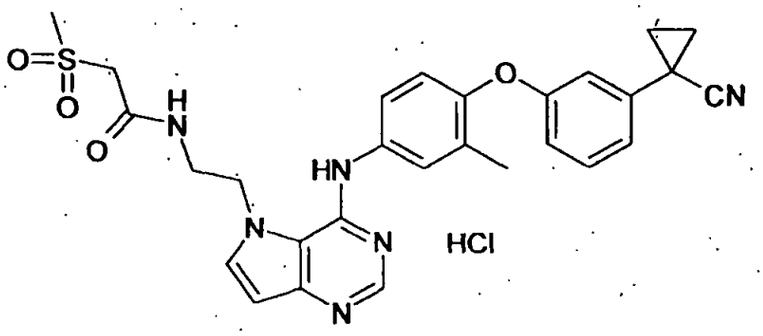
^{1}H-NMR (DMSO-d_6) δ: 0.47-0.55 (2H, m), 0.74-0.84 (2H, m), 1.49-1.64 (1H, m), 2.21 (3H, s), 3.21-3.34 (2H. m), 5.02 (2H, t, J= 6.2 Hz), 5.85 (1H, dd, J= 9.4 Hz, 15.7 Hz), 6.44 (1H, d, J= 15.7 Hz), 6.66-6.74 (2H, m), 6.90-6.99 (2H, m), 7.09 (1H, d, J= 7.8 Hz), 7.27 (1H, t, J= 7.8 Hz), 7.38 (1H, dd, J= 2.6 Hz, 8.7 Hz), 7.48 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.3 Hz), 8.37 (3H, br s), 8.66 (1H, s), 9.93 (1H, br s).

(vi) Production of N-(2-{4-[(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide hydrochloride

Using 5-(2-aminoethyl)-N-(4-{3-[(E)-2-cyclopropylvinyl]phenoxy}-3-methylphenyl)-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (149 mg), methylsulfonylacetic acid (85.1 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (118 mg), triethylamine (0.4 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (178 mg) and 4N hydrogen chloride/ethyl acetate solution and in the same manner as in Example E-27(iii), the title compound (123 mg) was obtained as yellow crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.47-0.56 (2H, m), 0.74-0.86 (2H, m), 1.47-1.66 (1H, m), 2.22 (3H, s), 3.06 (3H, m), 3.49-3.63 (2H, m), 4.06 (2H, s), 4.69 (2H, t, J= 6.2 Hz), 5.86 (1H, dd, J= 9.2 Hz, 15.8 Hz), 6.44 (1H, d, J= 15.8 Hz), 6.64 (1H, d, J= 3.0 Hz), 6.70 (1H, dd, J= 1.8 Hz, 8.0 Hz), 6.90-7.00 (2H, m), 7.10 (1H, d, J= 8.0 Hz), 7.28 (1H, t, J= 8.0 Hz), 7.43 (1H, dd, J= 2.5 Hz, 8.6 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.66 (1H, s), 8.79 (1H, t, J= 5.7 Hz), 9.85 (1H, br s).

Example E-29



Production of N-{2-[4-({4-[3-(1-cyanocyclopropyl)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of tert-butyl {2-[4-({4-[3-(1-cyanocyclopropyl)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (350 mg), 1-[3-(4-amino-2-methylphenoxy)phenyl]cyclopropanecarbonitrile (351 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example E-27(i), the title compound (590 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.43 (2H, m), 1.47 (9H, s), 1.66-1.75 (2H, m), 2.21 (3H, s), 3.43-3.57 (2H, m), 4.41-4.53 (2H, m), 5.01 (1H, t, J= 5.8 Hz), 6.59 (1H, d, J= 3.2 Hz), 6.76-6.83 (1H, m), 6.86-6.95 (2H, m), 6.98-7.05 (1H, m), 7.16 (1H, d, J= 3.2 Hz), 7.24 (1H, t, J= 7.9

Hz), 7.58-7.76 (2H, m), 8.35 (1H, br s), 8.50 (1H, s).

(ii) Production of 1-[3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarbonitrile dihydrochloride

Using tert-butyl {2-[4-({4-[3-(1-cyanocyclopropyl)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (586 mg), 6N hydrochloric acid (1 mL) and ethanol (6 mL) and in the same manner as in Example E-27(ii), the title compound (478 mg) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.47-1.58 (2H, m), 1.71-1.82 (2H, m), 2.21 (3H, s), 3.19-3.49 (2H, m), 4.98 (2H, t, J= 6.1 Hz), 6.71 (1H, d, J= 3.0 Hz), 6.80 (1H, dd, J= 2.3 Hz, 7.7 Hz), 6.98 (1H, t, J= 2.3 Hz), 7.01 (1H, d, J= 8.7 Hz), 7.04-7.09 (1H, m), 7.39 (1H, t, J= 7.7 Hz), 7.42 (1H, dd, J= 2.3 Hz, 8.7 Hz), 7.51 (1H, d, J= 2.3 Hz), 8.01 (1H, d, J= 3.0 Hz), 8.26 (3H, br s), 8.66 (1H, s), 9.81 (1H, br s).

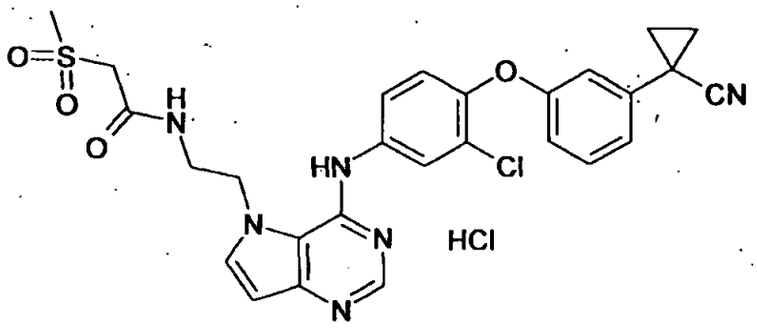
(iii) Production of N-{2-[4-({4-[3-(1-cyanocyclopropyl)phenoxy]-3-methylphenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

Using 1-[3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-methylphenoxy)phenyl]cyclopropanecarbonitrile dihydrochloride (150 mg), methylsulfonylacetic acid (65.2 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (82.1 mg), triethylamine (0.4 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (117 mg) and 4N hydrogen chloride/ethyl acetate solution and in the same manner as in Example E-27(iii), the title compound (133 mg) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 1.49-1.57 (2H, m), 1.73-1.81 (2H, m),

2.21 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.06 (2H, s), 4.70 (2H, t, J= 6.2 Hz), 6.63 (1H, d, J= 3.0 Hz), 6.79 (1H, dd, J= 2.5 Hz, 8.0 Hz), 6.98 (1H, t, J= 2.5 Hz), 7.01 (1H, d, J= 8.0 Hz), 7.03-7.09 (1H, m), 7.38 (1H, t, J= 8.0 Hz), 7.46 (1H, dd, J= 2.6 Hz, 8.7 Hz), 7.54 (1H, d, J= 2.6 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.66 (1H, s), 8.81 (1H, t, J= 5.5 Hz), 9.87 (1H, s).

Example E-30



Production of N-{2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

(i) Production of 1-[3-(2-chloro-4-nitrophenoxy)phenyl]cyclopropanecarbonitrile

Using 3-chloro-4-fluoronitrobenzene (362 mg), 1-(3-hydroxyphenyl)cyclopropanecarbonitrile (350 mg), potassium carbonate (493 mg) and N,N-dimethylformamide (7 mL) and in the same manner as in Example E-18(iv), the title compound (650 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.39-1.48 (2H, m), 1.74-1.84 (2H, m), 6.90 (1H, d, J= 9 Hz), 6.95-7.01 (1H, m), 7.04 (1H, t, J= 2.0 Hz), 7.20 (1H, d, J= 8.0 Hz), 7.42 (1H, t, J= 8.0 Hz), 8.08 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.40 (1H, d, J= 2.6 Hz).

(ii) Production of 1-[3-(4-amino-2-chlorophenoxy)phenyl]cyclopropanecarbonitrile

Using 1-[3-(2-chloro-4-

nitrophenoxy)phenyl]cyclopropanecarbonitrile (643 mg), reduced iron (570 mg), calcium chloride (113 mg) and ethanol (18 mL)/water (2 mL) and in the same manner as in Example E-18(v), the title compound (508 mg) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.34-1.41 (2H, m), 1.66-1.74 (2H, m), 3.68 (2H, br s), 6.57 (1H, dd, J= 2.8 Hz, 8.5 Hz), 6.68-6.74 (1H, m), 6.78 (1H, d, J= 2.8 Hz), 6.80 (1H, t, J= 2.1 Hz), 6.88 (1H, d, J= 8.5 Hz), 6.95-7.01 (1H, m), 7.23 (1H, t, J= 8.0 Hz).

(iii) Production of tert-butyl {2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (350 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]cyclopropanecarbonitrile (349 mg) and isopropyl alcohol (8 mL) and in the same manner as in Example E-27(i), the title compound (632 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 1.36-1.45 (2H, m), 1.50 (9H, s), 1.66-1.77 (2H, m), 3.43-3.57 (2H, m), 4.40-4.55 (2H, m), 5.07 (1H, t, J= 5.5 Hz), 6.60 (1H, d, J= 3.0 Hz), 6.84 (1H, dd, J= 2.2 Hz, 8.0 Hz), 6.91 (1H, t, J= 2.2 Hz), 7.03 (1H, d, J= 9.1 Hz), 7.05-7.11 (1H, m), 7.18 (1H, d, J= 3.0 Hz), 7.28 (1H, t, J= 8.0 Hz), 7.87 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.02 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.58 (1H, s).

(iv) Production of 1-[3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)phenyl]cyclopropanecarbonitrile dihydrochloride

tert-Butyl {2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (627 mg) was dissolved in a mixed solvent of ethanol (7 mL)/tetrahydrofuran (1

mL), 6N hydrochloric acid (1 mL) was added thereto, and the mixture was stirred at 50°C for 14 hr. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in concentrated hydrochloric acid (2 mL), and the mixture was stirred at room temperature for 10 min. Ethanol was added to the reaction mixture and the resulting precipitate was collected by filtration to give the title compound (433 mg) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 1.48-1.60 (2H, m), 1.72-1.84 (2H, m), 3.21-3.37 (2H, m), 5.01 (2H, t, J= 6.4 Hz), 6.74 (1H, d, J= 3.0 Hz), 6.85 (1H, dd, J= 8.0 Hz, 2.2 Hz), 7.03 (1H, t, J= 2.2 Hz), 7.08-7.15 (1H, m), 7.23 (1H, d, J= 8.9 Hz), 7.42 (1H, t, J= 8.0 Hz), 7.61 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.90 (1H, d, J= 2.5 Hz), 8.05 (1H, d, J= 3.0 Hz), 8.29 (3H, br s), 8.71 (1H, s), 10.05 (1H, br s).

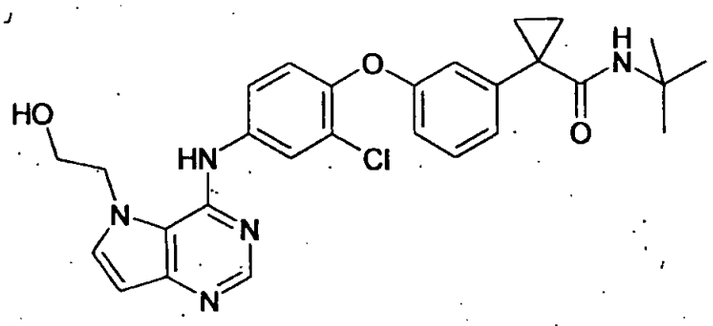
(v) Production of N-{2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide hydrochloride

Using 1-[3-(4-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-2-chlorophenoxy)phenyl]cyclopropanecarbonitrile dihydrochloride (149 mg), methylsulfonylacetic acid (60.0 mg), tetrahydrofuran (0.8 mL)/N,N-dimethylformamide (0.8 mL), 1-hydroxybenzotriazole (77.4 mg), triethylamine (0.4 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (110 mg) and 4N hydrogen chloride/ethyl acetate solution and in the same manner as in Example E-27(iii), the title compound (131 mg) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6) δ: 1.50-1.60 (2H, m), 1.74-1.83 (2H, m), 3.06 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 4.06 (2H, s), 4.70 (2H, t, J= 6.0 Hz), 6.66 (1H, d, J= 3.0 Hz), 6.85 (1H, dd, J= 2.2 Hz, 8.0 Hz), 7.02 (1H, t, J= 2.2 Hz),

7.08-7.14 (1H, m), 7.24 (1H, d, J= 9.0 Hz), 7.41 (1H, t, J= 8.0 Hz), 7.64 (1H, dd, J= 2.5 Hz, 9.0 Hz), 7.92 (1H, d, J= 2.5 Hz), 7.93 (1H, d, J= 3.0 Hz), 8.71 (1H, s), 8.77 (1H, t, J= 5.8 Hz), 9.91 (1H, br s).

Example E-31



Production of N-(tert-butyl)-1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide

(i) Production of N-(tert-butyl)-1-(3-methoxyphenyl)cyclopropanecarboxamide

1-(3-Methoxyphenyl)cyclopropanecarboxylic acid (400 mg) was dissolved in tetrahydrofuran (6 mL), a catalytic amount of N,N-dimethylformamide and thionyl chloride (0.4 mL) were added thereto, and the mixture was stirred at room temperature for 6 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (4 mL). The solution was added dropwise to a mixture cooled to 0°C of tert-butylamine (0.25 mL), triethylamine (1 mL) and tetrahydrofuran (3 mL), and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=95:5→67:33) to give the title compound (477 mg) as a pale-yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.97 (2H, q, J= 3.7 Hz), 1.22 (9H, s), 1.52 (2H, q, J= 3.7 Hz), 3.82 (3H, s), 5.22 (1H, br s), 6.81-6.87 (1H, m), 6.90-6.94 (1H, m), 6.95-7.01 (1H, m), 7.27 (1H, t, J= 7.9 Hz).

(ii) Production of N-(tert-butyl)-1-(3-hydroxyphenyl)cyclopropanecarboxamide

Using N-(tert-butyl)-1-(3-methoxyphenyl)cyclopropanecarboxamide (470 mg), benzotrifluoride (10 mL) and 1N boron tribromide/dichloromethane solution (4 mL) and in the same manner as in Example E-18(iii), the title compound (245 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.95-1.04 (2H, m), 1.22 (9H, s), 1.50-1.58 (2H, m), 5.36 (1H, br s), 6.13 (1H, br s), 6.76-6.88 (2H, m), 6.90-6.98 (1H, m), 7.19-7.29 (1H, m).

(iii) Production of N-(tert-butyl)-1-[3-(2-chloro-4-nitrophenoxy)phenyl]cyclopropanecarboxamide

Using N-(tert-butyl)-1-(3-hydroxyphenyl)cyclopropanecarboxamide (242 mg), 3-chloro-4-fluoronitrobenzene (237 mg), potassium carbonate (223 mg) and N,N-dimethylformamide (5 mL) and in the same manner as in Example E-18(iv), the title compound (397 mg) was obtained as white crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.96-1.01 (2H, m), 1.23 (9H, s), 1.52-1.59 (2H, m), 5.08 (1H, br s), 6.88 (1H, d, J= 9.1 Hz), 6.98-7.04 (1H, m), 7.08-7.13 (1H, m), 7.27-7.32 (1H, m), 7.43 (1H, t, J= 8.0 Hz), 8.07 (1H, dd, J= 2.8 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.8 Hz).

(iv) Production of 1-[3-(4-amino-2-chlorophenoxy)phenyl]-N-(tert-butyl)cyclopropanecarboxamide

N-(tert-butyl)-1-[3-(2-chloro-4-nitrophenoxy)phenyl]cyclopropanecarboxamide (392 mg) was dissolved in a mixed solvent of methanol (7.5 mL)/ethyl acetate (7.5 mL), 5% platinum-activated carbon (44.4 mg)

was added thereto and the mixture was stirred under a hydrogen atmosphere at room temperature for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (hexane:ethyl acetate=95:5→50:50) to give the title compound (324 mg) as a colorless oil.

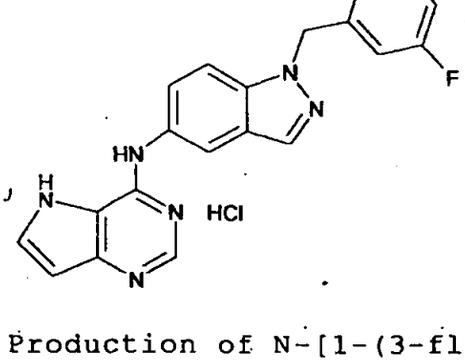
^{1}H-NMR ($CDCl_3$) δ: 0.91-0.98 (2H, m), 1.21 (9H, s), 1.45-1.52 (2H, m), 3.70 (2H, s), 5.17 (1H, br s), 6.59 (1H, dd, J= 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.81-6.87 (2H, m), 6.91 (1H, d, J= 8.6 Hz), 6.99-7.06 (1H, m), 7.21-7.31 (1H, m).

(v) Production of N-(tert-butyl)-1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (120 mg), 1-[3-(4-amino-2-chlorophenoxy)phenyl]-N-(tert-butyl)cyclopropanecarboxamide (160 mg), isopropyl alcohol (4 mL) and 1N aqueous sodium hydroxide solution (1.5 mL) and in the same manner as in Example E-18(vi), the title compound (155 mg) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.96 (2H, q, J= 3.7 Hz), 1.21 (9H, s), 1.49 (2H, q, J= 3.7 Hz), 4.14-4.22 (2H, m), 4.37-4.46 (2H, m), 5.19 (1H, s), 6.06 (1H, br s), 6.19 (1H, d, J= 3.2 Hz), 6.89-6.98 (2H, m), 7.02 (1H, d, J= 3.2 Hz), 7.04-7.11 (2H, m), 7.31 (1H, t, J= 7.8 Hz), 7.52 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.81 (1H, d, J= 2.5 Hz), 8.29 (1H, s), 9.58 (1H, s).

Example G-1

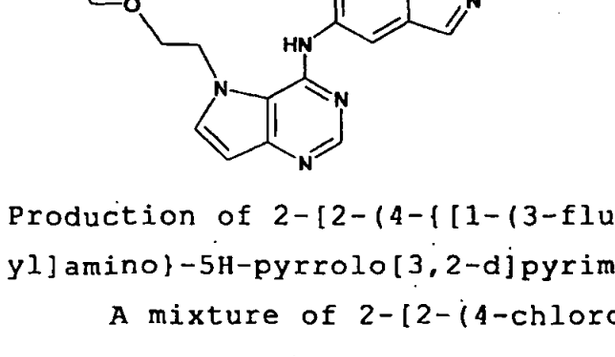


Production of N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine hydrochloride

A solution of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (153 mg) and 1-(3-fluorobenzyl)-1H-indazol-5-amine (362 mg) in N,N-dimethylformamide (2 mL) was stirred at 120°C for 2.5 hr. The reaction mixture was cooled to room temperature, ethyl acetate (30 mL) was added thereto and the mixture was stirred at room temperature for 30 min. The resulting crystals were collected by filtration, washed with ethyl acetate and dried under reduced pressure to give the title compound (361 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 5.70 (2H, s), 6.57 (1H, d, J= 2 Hz), 7.00-7.20 (3H, m), 7.36 (1H, m), 7.70-7.90 (3H, m), 8.17 (1H, s), 8.41 (1H, m), 8.59 (1H, s), 10.97 (1H, br s), 12.58 (1H, br s).

Example G-2



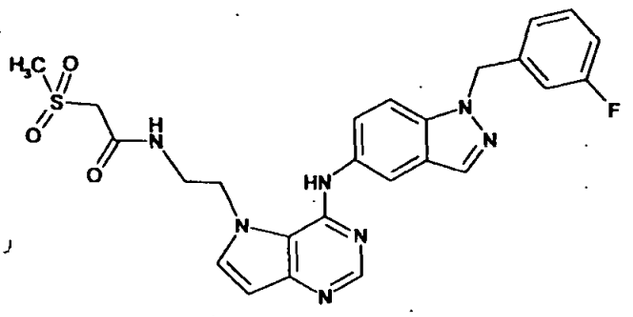
Production of 2-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-

d]pyrimidin-5-yl)ethoxy]ethyl benzoate (150 mg), 1-(3-fluorobenzyl)-1H-indazol-5-amine (156 mg) and 1-methyl-2-pyrrolidone (0.863 mL) was stirred with heating at 140°C for 2 hr. The reaction mixture was diluted with ethyl acetate (80 mL), and the organic layer was washed with aqueous sodium bicarbonate (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=70:30→0:100), and the objective fractions were concentrated under reduced pressure. The obtained residue was dissolved in methanol (1.89 mL), 1N aqueous sodium hydroxide solution (0.433 mL) was added, and the mixture was stirred at room temperature for 2 hr. 1N hydrochloric acid (0.433 mL) was added to the mixture, and the mixture was diluted with ethyl acetate (80 mL), and the organic layer was washed with saturated brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate:methanol=100:0→90:10) and crystallized from isopropyl ether to give the title compound (153 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.50 (4H, br s), 3.84 (2H, t, J= 4 Hz), 4.64 (2H, t, J= 4 Hz), 4.69 (1H, m), 5.69 (2H, s), 6.47 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.36 (1H, m), 7.53 (1H, d, J= 9 Hz), 7.60-7.70 (2H, m), 8.05 (1H, s), 8.09 (1H, s), 8.23 (1H, s), 8.76 (1H, br s).

Example G-3



Production of N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

(i) Production of tert-butyl [2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (0.5 g) and 1-(3-fluorobenzyl)-1H-indazol-5-amine (608 mg) in isopropyl alcohol (5 mL) was stirred at 80°C for 12 hr. Aqueous sodium bicarbonate (30 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (80 mL). The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=7:3→ethyl acetate) to give the title compound (820 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 3.50 (2H, m), 4.46 (2H,m), 5.07 (1H, m), 5.58 (2H, s), 6.57 (1H, d, J= 3 Hz), 6.80-7.00 (3H, m), 7.14 (1H, d, J= 3 Hz), 7.20-7.40 (2H, m), 7.74 (1H, dd, J= 2 Hz, 9 Hz), 7.99 (1H, s), 8.05 (1H, d, J= 1 Hz), 8.45 (1H, s), 8.53 (1H, br s).

(ii) Production of 5-(2-aminoethyl)-N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride

A mixture of tert-butyl [2-(4-{[1-(3-fluorobenzyl)-

1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (780 mg), 2N hydrochloric acid (11.1 mL) and tetrahydrofuran (22.2 mL) was stirred at 60°C for 20 hr. The solvent was evaporated under reduced pressure, ethanol was added to the mixture, and the mixture was further concentrated. The precipitated powder was collected by filtration and washed with isopropyl ether to give the title compound (668 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 3.32 (2H, m), 5.08 (2H, m), 5.74 (2H, s), 6.72 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.38 (1H, m), 7.52 (1H, dd, J= 2 Hz, 9 Hz), 7.80 (1H, d, J= 9 Hz), 7.91 (1H, d, J= 2 Hz), 8.07 (1H, m), 8.20 (1H, s), 8.45 (3H, br s), 8.60 (1H, s).

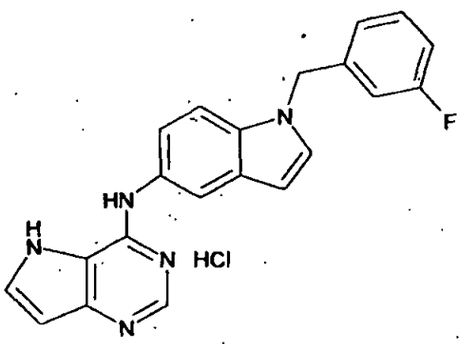
(iii) Production of N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide

A mixture of 5-(2-aminoethyl)-N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (183 mg), methylsulfonylacetic acid (74.2 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=90:10) and crystallized from isopropyl ether to give the title compound (134 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.07 (3H, s), 3.48 (2H, q, J= 6 Hz),

4.04 (2H, s), 4.56 (2H, t, J= 6 Hz), 5.69 (2H, s), 6.45 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.30-7.40 (1H, m), 7.57 (2H, m), 7.68 (1H, d, J= 9 Hz), 7.95 (1H, m), 8.10 (1H, s), 8.21 (1H, s), 8.58 (1H, br s), 8.65 (1H, t, J= 6 Hz).

Example G-4

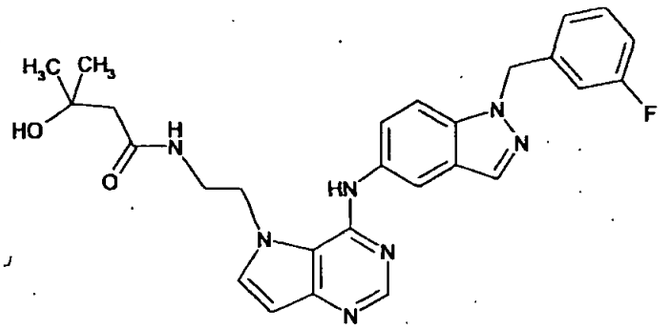


Production of N-[1-(3-fluorobenzyl)-1H-indol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine hydrochloride

A solution of 4-chloro-5H-pyrrolo[3,2-d]pyrimidine (153 mg) and 1-(3-fluorobenzyl)-1H-indol-5-amine (360 mg) in N,N-dimethylformamide (2 mL) was stirred at 120°C for 2 hr. The reaction mixture was cooled to room temperature, ethyl acetate (30 mL) was added thereto, and the mixture was stirred at room temperature for 30 min. The resulting crystals were collected by filtration, washed with ethyl acetate and dried under reduced pressure to give the title compound (377 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 5.46 (2H, s), 6.53 (2H, d, J= 3 Hz), 7.05 (3H, m), 7.36 (1H, m), 7.49 (2H, m), 7.56 (1H, d, J= 3 Hz), 7.79 (1H, br s), 8.16 (1H, br s), 8.51 (1H, s), 10.61 (1H, br s), 12.45 (1H, br s).

Example G-5

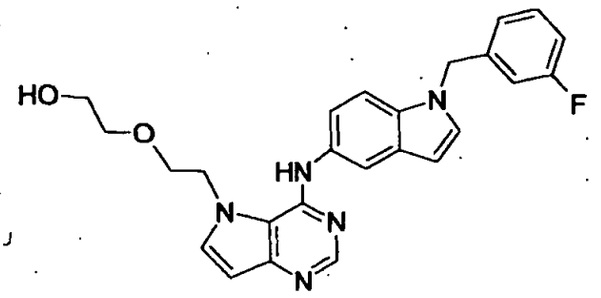


Production of N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide

A mixture of 5-(2-aminoethyl)-N-[1-(3-fluorobenzyl)-1H-indazol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine trihydrochloride (183 mg), 3-hydroxy-3-methylbutanoic acid (0.058 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 4 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) and crystallized from isopropyl ether to give the title compound (100 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.12 (6H, s), 2.20 (2H, s), 3.44 (2H, q, J= 7 Hz), 4.52 (2H, t, J= 7 Hz), 4.69 (1H, s), 5.69 (2H, s), 6.44 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.30-7.40 (1H, m), 7.50-7.70 (3H, m), 8.00 (1H, d, J= 2 Hz), 8.09 (1H, s), 8.20 (1H, s), 8.23 (1H, t, J= 7 Hz), 8.76 (1H, br s).

Example G-6



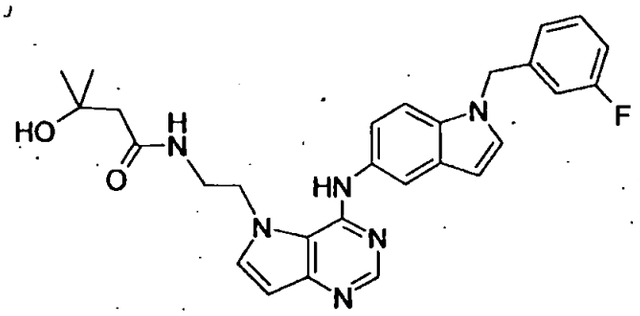
Production of 2-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol

A mixture of 2-[2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethyl benzoate (150 mg), 1-(3-fluorobenzyl)-1H-indol-5-amine (155 mg) and 1-methyl-2-pyrrolidone (0.863 mL) was stirred with heating at 140°C for 2 hr. The reaction mixture was diluted with ethyl acetate (80 mL) and washed with aqueous sodium bicarbonate (30 mL). The organic layer was separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=70:30→0:100→ethyl acetate:methanol=95:5), and the objective fractions were concentrated under reduced pressure. The obtained residue was dissolved in methanol (1.89 mL), 1N aqueous sodium hydroxide solution (0.433 mL) was added thereto, and the mixture was stirred at room temperature for 2 hr. 1N hydrochloric acid (0.433 mL) was added to the mixture, and the mixture was diluted with ethyl acetate (80 mL). The organic layer was washed with saturated brine (30 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (ethyl acetate:methanol=100:0→90:10) and crystallized from isopropyl ether/ethyl acetate to give the title compound (107 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.49 (4H, br s), 3.83 (2H, t, J= 4 Hz), 4.61 (2H, t, J= 4 Hz), 4.67 (1H, t, J= 4 Hz), 5.45

(2H, s), 6.44 (1H, dd, J= 1.5 Hz, 3 Hz), 6.47 (1H, d, J= 3 Hz), 6.90-7.10 (3H, m), 7.25 (1H, d, J= 9 Hz), 7.3-7.5 (2H, m), 7.51 (1H, d, J= 3 Hz), 7.59 (1H, d, J= 3 Hz), 7.81 (1H, s), 8.17 (1H, s), 8.58 (1H, br s).

Example G-7



Production of N-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide

(i) Production of tert-butyl [2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A solution of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (0.5 g) and 1-(3-fluorobenzyl)-1H-indol-5-amine (606 mg) in isopropyl alcohol (5 mL) was stirred at 80°C for 12 hr. Aqueous sodium bicarbonate (30 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (80 mL). The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, hexane:ethyl acetate=7:3→ethyl acetate→ethyl acetate:methanol=95:5) to give the title compound (840 mg) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 3.45 (2H, m), 4.38 (2H,t, J= 7 Hz), 5.17 (1H, m), 5.29 (2H, s), 6.51 (1H, dd, J= 1 Hz, 3 Hz), 6.53 (1H, d, J= 3 Hz), 6.78 (1H, d, J= 9 Hz), 6.80-7.00 (2H, m), 7.10 (2H, t, J= 3 Hz), 7.18-7.30 (2H,

m), 7.47 (1H, d, J= 9 Hz), 7.89 (1H, br s), 8.20 (1H, br s), 8.43 (1H, s).

(ii) Production of 5-(2-aminoethyl)-N-[1-(3-fluorobenzyl)-1H-indol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

A mixture of tert-butyl [2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (830 mg), 2N hydrochloric acid (11.8 mL) and tetrahydrofuran (23.6 mL) was stirred at 60°C for 20 hr. The solvent was evaporated under reduced pressure, ethanol was added to the mixture, and the mixture was further concentrated. The precipitated powder was collected by filtration and washed with isopropyl ether to give the title compound (828 mg) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 3.27 (2H, m), 5.07 (2H, m), 5.43 (2H, s), 6.50-6.70 (2H, m), 6.80-7.30 (4H, m), 7.37 (1H, m), 7.68 (1H, m), 7.86 (1H, s), 8.04 (1H, d, J= 3 Hz), 8.44 (1H, s), 8.50 (3H, br s), 8.55 (1H, s), 10.0I (1H, br s).

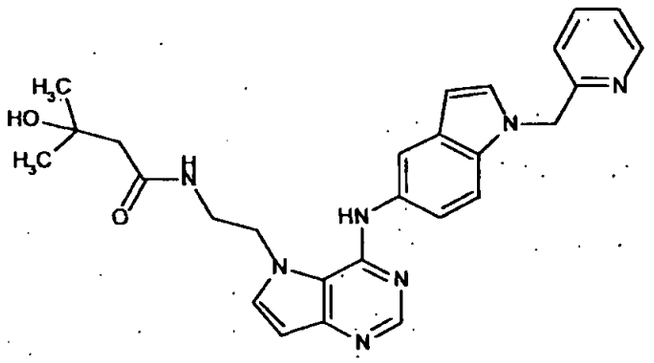
(iii) Production of N-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide

A mixture of 5-(2-aminoethyl)-N-[1-(3-fluorobenzyl)-1H-indol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (183 mg), 3-hydroxy-3-methylbutanoic acid (0.058 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (103 mg), 1-hydroxybenzotriazole (72.5 mg), triethylamine (0.15 mL) and N,N-dimethylformamide (6.9 mL) was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over anhydrous magnesium sulfate. After concentration under reduced

pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, ethyl acetate→ethyl acetate:methanol=85:15) and crystallized from isopropyl ether to give the title compound (43 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.12 (6H, s), 2.20 (2H, s), 3.44 (2H, q, J= 7 Hz), 4.50 (2H, t, J= 7 Hz), 4.70 (1H, br s), 5.46 (2H, s), 6.41 (1H, d, J= 3 Hz), 6.47 (1H, d, J= 3 Hz), 6.9-7.2 (3H, m), 7.20-7.50 (3H, m), 7.52 (2H, t, J= 3 Hz), 7.76 (1H, s), 8.15 (1H, s), 8.19 (1H, t, J= 6 Hz), 8.57 (1H, br s).

Example G-8



Production of 3-hydroxy-3-methyl-N-[2-(4-{[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]butanamide

(i) Production of 5-nitro-1-(pyridin-2-ylmethyl)-1H-indole

To a solution of 5-nitroindole (1.62 g) and 2-(chloromethyl)pyridine hydrochloride (1.80 g) in N,N-dimethylformamide (20 mL) was added potassium carbonate (3.46 g) under ice-cooling, and the mixture was stirred at room temperature for 16 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl

acetate/diisopropyl ether to give the title compound (2.05 g) as yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 5.49 (2H, s), 6.75-6.80 (2H, m), 7.15-7.25 (1H, m), 7.32 (1H, d, J= 9.0 Hz), 7.36 (1H, d, J= 3.3 Hz), 7.58 (1H, dt, J= 2.1 Hz, 7.8 Hz), 8.07 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.55-8.65 (2H, m).

(ii) Production of 1-(pyridin-2-ylmethyl)-1H-indol-5-amine

To a solution of 5-nitro-1-(pyridin-2-ylmethyl)-1H-indole (507 mg) in ethyl acetate (10 mL)/methanol (2 mL) was added 5% platinum-activated carbon (84.5 mg) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 6 hr. The platinum-activated carbon was filtered off, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=70:30→100:0) and further recrystallized from ethyl acetate/hexane to give the title compound (357 mg) as a white-peach powder.

^{1}H-NMR ($CDCl_3$) δ: 3.48 (2H, br s), 5.38 (2H, s), 6.39 (1H, d, J= 3.0 Hz), 6.55-6.70 (2H, m), 6.94 (1H, s), 7.03 (1H, d, J= 8.7 Hz), 7.10-7.20 (2H, m), 7.49 (1H, t, J= 7.8 Hz), 8.57 (1H, d, J= 4.2 Hz).

(iii) Production of tert-butyl [2-(4-{[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate

A mixture of tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (297 mg), 1-(pyridin-2-ylmethyl)-1H-indol-5-amine (246 mg) and isopropyl alcohol (5.0 mL) was stirred at 80°C for 16 hr. Under ice-cooling, aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→90:10) to give the title compound (498 mg) as a pale-purple powder.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 3.45-3.55 (2H, m), 4.35-4.45 (2H, m), 4.9-5.0 (1H, m), 5.45 (2H, s), 6.53 (1H, d, J = 3.0 Hz), 6.55 (1H, d, J = 3.0 Hz), 6.71 (1H, d, J = 8.1 Hz), 7.10-7.30 (4H, m), 7.40-7.50 (1H, m), 7.52 (1H, dt, J = 1.8, 7.8 Hz), 7.90 (1H, s), 8.17 (1H, br s), 8.44 (1H, s), 8.58 (1H, d, J = 4.2 Hz).

(iv) Production of 5-(2-aminoethyl)-N-[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine tetrahydrochloride

A mixture of tert-butyl [2-(4-{[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (439 mg) and 10% (W/W) hydrochloric acid/methanol (5 mL) was stirred at 65°C for 18 hr. The reaction mixture was concentrated under reduced pressure, and the precipitate was collected by filtration and washed with diethyl ether to give the title compound (422 mg) as pale-green crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.2-3.4 (2H, m), 4.90-5.10 (2H, m), 5.63 (2H, s), 6.57 (1H, d, J= 3.3 Hz), 6.69 (1H, d, J= 3.3 Hz), 7.08 (1H, d, J= 7.2 Hz), 7.20 (1H, d, J= 8.7 Hz), 7.35-7.45 (1H, m), 7.52 (1H, d, J= 8.7 Hz), 7.61 (1H, d, J= 3.3 Hz), 7.67 (1H, s), 7.85-7.95 (1H, m), 8.01 (1H, d, J= 2.7 Hz), 8.25-8.4 (3H, m), 8.56 (1H, s), 8.61 (1H, d, J= 5.1 Hz), 9.97 (1H, s).

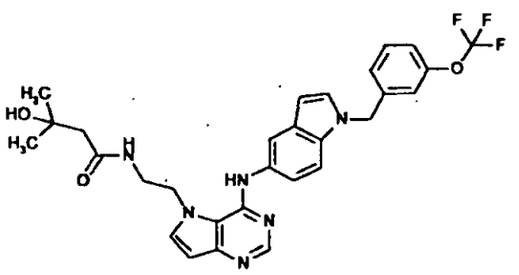
(v) Production of 3-hydroxy-3-methyl-N-[2-(4-{[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]butanamide

To a solution of 5-(2-aminoethyl)-N-[1-(pyridin-2-ylmethyl)-1H-indol-5-yl]-5H-pyrrolo[3,2-d]pyrimidin-4-amine tetrahydrochloride (200 mg), 3-hydroxy-3-

methylbutanoic acid (67 mg) and 1-hydroxybenzotriazole (85 mg) in N,N-dimethylformamide (5.0 mL) were added triethylamine (0.52 mL) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (120 mg) under ice-cooling, and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→70:30) and further recrystallized from ethyl acetate/diisopropyl ether to give the title compound (85.3 mg) as colorless crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.26 (6H, s), 2.37 (2H, s), 3.55-3.7 (2H, m), 4.35-4.45 (2H, m), 5.45 (2H, s), 6.55 (2H, dd, J= 3.3 Hz, 7.8 Hz), 6.73 (1H, d, J= 7.8 Hz), 6.75-6.85 (1H, m), 7.1-7.25 (3H, m), 7.39 (1H, dd, J= 1.8 Hz, 8.7 Hz), 7.53 (1H, dt, J= 1.8 Hz, 7.8 Hz), 7.87 (1H, d, J= 1.5 Hz), 8.22 (1H, s), 8.43 (1H, s), 8.58 (1H, d, J= 4.8 Hz).

Example G-9



Production of 3-hydroxy-3-methyl-N-{2-[4-({1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}butanamide

(i) Production of 5-nitro-1-[3-(trifluoromethoxy)benzyl]-1H-indole

Using 5-nitroindole (538 mg), 1-(bromomethyl)-3-

(trifluoromethoxy)benzene (0.96 g), potassium carbonate (551 mg) and N,N-dimethylformamide (8.0 mL) and in the same manner as in Example G-8(i), the title compound (0.95 g) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 5.39 (2H, s), 6.76 (1H, d, J= 3.3 Hz), 6.90-7.00 (2H, m), 7.15 (1H, d, J= 8.1 Hz), 7.20-7.30 (2H, m), 7.35 (1H, t, J= 8.1 Hz), 8.09 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.62 (1H, d, J= 2.4 Hz).

(ii) Production of 1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-amine

Using 5-nitro-1-[3-(trifluoromethoxy)benzyl]-1H-indole (504 mg), 5% platinum-activated carbon (84 mg) and ethyl acetate (15 mL) and in the same manner as in Example G-8(ii), the title compound (466 mg) was obtained as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 3.50 (2H, br s), 5.26 (2H, s), 6.37 (1H, d, J= 3.0 Hz), 6.62 (1H, dd, J= 2.4 Hz, 8.7 Hz), 6.90-7.10 (5H, m), 7.08 (1H, d, J= 8.7 Hz), 7.25-7.35 (1H, m).

(iii) Production of tert-butyl {2-[4-({1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (405 mg), 1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-amine (459 mg) and isopropyl alcohol (8.0 mL) and in the same manner as in Example G-8(iii), the title compound (692 mg) was obtained as a white amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 3.45-3.55 (2H, m), 4.35-4.45 (2H, m), 4.93 (1H, br s), 5.33 (2H, s), 6.52 (1H, d, J = 3.3 Hz), 6.55 (1H, d, J = 3.0 Hz), 6.95-7.05 (2H, m), 7.10-7.25 (4H, m), 7.30 (1H, t, J = 8.2 Hz), 7.45-7.55 (1H, m), 7.90 (1H, s), 8.18 (1H, br s), 8.44 (1H, s).

(iv) Production of 5-(2-aminoethyl)-N-{1-[3-

(trifluoromethoxy)benzyl]-1H-indol-5-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride

Using tert-butyl {2-[4-({1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}carbamate (675 mg), 10% (W/W) hydrochloric acid/methanol (8.0 mL) and methanol (6.0 mL) and in the same manner as in Example G-8(iv), the title compound (568 mg) was obtained as an orange powder.

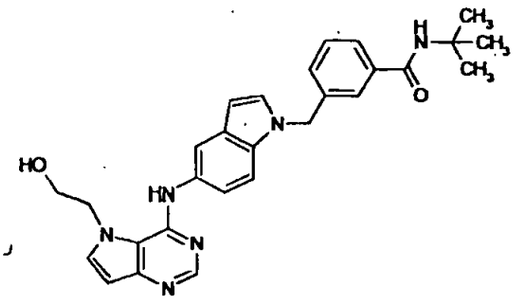
^{1}H-NMR (DMSO-d_6) δ: 3.20-3.35 (2H, m), 4.90-5.10 (2H, m), 5.54 (2H, s), 6.55 (1H, d, J= 3.3 Hz), 6.68 (1H, d, J= 3.0 Hz), 7.15-7.30 (4H, m), 7.46 (1H, t, J= 7.8 Hz), 7.53 (1H, d, J= 8.7 Hz), 7.63 (1H, d, J= 3.3 Hz), 7.67 (1H, s), 8.01 (1H, d, J= 3.0 Hz), 8.25-8.45 (3H, m), 8.55 (1H, s), 9.93 (1H, s).

(v) Production of 3-hydroxy-3-methyl-N-{2-[4-({1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}butanamide

Using 5-(2-aminoethyl)-N-{1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 3-hydroxy-3-methylbutanoic acid (62 mg), 1-hydroxybenzotriazole (76 mg), triethylamine (0.48 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example G-8(v), the title compound (143 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (6H, s), 2.38 (2H, s), 3.55-3.70 (2H, m), 4.35-4.50 (2H, m), 5.32 (2H, s), 6.54 (2H, t, J= 3.6 Hz), 6.80-6.90 (1H, m), 6.95-7.05 (2H, m), 7.10-7.20 (3H, m), 7.20-7.45 (3H, m), 7.88 (1H, s), 8.25 (1H, s), 8.43 (1H, s).

Example G-10



Production of N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide

(i) Production of methyl 3-[(5-nitro-1H-indol-1-yl)methyl]benzoate

Using 5-nitroindole (0.87 g), methyl 3-(bromomethyl)benzoate (1.35 g), potassium carbonate (0.89 g) and N,N-dimethylformamide (10 mL) and in the same manner as in Example G-8(i), the title compound (0.83 g) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s), 5.41 (2H, s), 6.75 (1H, d, J= 3.3 Hz), 7.20-7.35 (3H, m), 7.39 (1H, t, J= 7.8 Hz), 7.88 (1H, s), 7.97 (1H, d, J= 7.8 Hz), 8.07 (1H, dd, J= 2.4 Hz, 9.1 Hz), 8.60 (1H, d, J= 1.8 Hz).

(ii) Production of 3-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid

To a suspension of methyl 3-[(5-nitro-1H-indol-1-yl)methyl]benzoate (0.75 g) in methanol (12 mL) was added 1N aqueous sodium hydroxide solution (12 mL) and the mixture was stirred at room temperature for 1.5 hr. Tetrahydrofuran (12 mL) was added to the mixture and the mixture was stirred at room temperature for 5 hr. Under ice-cooling, 1N hydrochloric acid (12 mL) was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The precipitate was collected by filtration, and washed with ethanol and diisopropyl ether to give the title compound (621 mg) as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 5.55 (2H, s), 6.80 (1H, d, J= 2.4 Hz), 7.15-7.35 (2H, m), 7.67 (1H, d, J= 9.0 Hz), 7.70-7.85 (3H, m), 7.99 (1H, d, J= 7.8 Hz), 8.57 (1H, s).

(iii) Production of N-(tert-butyl)-3-[(5-nitro-1H-indol-1-yl)methyl]benzamide

To a suspension of 3-[(5-nitro-1H-indol-1-yl)methyl]benzoic acid (600 mg) and tert-butylamine (222 mg) in N,N-dimethylformamide (5.0 mL) were added triethylamine (0.45 mL) and diethyl cyanophosphate (0.49 mL) under ice-cooling, and the mixture was stirred at room temperature for 21 hr. tert-Butylamine (0.32 mL) was added to the mixture, and the mixture was stirred at room temperature for 20 hr. Aqueous sodium bicarbonate was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=35:65→70:30) to give the title compound (266 mg) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 5.39 (2H, s), 5.87 (1H, br s), 6.70-6.75 (1H, m), 7.10 (1H, d, J= 7.8 Hz), 7.25-7.30 (2H, m), 7.33 (1H, t, J= 7.8 Hz), 7.55 (1H, d, J= 7.8 Hz), 7.67 (1H, s), 8.06 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.60 (1H, d, J= 2.1 Hz).

(iv) Production of 3-[(5-amino-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide

Using N-(tert-butyl)-3-[(5-nitro-1H-indol-1-yl)methyl]benzamide (263 mg), 5% platinum-activated carbon (44 mg) and ethyl acetate (10 mL) and in the same manner as in Example G-8(ii), the title compound (241 mg) was obtained as a pale-yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 3.50 (2H, br s), 5.28 (2H, s), 5.84 (1H, br s), 6.37 (1H, d, J= 3.0 Hz), 6.62

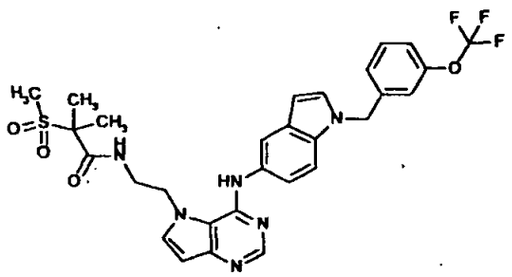
(1H, dd, J= 2.4 Hz, 8.7 Hz), 6.94 (1H, d, J= 2.1 Hz), 7.00-7.15 (3H, m), 7.25-7.35 (1H, m), 7.54 (1H, d, J= 7.5 Hz), 7.60 (1H, s).

(v) Production of N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (105 mg), 3-[(5-amino-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide (123 mg) and isopropyl alcohol (5.0 mL) was stirred at 80°C for 16 hr. Under ice-cooling, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (1.5 mL) and tetrahydrofuran (3.0 mL) and the mixture was stirred at room temperature for 18 hr. The reaction mixture was neutralized with 1N hydrochloric acid, and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/methanol to give the title compound (90 mg) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 4.00-4.10 (2H, m), 4.25-4.35 (2H, m), 5.33 (2H, s), 5.90 (1H, br s), 6.14 (1H, d, J= 3.0 Hz), 6.52 (1H, d, J= 2.7 Hz), 6.87 (1H, d, J= 3.0 Hz), 7.10-7.35 (5H, m), 7.54 (1H, d, J= 7.5 Hz), 7.63 (1H, s), 7.76 (1H, s), 8.19 (1H, s), 9.15 (1H, s).

Example G-11

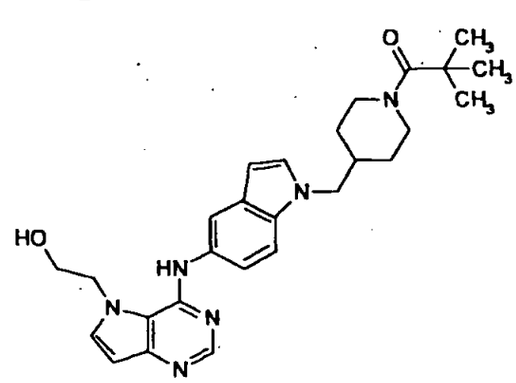


Production of 2-methyl-2-(methylsulfonyl)-N-{2-[4-({1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}propanamide

Using 5-(2-aminoethyl)-N-{1-[3-(trifluoromethoxy)benzyl]-1H-indol-5-yl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine dihydrochloride (200 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (87 mg), 1-hydroxybenzotriazole (76 mg), triethylamine (0.48 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (106 mg) and N,N-dimethylformamide (5.0 mL) and in the same manner as in Example G-8(v), the title compound (100 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.61 (6H, s), 2.84 (3H, s), 3.65-3.75 (2H, m), 4.35-4.45 (2H, m), 5.34 (2H, s), 6.55 (1H, d, J= 3.0 Hz), 6.60 (1H, d, J= 3.0 Hz), 7.00-7.45 (9H, m), 7.86 (1H, s), 7.91 (1H, br s), 8.46 (1H, s).

Example G-12



Production of 2-{4-[(1-{[1-(2,2-dimethylpropanoyl)piperidin-4-yl]methyl}-1H-indol-5-yl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

(i) Production of tert-butyl 4-[(5-nitro-1H-indol-1-yl)methyl]piperidine-1-carboxylate

To a solution of tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (1.29 g) and triethylamine (1.17 mL) in tetrahydrofuran (30 mL) was added dropwise methanesulfonyl chloride (0.56 mL) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. Aqueous sodium bicarbonate was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate. . The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow oil. To a solution of 5-nitroindole (811 mg) in N,N-dimethylformamide (5.0 mL) was added sodium hydride (60% in oil (220 mg)) under ice-cooling, and the mixture was stirred at 0°C for 10 min. Under ice-cooling, to the reaction mixture was added dropwise a solution of the yellow oil obtained above in N,N-dimethylformamide (5.0 mL) and the mixture was stirred at room temperature for 1 hr, and at 60°C for 18 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=30:70→50:50) to give the title compound (1.79 g) as a yellow amorphous form.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.45 (9H, s), 1.50-1.60 (2H, m), 1.90-2.05 (1H, m), 2.55-2.70 (2H, m), 4.00-4.20 (4H, m), 6.69 (1H, d, J= 3.0 Hz), 7.20 (1H, d, J= 3.0 Hz), 7.34 (1H, d, J= 9.0 Hz), 8.12 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.60 (1H, d, J= 2.1 Hz).

(ii) Production of tert-butyl 4-[(5-amino-1H-indol-1-yl)methyl]piperidine-1-carboxylate

Using tert-butyl 4-[(5-nitro-1H-indol-1-yl)methyl]piperidine-1-carboxylate (0.90 g), 5% platinum-activated carbon (0.15 g) and ethyl acetate (10 mL) and in the same manner as in Example G-8(ii), the title compound (0.83 g) was obtained as a pale-red amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.25 (2H, m), 1.44 (9H, s), 1.50-1.60 (2H, m), 1.90-2.05 (1H, m), 2.55-2.70 (2H, m), 3.91 (2H, d, J= 7.2 Hz), 4.00-4.20 (2H, m), 6.28 (1H, d, J= 3.0 Hz), 6.67 (1H, dd, J= 2.1 Hz, 8.7 Hz), 6.92 (1H, d, J= 2.1 Hz), 6.96 (1H, d, J= 3.3 Hz), 7.12 (1H, d, J= 8.7 Hz).

(iii) Production of tert-butyl 4-{[5-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-1H-indol-1-yl]methyl}piperidine-1-carboxylate

A mixture of 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (686 mg), tert-butyl 4-[(5-amino-1H-indol-1-yl)methyl]piperidine-1-carboxylate (824 mg) and isopropyl alcohol (20 mL) was stirred at 80°C for 12 hr. Under ice-cooling, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (1.04 g) as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.45 (9H, s), 1.50-1.60 (2H, m), 1.95-2.10 (1H, m), 2.55-2.70 (2H, m), 3.98 (2H, d, J= 7.5 Hz), 4.05-4.20 (2H, m), 4.55-4.70 (4H, m), 6.43 (1H, d, J= 3.3 Hz), 6.63 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 3.3 Hz), 7.25-7.35 (3H, m), 7.35-7.45 (3H, m), 7.50-7.65 (2H, m), 7.90-8.00 (2H, m), 8.48 (1H, s).

(iv) Production of 2-(4-{[1-(piperidin-4-ylmethyl)-1H-

indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate dihydrochloride

To a solution of tert-butyl 4-{[5-({5-[2-(benzoyloxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)-1H-indol-1-yl]methyl}piperidine-1-carboxylate (820 mg) in methanol (10 mL) was added 10% (W/W) hydrochloric acid/methanol (10 mL) and the mixture was stirred at room temperature for 17 hr. The reaction mixture was concentrated under reduced pressure, ethanol was added thereto, and the mixture was concentrated again. This operation was repeated twice. Diisopropyl ether was added, and the mixture was concentrated. The obtained powder was collected by filtration, and washed with diisopropyl ether to give the title compound (621 mg) as a pale-yellow powder.

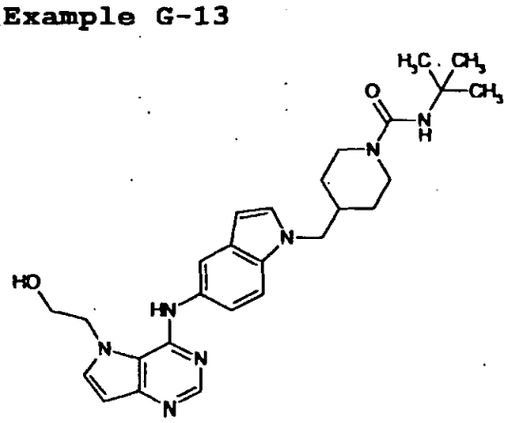
^{1}H-NMR (DMSO-d_6) δ: 1.35-1.55 (2H, m), 1.60-1.70 (2H, m), 2.05-2.20 (1H, m), 2.70-2.90 (2H, m), 3.20-3.30 (2H, m), 4.14 (2H, d, J= 6.9 Hz), 4.60-4.70 (2H, m), 5.10-5.20 (2H, m), 6.45 (1H, d, J= 3.0 Hz), 6.65 (1H, d, J= 2.7 Hz), 7.15 (1H, d, J= 9.6 Hz), 7.40-7.50 (3H, m), 7.55 (1H, d, J= 8.7 Hz), 7.66 (1H, t, J= 7.5 Hz), 7.81 (2H, d, J= 8.1 Hz), 8.07 (1H, d, J= 3.0 Hz), 8.53 (1H, s), 8.55-8.70 (1H, br m), 8.90-9.00 (1H, br m), 9.90 (1H, br s).

(v) Production of 2-{4-[(1-{[1-(2,2-dimethylpropanoyl)piperidin-4-yl]methyl}-1H-indol-5-yl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethanol

To a suspension of 2-(4-{[1-(piperidin-4-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate dihydrochloride (200 mg) in tetrahydrofuran (5.0 mL) were added dropwise triethylamine (0.23 mL) and 2,2-dimethylpropanoyl chloride (0.045 mL) under ice-cooling. The mixture was stirred at 0°C for 30 min and at room temperature for 30 min. Under ice-cooling, water was added to the reaction

mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (1.5 mL) and tetrahydrofuran (4.0 mL) and the mixture was stirred at room temperature for 15 hr. The reaction mixture was neutralized with 1N hydrochloric acid and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/methanol/diisopropyl ether to give the title compound (104 mg) as pale-yellow crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.10-1.30 (2H, m), 1.27 (9H, s), 1.55-1.70 (2H, m), 2.05-2.20 (1H, m), 2.60-2.75 (2H, m), 3.98 (2H, d, J= 7.2 Hz), 4.05-4.15 (2H, m), 4.30-4.50 (4H, m), 6.10 (1H, d, J= 3.0 Hz), 6.46 (1H, d, J= 3.0 Hz), 6.85 (1H, d, J= 3.0 Hz), 7.04 (1H, d, J= 3.0 Hz), 7.25-7.35 (1H, m), 7.35-7.45 (1H, m), 7.75 (1H, s), 8.18 (1H, s), 9.27 (1H, br s).

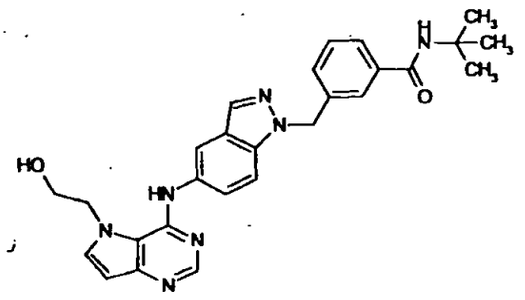
Example G-13



Production of N-(tert-butyl)-4-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]piperidine-1-carboxamide

To a suspension of 2-(4-{[1-(piperidin-4-ylmethyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate dihydrochloride (200 mg) in tetrahydrofuran (5.0 mL) were added dropwise triethylamine (0.23 mL) and 2-isocyanate-2-methylpropane (0.045 mL) under ice-cooling. The reaction mixture was stirred at room temperature for 1.5 hr, water was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5). To the obtained compound were added 1N aqueous sodium hydroxide solution (1.6 mL) and tetrahydrofuran (4.0 mL) and the mixture was stirred at room temperature for 15 hr. The reaction mixture was neutralized with 1N hydrochloric acid and aqueous sodium bicarbonate and brine were added. The mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/methanol/diisopropyl ether to give the title compound (112 mg) as pale-yellow crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.34 (9H, s), 1.50-1.65 (2H, m), 1.95-2.10 (1H, m), 2.55-2.70 (2H, m), 3.85-3.95 (2H, m), 3.99 (2H, d, J= 7.2 Hz), 4.05-4.15 (2H, m), 4.29 (1H, s), 4.30-4.40 (2H, m), 6.19 (1H, d, J= 3.0 Hz), 6.45-6.50 (1H, m), 6.90-6.95 (1H, m), 7.05-7.10 (1H, m), 7.25-7.45 (2H, m), 7.75 (1H, s), 8.23 (1H, s), 9.20 (1H, br s).

Example G-14



Production of N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indazol-1-yl)methyl]benzamide

(i) Production of methyl 3-[(5-nitro-1H-indazol-1-yl)methyl]benzoate

To a solution of 5-nitroindazole (816 mg) and methyl 3-(bromomethyl)benzoate (2.29 g) in N,N-dimethylformamide (10 mL) was added potassium carbonate (2.07 g) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→50:50) to give the title compound (805 mg) as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 5.68 (2H, s), 7.30-7.45 (3H, m), 7.90-8.00 (2H, m), 8.23 (1H, dd, J= 1.8 Hz, 9.0 Hz), 8.20-8.25 (1H, m), 8.74 (1H, d, J= 1.8 Hz).

(ii) Production of 3-[(5-nitro-1H-indazol-1-yl)methyl]benzoic acid

Using methyl 3-[(5-nitro-1H-indazol-1-yl)methyl]benzoate (0.79 g), 1N aqueous sodium hydroxide solution (12 mL), methanol (15 mL) and tetrahydrofuran (15 mL) and in the same manner as in Example G-10(ii), the title compound (732 mg) was obtained as a pale-

yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 5.86 (2H, s), 7.40-7.55 (2H, m), 7.75-7.90 (2H, m), 8.00 (1H, d, J= 9.3 Hz), 8.25 (1H, dd, J= 2.1 Hz, 9.3 Hz), 8.48 (1H, s), 8.86 (1H, d, J= 2.1 Hz), 13.07 (1H, br s).

(iii) Production of N-(tert-butyl)-3-[(5-nitro-1H-indazol-1-yl)methyl]benzamide

To a suspension of 3-[(5-nitro-1H-indazol-1-yl)methyl]benzoic acid (595 mg) in tetrahydrofuran (10 mL) were added N,N-dimethylformamide (one drop) and thionyl chloride (0.144 mL) and the mixture was stirred at room temperature for 3.5 hr. To a solution of tert-butylamine (0.73 g) and triethylamine (0.25 g) in N,N-dimethylformamide (4.0 mL) was added the above-mentioned reaction mixture under ice-cooling, and the mixture was stirred at room temperature for 4.5 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=30:70→50:50) to give the title compound (0.56 g) as a pale-yellow amorphous form.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 5.66 (2H, s), 5.88 (1H, br s), 7.20-7.30 (1H, m), 7.35 (1H, t, J= 7.5 Hz), 7.40 (1H, d, J= 9.0 Hz), 7.56 (1H, d, J= 7.5 Hz), 7.73 (1H, s), 8.23 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.25 (1H, s), 8.74 (1H, d, J= 2.1 Hz).

(iv) Production of 3-[(5-amino-1H-indazol-1-yl)methyl]-N-(tert-butyl)benzamide

Using N-(tert-butyl)-3-[(5-nitro-1H-indazol-1-yl)methyl]benzamide (0.55 g), 5% platinum-activated carbon (92 mg) and ethyl acetate (20 mL) and in the same manner as in Example G-8(ii), the title compound (0.47

g) was obtained as a white powder.

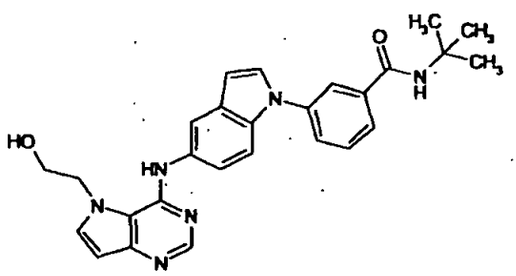
^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 3.61 (2H, br s), 5.55 (2H, s), 5.86 (1H, br s), 6.81 (1H, d, J= 9.0 Hz), 6.95-7.00 (1H, m), 7.14 (1H, d, J= 8.7 Hz), 7.20 (1H, d, J= 7.5 Hz), 7.30 (1H, t, J= 7.5 Hz), 7.56 (1H, d, J= 8.1 Hz), 7.63 (1H, s), 7.83 (1H, s).

(v) Production of N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indazol-1-yl)methyl]benzamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (151 mg), 3-[(5-amino-1H-indazol-1-yl)methyl]-N-(tert-butyl)benzamide (177 mg), isopropyl alcohol (8.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and tetrahydrofuran (4.0 mL) and in the same manner as in Example G-10(v), the title compound (169 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.59 (2H, s), 5.92 (1H, br s), 6.18 (1H, d, J= 3.0 Hz), 6.93 (1H, d, J= 3.6 Hz), 7.25-7.35 (4H, m), 7.40-7.50 (1H, m), 7.56 (1H, d, J= 7.2 Hz), 7.65 (1H, s), 7.88 (1H, s), 7.98 (1H, s), 8.22 (1H, s), 9.33 (1H, br s).

Example G-15



Production of N-(tert-butyl)-3-(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)benzamide

(i) Production of ethyl 3-(5-nitro-1H-indol-1-yl)benzoate

A mixed solution of 5-nitroindole (1.62 g), ethyl

3-iodobenzoate (3.04 g), N,N-dimethylenediamine (0.97 g), potassium carbonate (1.66 g), copper(I) iodide (0.19 g) and toluene (10 mL) was stirred at 120°C for 24 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60) to give the title compound (0.95 g) a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J= 7.0 Hz), 4.44 (2H, q, J= 7.0 Hz), 6.89 (1H, d, J= 3.3 Hz), 7.50-7.55 (2H, m), 7.60-7.75 (2H, m), 8.10-8.20 (3H, m), 8.66 (1H, d, J= 2.4 Hz).

(ii) Production of 3-(5-nitro-1H-indol-1-yl)benzoic acid

Using ethyl 3-(5-nitro-1H-indol-1-yl)benzoate (0.95 g), 1N aqueous sodium hydroxide solution (15 mL), ethanol (15 mL) and tetrahydrofuran (15 mL) and in the same manner as in Example G-10(ii), the title compound (0.71 g) was obtained as a yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 6.95-7.05 (1H, m), 7.60-7.75 (2H, m), 7.83 (1H, d, J= 7.2 Hz), 7.90-8.10 (4H, m), 8.68 (1H, s).

(iii) Production of N-(tert-butyl)-3-(5-nitro-1H-indol-1-yl)benzamide

Using 3-(5-nitro-1H-indol-1-yl)benzoic acid (565 mg), thionyl chloride (0.144 mL), tetrahydrofuran (10 mL), tert-butylamine (0.73 g), triethylamine (0.25 g) and N,N-dimethylformamide (4.0 mL) and in the same manner as in Example G-14(iii), the title compound (0.32 g) was obtained as a yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 5.99 (1H, br s), 6.89 (1H, d, J= 3.3 Hz), 7.50-7.65 (4H, m), 7.65-7.75 (1H, m), 7.93 (1H, s), 8.13 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.66

8.10 (1H, m).

(ii) Production of 7-chloro-5-nitro-1H-indole

To a solution of 7-chloro-5-nitroindoline (2.09 g) in ethyl acetate (100 mL) was added manganese oxide (9.13 g), and the mixture was stirred at 60°C for 15 hr. Manganese oxide was filtered off, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate) and washed with hexane to give the title compound (1.92 g) as a pale-brown powder.

^{1}H-NMR ($CDCl_3$) δ: 6.79-6.82 (1H, m), 7.40-7.45 (1H, m), 8.15 (1H, d, J= 1.8 Hz), 8.53 (1H, d, J= 1.8 Hz), 8.65-8.85 (1H, m).

(iii) Production of methyl 3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzoate

Using 7-chloro-5-nitro-1H-indole (950 mg), methyl 3-(bromomethyl)benzoate (1.22 g), potassium carbonate (0.80 g) and N,N-dimethylformamide (15 mL) and in the same manner as in Example G-8(i), the title compound (1.43 g) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s), 5.84 (2H, s), 6.80 (1H, d, J= 3.3 Hz), 7.13 (1H, dd, J= 0.9 Hz, 7.8 Hz), 7.25-7.30 (1H, m), 7.38 (1H, t, J= 7.8 Hz), 7.79 (1H, s), 7.95 (1H, d, J= 8.1 Hz), 8.07 (1H, d, J= 2.1 Hz), 8.50 (1H, d, J= 2.1 Hz).

(iv) Production of 3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzoic acid

Using methyl 3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzoate (1.30 g), 1N aqueous sodium hydroxide solution (20 mL), methanol (20 mL) and tetrahydrofuran (30 mL) and in the same manner as in Example G-10(ii), the title compound (1.20 g) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 5.92 (2H, s), 6.99 (1H, d, J= 3.0

Hz), 7.26 (1H, d, J= 7.5 Hz), 7.44 (1H, t, J= 7.5 Hz), 7.56 (1H, s), 7.82 (1H, d, J= 7.5 Hz), 7.88 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 1.8 Hz), 8.62 (1H, d, J= 1.8 Hz), 12.90-13.10 (1H, br).

(v) Production of N-(tert-butyl)-3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzamide

Using 3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzoic acid (595 mg), thionyl chloride (0.13 mL), tetrahydrofuran (10 mL), tert-butylamine (0.66 g), triethylamine (0.23 g) and N,N-dimethylformamide (4.0 mL) and in the same manner as in Example G-14(iii), the title compound (460 mg) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 5.83 (2H, s), 5.86 (1H, br s), 6.79 (1H, t, J= 3.3 Hz), 7.02 (1H, d, J= 7.8 Hz), 7.20-7.30 (1H, m), 7.33 (1H, t, J= 7.8 Hz), 7.53 (1H, d, J= 7.8 Hz), 7.58 (1H, s), 8.07 (1H, d, J= 2.4 Hz), 8.49 (1H, d, J= 2.4 Hz).

(vi) Production of 3-[(5-amino-7-chloro-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide

N-(tert-Butyl)-3-[(7-chloro-5-nitro-1H-indol-1-yl)methyl]benzamide (212 mg) was suspended in ethanol (10 mL)/water (1 mL), calcium chloride (30.5 mg) was added, and the mixture was dissolved at 90°C. Reduced iron (184 mg) was added to the mixture, and the mixture was stirred at 90°C for 4 hr. The reaction mixture was allowed to return to room temperature, and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure, ethyl acetate was added thereto, and the mixture was washed with brine. The mixture was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (203 mg) as a yellow amorphous form.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 3.45-3.60 (2H, br), 5.69 (2H, s), 5.84 (1H, br s), 6.37 (1H, d, J= 3.3 Hz), 6.61

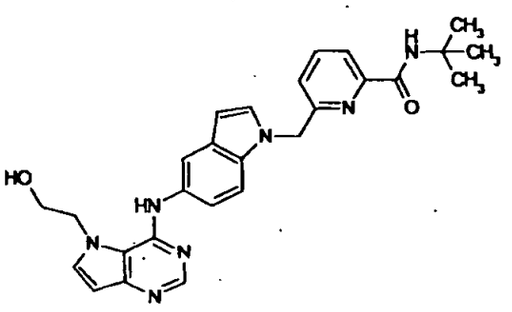
(1H, d, J= 2.0 Hz), 6.82 (1H, d, J= 2.0 Hz), 6.95-7.05 (1H, m), 7.02 (1H, d, J= 3.3 Hz), 7.29 (1H, t, J= 7.8 Hz), 7.50-7.55 (1H, m), 7.53 (1H, d, J= 7.8 Hz).

(vii) Production of N-(tert-butyl)-3-[(7-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (151 mg), 3-[(5-amino-7-chloro-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide (196 mg), isopropyl alcohol (8.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and tetrahydrofuran (4.0 mL) and in the same manner as in Example G-10(v), the title compound (157 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.75 (2H, s), 5.89 (1H, s), 6.17 (1H, d, J= 3.0 Hz), 6.53 (1H, d, J= 3.0 Hz), 6.92 (1H, d, J= 3.0 Hz), 7.05 (1H, d, J= 7.2 Hz), 7.09 (1H, d, J= 3.0 Hz), 7.25-7.35 (2H, m), 7.50-7.55 (2H, m), 7.65-7.70 (1H, m), 8.22 (1H, s), 9.22 (1H, s).

Example G-18



Production of N-(tert-butyl)-6-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]pyridine-2-carboxamide

(i) Production of ethyl 6-(hydroxymethyl)pyridine-2-carboxylate

To a solution of diethyl pyridine-2,6-dicarboxylate (4.46 g) in ethanol (50 mL) was added sodium borohydride (454 mg) and the mixture was stirred at room temperature

for 3 hr. The reaction mixture was concentrated under reduced pressure, brine was added thereto, and the mixture was extracted with ethyl acetate. The aqueous layer was salted out, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→100:0) to give the title compound (2.42 g) as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J= 7.2 Hz), 3.53 (1H, t, J= 5.4 Hz), 4.46 (2H, q, J= 7.2 Hz), 4.86 (2H, d, J= 5.4 Hz), 7.49 (1H, d, J= 7.8 Hz), 7.84 (1H, t, J= 7.8 Hz), 8.02 (1H, d, J= 7.8 Hz).

(ii) Production of ethyl 6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxylate

To a solution of ethyl 6-(hydroxymethyl)pyridine-2-carboxylate (1.00 g) and triethylamine (0.84 mL) in tetrahydrofuran (20 mL) was added dropwise methanesulfonyl chloride (0.43 mL) under ice-cooling, and the mixture was stirred at room temperature for 1.5 hr. Under ice-cooling, to the reaction mixture were added aqueous sodium bicarbonate and brine, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the obtained compound were added 5-nitroindole (757 mg), potassium carbonate (0.97 g) and N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 24 hr at 60°C for 20 hr, and at 80°C for 1 hr. Under ice-cooling, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The aqueous layer was salted out, and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate concentrated under reduced

pressure, and the residue was recrystallized from ethyl acetate to give the title compound (1.31 g) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, t, J= 7.2 Hz), 4.51 (2H, q, J= 7.2 Hz), 5.62 (2H, s), 6.76 (1H, d, J= 7.8 Hz), 6.79 (1H, d, J= 3.0 Hz), 7.30 (1H, d, J= 9.0 Hz), 7.36 (1H, d, J= 3.0 Hz), 7.70 (1H, t, J= 7.8 Hz), 8.02 (1H, d, J= 7.8 Hz), 8.08 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.63 (1H, d, J= 2.1 Hz).

(iii) Production of 6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxylic acid

Using ethyl 6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxylate (1.20 g), 1N aqueous sodium hydroxide solution (20 mL), ethanol (20 mL) and tetrahydrofuran (40 mL) and in the same manner as in Example G-10(ii), the title compound (1.01 g) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6) δ: 5.68 (2H, s), 6.80-6.85 (1H, m), 6.89 (1H, d, J= 7.2 Hz), 7.67 (1H, d, J= 8.1 Hz), 7.70-7.90 (3H, m), 7.99 (1H, d, J= 9.0 Hz), 8.60 (1H, s).

(iv) Production of N-(tert-butyl)-6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxamide

Using 6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxylic acid (0.95 g), thionyl chloride (0.23 mL), tetrahydrofuran (20 mL), tert-butylamine (1.17 g), triethylamine (0.40 g) and N,N-dimethylformamide (8.0 mL) and in the same manner as in Example G-14(iii), the title compound (636 mg) was obtained as a pale-yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s), 5.51 (2H, s), 6.78 (1H, d, J= 3.3 Hz), 6.98 (1H, d, J= 7.8 Hz), 7.30-7.40 (2H, m), 7.66 (1H, br s), 7.76 (1H, t, J= 7.8 Hz), 8.05-8.15 (2H, m), 8.63 (1H, d, J= 2.1 Hz).

(v) Production of 6-[(5-amino-1H-indol-1-yl)methyl]-N-(tert-butyl)pyridine-2-carboxamide

To a solution of N-(tert-butyl)-6-[(5-nitro-1H-indol-1-yl)methyl]pyridine-2-carboxamide (211 mg) in ethyl acetate (8.0 mL) was added 5% platinum-activated carbon (35 mg) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 5 hr. Under a nitrogen atmosphere, 10% palladium/carbon (69 mg) was added to the reaction mixture, and the mixture was further stirred under a hydrogen atmosphere at room temperature for 2.5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=50:50→80:20) to give the title compound (160 mg) as a pale-pink amorphous.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 3.52 (2H, br s), 5.39 (2H, s), 6.41 (1H, d, J= 3.0 Hz), 6.64 (1H, dd, J= 2.4 Hz, 8.7 Hz), 6.82 (1H, d, J= 8.1 Hz), 6.97 (1H, d, J= 2.4 Hz), 7.00-7.10 (1H, m), 7.11 (1H, d, J= 3.0 Hz), 7.68 (1H, t, J= 7.5 Hz), 7.89 (1H, br s), 8.03 (1H, d, J= 7.5 Hz).

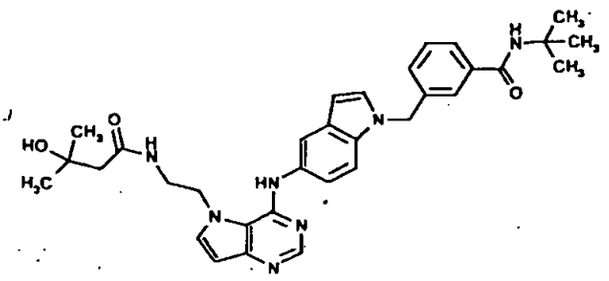
(vi) Production of N-(tert-butyl)-6-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]pyridine-2-carboxamide

Using 2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl benzoate (136 mg), 6-[(5-amino-1H-indol-1-yl)methyl]-N-(tert-butyl)pyridine-2-carboxamide (160 mg), isopropyl alcohol (8.0 mL), 1N aqueous sodium hydroxide solution (2.0 mL) and tetrahydrofuran (4.0 mL) and in the same manner as in Example G-10(v), the title compound (137 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.46 (2H, s), 6.16 (1H, d, J= 3.0 Hz), 6.57 (1H, d, J= 3.0 Hz), 6.85-6.90 (2H, m), 7.19 (1H, d, J= 3.0 Hz), 7.20-7.30 (1H, m), 7.35 (1H, d, J= 9.0 Hz),

7.69 (1H, t, J= 7.5 Hz), 7.81 (1H, s), 7.92 (1H, s), 8.04 (1H, d, J= 7.5 Hz), 8.20 (1H, s), 9.15 (1H, br s).

Example G-19



Production of N-(tert-butyl)-3-({5-[(5-{2-[(3-hydroxy-3-methylbutanoyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-1H-indol-1-yl}methyl)benzamide

(i) Production of tert-butyl (2-{4-[(1-{3-[(tert-butylamino)carbonyl]benzyl}-1H-indol-5-yl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate

Using tert-butyl [2-(4-chloro-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]carbamate (297 mg), 3-[(5-amino-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide (354 mg) and isopropyl alcohol (8.0 mL) and in the same manner as in Example G-8(iii), the title compound (478 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.46 (9H, s), 3.45-3.55 (2H, m), 4.35-4.50 (2H, m), 4.93 (1H, br s), 5.33 (2H, s), 5.88 (1H, s), 6.49 (1H, d, J = 3.0 Hz), 6.55 (1H, d, J = 2.4 Hz), 7.10-7.30 (4H, m), 7.30 (1H, t, J = 7.8 Hz), 7.40-7.50 (1H, m), 7.54 (1H, d, J = 8.1 Hz), 7.64 (1H, s), 7.86 (1H, s), 8.16 (1H, br s), 8.43 (1H, s).

(ii) Production of 3-[(5-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide dihydrochloride

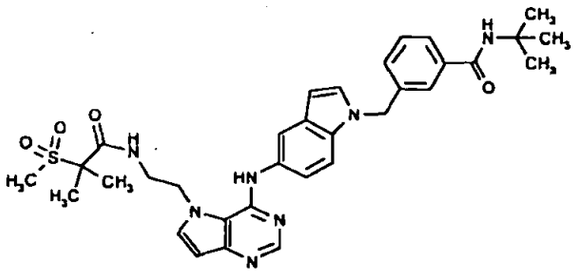
Using tert-butyl (2-{4-[(1-{3-[(tert-butylamino)carbonyl]benzyl}-1H-indol-5-yl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)carbamate (449 mg) and 10% (W/W) hydrochloric acid/methanol (5.0 mL) and in the same manner as in Example G-8(iv), the title

compound (400 mg) was obtained as a pale-orange powder.
^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 3.25-3.35 (2H, m), 4.90-5.05 (2H, m), 5.51 (2H, s), 6.56 (1H, d, J= 3.0 Hz), 6.69 (1H, d, J= 3.3 Hz), 7.20 (1H, d, J= 9.0 Hz), 7.29 (1H, d, J= 7.2 Hz), 7.37 (1H, t, J= 7.8 Hz), 7.51 (1H, d, J= 9.0 Hz), 7.62 (1H, d, J= 3.0 Hz), 7.65-7.70 (2H, m), 7.68 (1H, s), 7.99 (1H, d, J= 3.0 Hz), 8.15-8.30 (3H, m), 8.58 (1H, s), 9.89 (1H, s).

(iii) Production of N-(tert-butyl)-3-({5-[(5-{2-[(3-hydroxy-3-methylbutanoyl)amino]ethyl}-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]-1H-indol-1-yl}methyl)benzamide

Using 3-[(5-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide dihydrochloride (150 mg), 3-hydroxy-3-methylbutanoic acid (48 mg), 1-hydroxybenzotriazole (59 mg), triethylamine (0.38 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (83 mg) and N,N-dimethylformamide (4.0 mL) and in the same manner as in Example G-8(v), the title compound (80 mg) was obtained as pale-yellow crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, s), 1.46 (9H, s), 2.44 (2H, s), 3.55-3.65 (2H, m), 4.45-4.55 (2H, m), 5.30 (2H, s), 5.99 (1H, s), 6.51 (1H, d, J= 3.0 Hz), 6.57 (1H, d, J= 3.3 Hz), 7.10-7.35 (6H, m), 7.55 (1H, d, J= 8.1 Hz), 7.64 (1H, s), 7.75-7.80 (1H, m), 8.05-8.10 (1H, m), 8.28 (1H, s), 9.55-9.65 (1H, br).

Example G-20



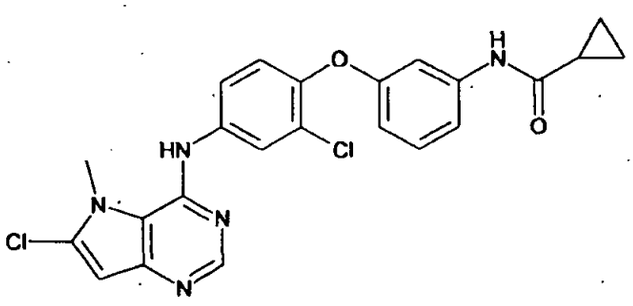
Production of N-(tert-butyl)-3-[(5-{[5-(2-{[2-methyl-2-(methylsulfonyl)propanoyl]amino}ethyl)-5H-pyrrolo[3,2-

d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide

Using 3-[(5-{[5-(2-aminoethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]-N-(tert-butyl)benzamide dihydrochloride (150 mg), 2-methyl-2-(methylsulfonyl)propanoic acid (68 mg), 1-hydroxybenzotriazole (59 mg), triethylamine (0.38 mL), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (83 mg) and N,N-dimethylformamide (4.0 mL) and in the same manner as in Example G-8(v), the title compound (91 mg) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (6H, s), 1.60 (9H, s), 2.84 (3H, s), 3.60-3.75 (2H, m), 4.30-4.45 (2H, m), 5.34 (2H, s), 5.90 (1H, s), 6.51 (1H, d, J= 2.7 Hz), 6.55-6.60 (1H, m), 7.00-7.10 (1H, m), 7.10-7.40 (6H, m), 7.53 (1H, d, J= 7.5 Hz), 7.65 (1H, s), 7.81 (1H, s), 7.89 (1H, s), 8.44 (1H, s).

Example H-1



Production of N-(3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide

(i) Production of 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine

To a solution of diisopropylamine (540 mg) in tetrahydrofuran (12 mL) was added n-butyllithium (2.7 mL) at 0°C. After stirring for 30 min, the mixture was cooled to -78°C, and 4-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (500 mg) was added thereto. The reaction

mixture was stirred for 1 hr, p-toluenesulfonyl chloride (690 mg) was added thereto, and the mixture was allowed to warm to -40°C over 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→30:70). After concentration under reduced pressure, the resulting crystals were collected by filtration, and washed with diisopropyl ether to give the title compound (191 mg) as crystals.

^{1}H-NMR ($CDCl_3$) δ: 4.13 (3H, s), 6.72 (1H, s), 8.68 (1H, s).

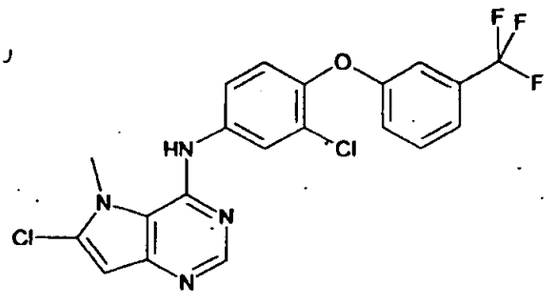
(ii) Production of N-(3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide

A mixture of 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (98 mg), N-[3-(4-amino-2-chlorophenoxy)phenyl]cyclopropanecarboxamide (167 mg) and isopropyl alcohol (7.0 mL) was stirred at 80°C for 3 hr. The reaction mixture was concentrated under reduced pressure, water and saturated aqueous sodium hydrogencarbonate were added thereto 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 subjected to silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→0:100). The objective fractions were concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane to give the title compound (146 mg) as a white powder.

^{1}H-NMR ($CDCl_3$) δ: 0.78-0.84 (2H, m), 0.99-1.05 (2H, m),

1.47-1.54 (1H, m), 4.07 (3H, s), 6.60 (1H, s), 6.75-6.77 (2H, m), 7.01-7.04 (2H, m), 7.20-7.26 (3H, m), 7.62 (1H, s), 8.10 (1H, br s), 8.47 (1H, s).

Example H-2

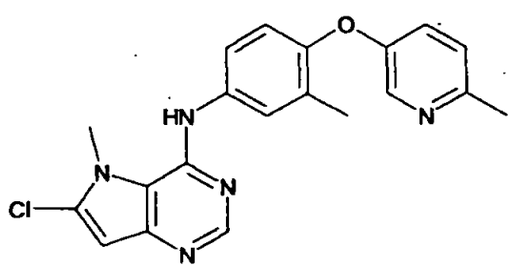


Production of 6-chloro-N-{3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine

Using 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (70 mg), 3-chloro-4-[3-(trifluoromethyl)phenoxy]aniline (109 mg) and isopropyl alcohol (7.0 mL) and in the same manner as in Example H-1(ii), the title compound (61 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 4.07 (3H, s), 6.73 (1H, s), 7.21-7.33 (3H, m), 7.46-7.67 (3H, m), 7.93 (1H, br s), 8.40 (1H, br s), 8.97 (1H, br s).

Example H-3



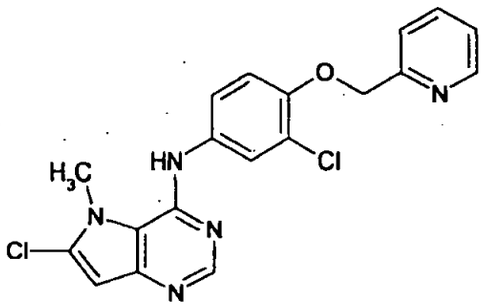
Production of 6-chloro-5-methyl-N-{3-methyl-4-[(6-methylpyridin-3-yl)oxy]phenyl}-5H-pyrrolo[3,2-d]pyrimidin-4-amine

Using 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-

d]pyrimidine (150 mg), 3-methyl-4-[(6-methylpyridin-3-yl)oxy]aniline (160 mg) and isopropyl alcohol (8.0 mL) and in the same manner as in Example H-1(ii), the title compound (116 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 2.17 (3H, s), 2.43 (3H, s), 4.04 (3H, s), 6.65 (1H, s), 6.94 (1H, d, J= 8.3 Hz), 7.16-7.25 (2H, m), 7.44-7.51 (2H, m), 7.16 (1H, d, J= 2.7 Hz), 8.28 (1H, s), 8.57 (1H, s).

Example H-4

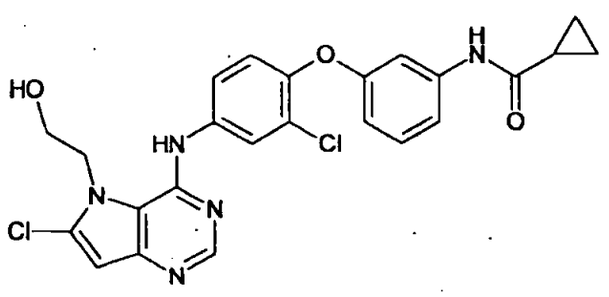


Production of 6-chloro-N-[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine

Using 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (150 mg), 3-chloro-4-(pyridin-2-ylmethoxy)aniline (210 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example H-1(ii), the title compound (170 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 4.03 (3H, s), 5.27 (2H, s), 6.64 (1H, s), 7.20-7.91 (6H, m), 8.25 (1H, s), 8.54 (1H, br s), 8.58-8.62 (1H, m).

Example H-5



Production of N-[3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide

(i) Production of 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine

4-Chloro-5H-pyrrolo[3,2-d]pyrimidine (2.00 g), (2-bromoethoxy)(tert-butyl)dimethylsilane (4.00 g) and cesium carbonate (6.40 g) were dissolved in N,N-dimethylformamide (10 mL) and the mixture was stirred at room temperature for 4 hr. Under ice-cooling, brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:hexane=20:80→40:60) to give the title compound (3.02 g) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: -0.24 (6H, s), 0.69 (9H, s), 3.90-3.93 (2H, m), 4.61-4.64 (2H, m), 6.76 (1H, s), 8.00 (1H, s), 8.61 (1H, s).

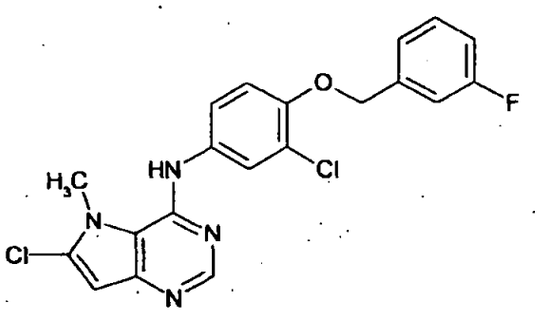
(ii) Production of N-[3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide

Using diisopropylamine (2.20 g), 1.6 M n-butyllithium (14 mL), tetrahydrofuran (50 mL), 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (500 mg), p-toluenesulfonyl chloride (6.10 g), N-[3-(4-amino-2-chlorophenoxy)phenyl]cyclopropanecarboxamide (190 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example H-1(i) and (ii), a compound was obtained. The obtained compound was dissolved in methanol (10 mL), 4N hydrogen chloride/ethyl acetate solution (3.0 mL) was added thereto, and the mixture was stirred at 80°C for 18

hr. Under ice-cooling, to the reaction mixture was added aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (73 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 0.75-0.77 (4H, m), 1.69-1.75 (1H, m), 3.88-3.91 (2H, m), 4.53-4.55 (2H, m), 6.62-6.68 (1H, m), 6.72 (1H, s), 7.20-7.96 (6H, m), 8.37 (1H, s), 9.87-9.97 (1H, m), 10.24 (1H, s).

Example H-6

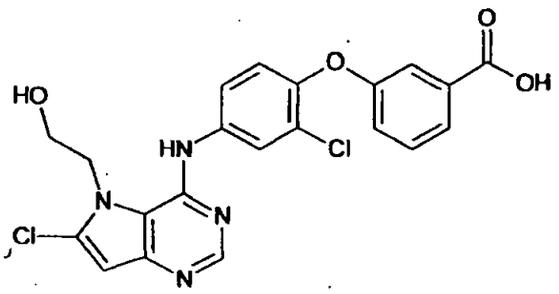


Production of 6-chloro-N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine

Using 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (150 mg), 3-chloro-4-[(3-fluorobenzyl)oxy]aniline (167 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example H-1(ii), the title compound (61 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 4.03 (3H, s), 5.24 (2H, s), 6.64 (1H, s), 7.14-7.50 (6H, m), 7.71-7.72 (1H, m), 8.26 (1H, s), 8.52 (1H, s).

Example H-7

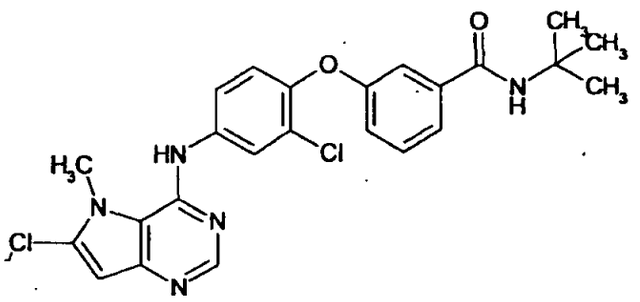


Production of 3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzoic acid

Using diisopropylamine (2.00 g), 1.6M n-butyllithium (13 mL), tetrahydrofuran (50 mL), 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (450 mg), p-toluenesulfonyl chloride (6.01 g), methyl 3-(4-amino-2-chlorophenoxy)benzoate (190 mg), isopropyl alcohol (10 mL), methanol (10 mL) and 4N hydrogen chloride/ethyl acetate solution (3.0 mL) and in the same manner as in Example H-1(i), (ii) and Example H-5(ii), a compound was obtained. To the obtained compound were added 1N aqueous sodium hydroxide solution (0.8 mL) and tetrahydrofuran (4.0 mL) and the mixture was stirred at room temperature for 2 days. The reaction mixture was neutralized with 1N hydrochloric acid and aqueous sodium bicarbonate and brine were added thereto. The mixture was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (127 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 3.83-3.91 (2H, m), 4.54-4.57 (2H, m), 6.49 (1H, br s), 6.73 (1H, s), 7.24-7.68 (6H, m), 7.98 (1H, s), 9.97 (1H, s), 13.14 (1H, br s).

Example H-8

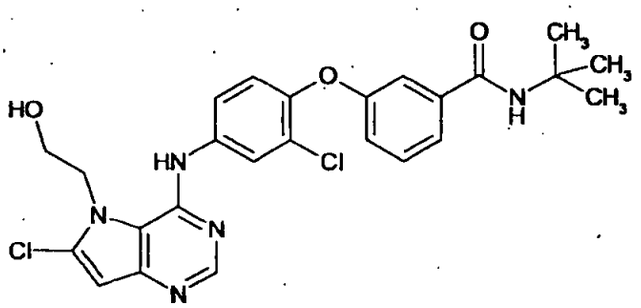


Production of N-(tert-butyl)-3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}benzamide

Using 4,6-dichloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine (110 mg), 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)benzamide (197 mg) and isopropyl alcohol (10 mL) and in the same manner as in Example H-1(ii), the title compound (86 mg) was obtained as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 4.06 (3H, s), 6.69 (1H, s), 7.06-7.64 (6H, m), 7.81 (1H, s), 7.89 (1H, br s), 8.34 (1H, s), 8.81 (1H, s).

Example H-9



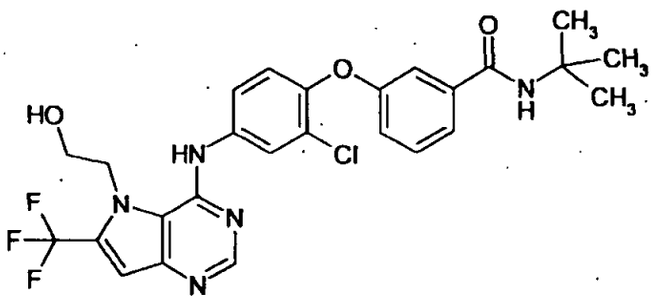
Production of N-(tert-butyl)-3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide

Using diisopropylamine (2.80 g), 1.6M n-butyllithium (16 mL), tetrahydrofuran (50 mL), 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (800 mg), p-toluenesulfonyl chloride (7.10 g), 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)benzamide (811 mg) and isopropyl alcohol (16 mL)

and in the same manner as in Example H-1(i) and (ii), a compound was obtained. The obtained compound was dissolved in methanol (10 mL), 4N hydrogen chloride/ethyl acetate solution (10 mL) was added thereto, and the mixture was stirred at 80°C for 18 hr. Under ice-cooling, to the reaction mixture was added aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography (eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (576 mg) as crystals.

^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 3.88-3.91 (2H, m), 4.53-4.57 (2H, m), 6.72 (1H, s), 7.06-7.61 (6H, m), 7.81 (1H, s), 7.96-7.97 (1H, m), 8.37 (1H, s), 9.52-10.53 (1H, m).

Example H-10



Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-6-(trifluoromethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide

(i) 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-6-(trifluoromethyl)-5H-pyrrolo[3,2-d]pyrimidine

Production of

To a solution of diisopropylamine (300 mg) in tetrahydrofuran (20 mL) was added 1.6 M n-butyllithium (2.0 mL) at 0°C. After stirring for 30 min, the mixture was cooled to -78°C, and 5-(2-{[tert-

butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (520 mg) was added thereto. The reaction mixture was stirred for 1 hr, S-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (2.00 g) was added thereto, and the mixture was allowed to warm to -40°C over 1 hr. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified by basic silica gel column chromatography (eluent, hexane:ethyl acetate=80:20→30:70). After concentration under reduced pressure, the resulting crystals were collected by filtration and washed with diisopropyl ether to give the title compound (29 mg) as crystals.

^{1}H-NMR ($CDCl_3$) δ: 0.02 (6H, s), 0.74 (9H, s), 3.92-3.96 (2H, m), 4.74-4.78 (2H, m), 7.17 (1H, s), 8.79 (1H, s).

(ii) Production of N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-6-(trifluoromethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide

Using 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-chloro-6-(trifluoromethyl)-5H-pyrrolo[3,2-d]pyrimidine (25 mg), 3-(4-amino-2-chlorophenoxy)-N-(tert-butyl)benzamide (26 mg) and isopropyl alcohol (1.5 mL) and in the same manner as in Example H-2(ii), a compound was obtained. The obtained compound was dissolved in methanol (2.0 mL), 4N hydrogen chloride/ethyl acetate solution (1.0 mL) was added thereto, and the mixture was stirred at 80°C for 18 hr. Aqueous sodium bicarbonate was added to the reaction mixture under ice-cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was separated and purified by silica gel column chromatography

(eluent, ethyl acetate:methanol=100:0→95:5) to give the title compound (9.2 mg) as crystals.

^{1}H-NMR ($CDCl_3$) δ: 1.36 (9H, s), 3.92-3.96 (2H, m), 4.61-4.64 (2H, m), 7.06-7.45 (5H, m), 7.55-7.61 (2H, m), 7.82 (1H, s), 7.97 (1H, s), 8.44 (1H, s), 9.50-10.55 (1H, m).

Formulation Example 1 (amount per tablet)

(1) Compound obtained in Example A-1	10.0 mg
(2) Lactose	60.0 mg
(3) Corn starch	35.0 mg
(4) Gelatin	3.0 mg
(5) Magnesium stearate	2.0 mg

A mixture of 10.0 mg of the compound obtained in Example A-1, 60.0 mg of lactose and 35.0 mg of corn starch is granulated through a 1 mm-mesh sieve using 0.03 ml of a 10% by weight aqueous solution of gelatin (3.0 mg of gelatin), after which the granules are dried at 40°C and filtered again. The obtained granules are mixed with 2.0 mg of magnesium stearate and compressed. The obtained core tablets are coated with a sugar coat comprising a suspension of sucrose, titanium dioxide, talc and gum arabic and polished with beeswax to yield sugar-coated tablets.

Formulation Example 2 (dose per tablet)

(1) Compound obtained in Example A-1	10.0 mg
(2) Lactose	70.0 mg
(3) Corn starch	50.0 mg
(4) Soluble starch	7.0 mg
(5) Magnesium stearate	3.0 mg

10.0 mg of the compound obtained in Example A-1 and 3.0 mg of magnesium stearate are granulated using 0.07 ml of an aqueous solution of soluble starch (7.0 mg of soluble starch), after which these granules are dried and mixed with 70.0 mg of lactose and 50.0 mg of corn starch. This mixture is compressed to yield tablets.

Experimental Example 1A Cloning of human HER2 gene and preparation of recombinant baculovirus

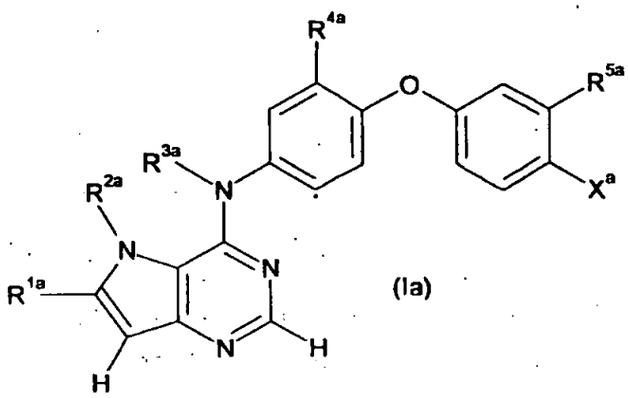
Human HER2 gene was cloned by RT-PCR using total RNA prepared from MCF7 cells as a template. The primer used for RT-PCR was prepared from nucleotide sequence (Genbank Accession No. M11730) information of HER2 gene by adding a nucleotide sequence encoding DYKDDDD peptide and a restriction enzyme recognition sequence to a nucleotide sequence (2176-3918 of Genbank Accession No. M11730) encoding the HER2 intracellular domain region, so that the protein contains an N-terminal DYKDDDD peptide tag. The primer nucleotide sequence is shown below.

HER2-U:5'-
AATTAAGTCGACATGGACTACAAAGACGATGACGACAAGCGACGGCAGCAGAAGAT
CCGGAAGTAC-3'(SEQ ID NO:1)
and
HER2-L:
5'-AATTAAGCATGCTCACACTGGCACGTCCAGACCCAGGTACTC-3'(SEQ ID NO:2)

The RT reaction was conducted using SuperScript First-Strand Synthesis System for RT-PCR (Invitrogen) and the PCR reaction was conducted using a KOD-plus kit (TOYOBO). The obtained PCR product was electrophoresed on agarose gel (1%), the DNA fragment amplified by PCR was recovered from the gel, and then digested with restriction enzymes Sal I and Sph I. The DNA treated with the restriction enzymes was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes Sal I and Sph I to give expression plasmid pFB-HER2. The nucleotide sequence of the insertion fragment was confirmed and found to be identical with the nucleotide sequence (2176-3918 of Genbank Accession M11730) of HER2

CLAIMS

1. A compound represented by the formula:



(Ia)

wherein

R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group substituted by a group represented by $-NR^{6a}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl

wherein n is an integer of 1 to 4, R^{6a} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

R^{3a} is a hydrogen atom or a C_{1-6} alkyl group,

R^{4a} is a halogen atom or a C_{1-6} alkyl group,

R^{5a} is a halogen atom or a C_{1-6} alkyl group, and

X^a is a hydrogen atom or a halogen atom,

or a salt thereof,

provided that N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide is excluded.

2. The compound of claim 1, wherein X^a is a hydrogen atom.

3. The compound of claim 2, wherein

R^{1a} is a hydrogen atom,

R^{2a} is a C_{1-6} alkyl group substituted by a group

represented by $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-C_{1-4}$ alkyl wherein R^{6aa} is a hydrogen atom or a methyl group, R^{7a} and R^{8a} are the same or different and each is a hydrogen atom or a methyl group,

R^{3a} is a hydrogen atom,

R^{4a} is a chlorine atom or a methyl group, and

R^{5a} is a fluorine atom, a chlorine atom or a methyl group.

4. The compound of claim 3, wherein R^{7a} and R^{8a} are methyl groups.

5. A compound selected from the following:

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(ethylsulfonyl)acetamide,

N-[2-(4-{[3-chloro-4-(3-chlorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-N,2-dimethyl-2-(methylsulfonyl)propanamide,

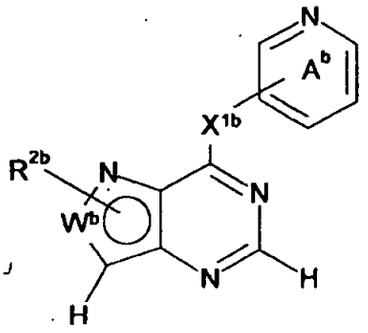
N-[2-(4-{[3-chloro-4-(3-methylphenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

N-[2-(4-{[3-chloro-4-(3-fluorophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide, and

N-[2-(4-{[4-(3-chlorophenoxy)-3-methylphenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-methyl-2-(methylsulfonyl)propanamide,

or a salt thereof, or a hydrate thereof.

6. A compound represented by the formula:



(Ib)

wherein

W^b is $C(R^{1b})$ or N,

ring A^b is an optionally substituted pyridine ring,

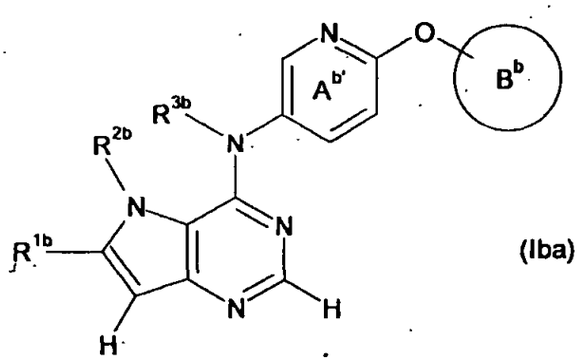
X^{1b} is $-NR^{3b}-Y^{1b}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^{3b}-$ wherein R^{3b} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3b} is optionally bonded to the carbon atom on the pyridine ring for ring A^b to form an optionally substituted ring structure, and Y^{1b} is a bond, or a C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene)-, each of which is optionally substituted, and

R^{1b} is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2b} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or R^{1b} and R^{2b}, or R^{2b} and R^{3b} are optionally bonded to form an optionally substituted ring structure,

or a salt thereof.

7. The compound of claim 6, which is a compound represented by the formula:



(Iba)

wherein ring $A^{b'}$ is an optionally further substituted pyridine ring, ring B^b is an optionally substituted C_{6-14} aryl group, and the other symbols are as defined in claim 6.

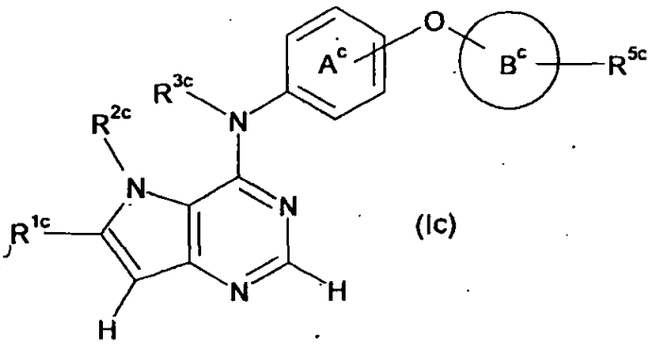
8. The compound of claim 7, wherein
R^{1b} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2b} is a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-C_{1-4}$ alkyl
wherein R^{6ba} is a hydrogen atom or a methyl group, n1 is an integer of 1 to 4, and $-(CH_2)_{n1}-$ is optionally substituted by C_{1-4} alkyl,
(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$
wherein R^{6bb} is a hydrogen atom or a methyl group, n2 is an integer of 1 to 4, and $-(CH_2)_{n2}-$ is optionally substituted by C_{1-4} alkyl,
(iii) $-O-(CH_2)_{n3}-OH$
wherein n3 is an integer of 1 to 4, and $-(CH_2)_{n3}-$ is optionally substituted by C_{1-4} alkyl, and
(iv) hydroxy,
R^{3b} is a hydrogen atom,
ring $A^{b'}$ is a pyridine ring optionally substituted by substituent(s) selected from the group consisting of halogen and methyl, and
ring B^b is a phenyl group optionally substituted by

substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen.

9. The compound of claim 7, wherein
ring $A^{b'}$ is a pyridine ring optionally substituted by halogen, and
ring B^{b} is a phenyl group optionally substituted at the 3-position by substituent(s) selected from the group consisting of optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy, C_{1-6} alkyl-carbamoyl and halogen.

10. A compound selected from the following:
2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,
N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
N-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,
N-{2-[4-({5-chloro-6-[3-(trifluoromethoxy)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide, and
N-(tert-butyl)-3-[(3-chloro-5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}pyridin-2-yl)oxy]benzamide,
or a salt thereof.

11. A compound represented by the formula:



(Ic)

wherein

R^{1c} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2c} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1c} and R^{2c}, or R^{2c} and R^{3c} are optionally bonded to form an optionally substituted ring structure,

R^{3c} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3c} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^c is an optionally substituted benzene ring,

R^{5c} is

(i) an optionally substituted amino group,

(ii) an optionally substituted carbamoyl group,

(iii) an optionally substituted ureido group,

(iv) an optionally substituted sulfamoyl group,

(v) an optionally substituted heterocyclic group,

(vi) an optionally substituted C_{2-6} alkoxy group

(vii) an optionally substituted aminomethyl group,

(viii) an optionally substituted carbamoylmethyl group,

(ix) an optionally substituted alkylsulfonyl group, or

(x) a cyano group, and

ring B^c is a C_{6-14} aryl group or a C_{5-8} cycloalkyl group, each of which is optionally further substituted besides R^{5c},

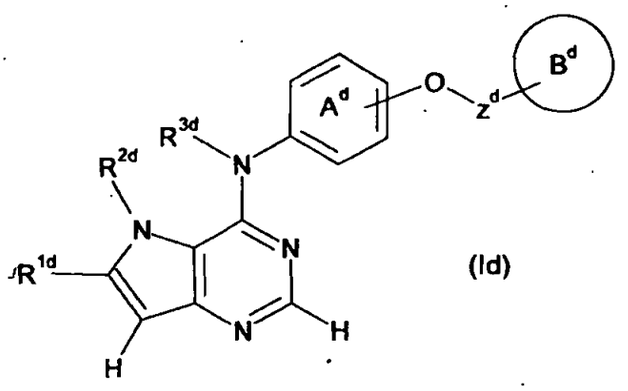
or a salt thereof,
provided that
N-(tert-butyl)-4-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide hydrochloride,
4-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2,2-dimethylpropyl)benzamide,
3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzonitrile,
3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzonitrile,
3-[2-chloro-4-(6,7-dihydro-9H-pyrimido[4',5':4,5]pyrrolo[2,1-c][1,4]oxazin-4-ylamino)phenoxy]benzonitrile hydrochloride, and
(2E)-N-[(2E)-3-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-6-yl)prop-2-en-1-yl]-4-(dimethylamino)but-2-enamide
are excluded.

12. The compound of claim 11, wherein R^{1c} is a hydrogen atom.

13. A compound selected from the following:
2-{2-[4-({3-chloro-4-[3-(1,3-thiazol-5-yl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol,
N-(tert-butyl)-3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]benzamide,
3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]-N-(2-hydroxy-1,1-dimethylethyl)benzamide,
N-(tert-butyl)-3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,
N-(3-{2-chloro-4-[(6-cyano-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide,
N-(tert-butyl)-5-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)-2-fluorobenzamide,
N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-3-hydroxy-3-methylbutanamide,
N-{2-[4-({3-chloro-4-[3-(dimethylamino)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
N-(tert-butyl)-2-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]acetamide,
N-{2-[4-({3-chloro-4-[3-(cyclopropylmethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
N-{2-[4-({3-chloro-4-[3-(2,2-dimethylpropoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide,
2-(methylsulfonyl)-N-{2-[4-({3-methyl-4-[3-(2,2,2-trifluoroethoxy)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}acetamide,
2-[4-({3-chloro-4-[3-(isopropylsulfonyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol, and
N-[2-(4-{[3-chloro-4-(3-cyanophenoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,
or a salt thereof.

14. A compound represented by the formula:



(Id)

wherein

R^{1d} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2d} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or,

R^{1d} and R^{2d}, or R^{2d} and R^{3d} are optionally bonded to form an optionally substituted ring structure,

R^{3d} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3d} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^d is an optionally substituted benzene ring,

Z^d is an optionally substituted C_{1-3} alkylene,

ring B^d is an optionally substituted heterocyclic group,

or a salt thereof,

provided that

ethyl 5-[(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl]-2-furoate,

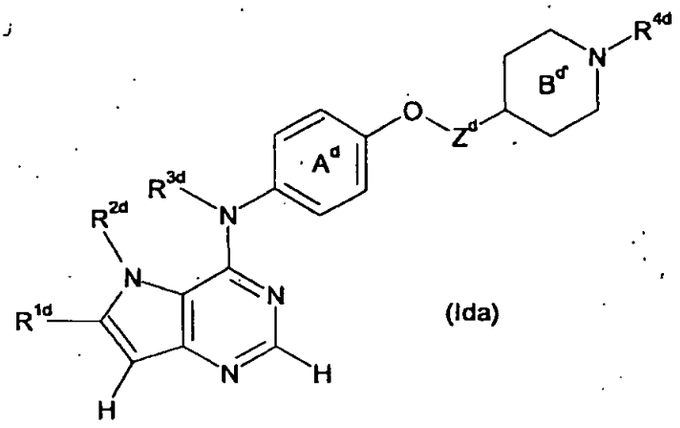
5-[(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)methyl]-2-furancarboxylic acid,

2-[2-(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethoxy]ethanol, and

N-[2-(4-{[3-chloro-4-(pyridin-2-ylmethoxy)phenyl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-

(methylsulfonyl)acetamide
are excluded.

15. The compound of claim 14, which is a compound represented by the formula:

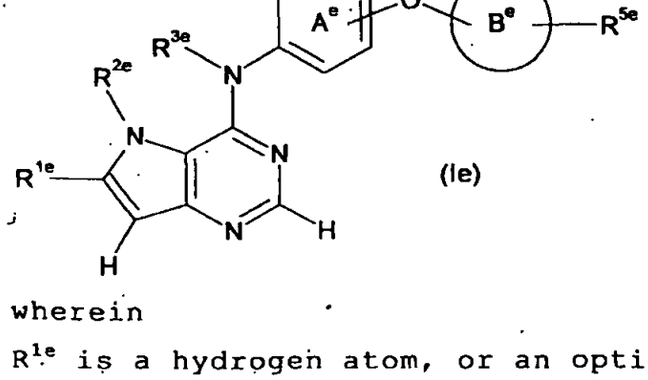


(Ida)

wherein R^{4d} is an acyl group or an optionally substituted ureido group, ring $B^{d'}$ is a piperidyl group optionally further substituted besides R^{4d}, and the other symbols are as defined in claim 14.

16. A compound selected from the following:
tert-butyl 4-{[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]methyl}piperidine-1-carboxylate, and
tert-butyl 4-[(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)methyl]piperidine-1-carboxylate,
or a salt thereof.

17. A compound represented by the formula:



(Ie)

wherein

R^{1e} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2e} is an optionally substituted group bonded via a carbon atom or a sulfur atom, or,

R^{1e} and R^{2e}, or R^{2e} and R^{3e} are optionally bonded to form an optionally substituted ring structure,

R^{3e} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3e} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

ring A^e is an optionally substituted benzene ring,

R^{5e} is

(i) a linear alkyl group substituted by optionally substituted heterocyclic group,

(ii) a linear alkyl group substituted by optionally substituted imino,

(iii) a linear alkyl group substituted by optionally substituted aryl, which is optionally further halogenated or hydroxylated,

(iv) an optionally substituted branched alkyl group,

(v) an optionally substituted alkenyl group,

(vi) a hydroxy group substituted by optionally substituted aryl,

(vii) a hydroxy group substituted by C_{1-6} alkyl,

(viii) a hydroxy group substituted by halogenated C_{2-6} alkyl,

(ix) a halogenated C_{2-6} alkyl group,

(x) an optionally substituted cycloalkyl group, or

(xi) a C_{1-6} alkyl-carbonyl group optionally substituted by optionally substituted aryl, and

ring B^e is a C_{6-14} aryl group optionally further substituted besides R^{5e},

or a salt thereof,

provided that

2-(2-{4-[(3-chloro-4-{4-[3-(1H-imidazol-1-yl)propyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol dihydrochloride,

2-(2-{4-[(3-chloro-4-{4-[4-(1H-1,2,3-triazol-1-yl)butyl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethoxy)ethanol, and

1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}ethanone

are excluded.

18. A compound selected from the following:

2-[4-({3-chloro-4-[3-(1,1-difluoroethyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethanol,

(1Z)-1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-one O-ethyloxime,

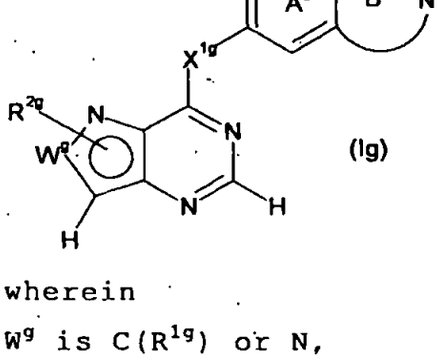
1-{3-[2-chloro-4-({5-[2-(2-hydroxyethoxy)ethyl]-5H-pyrrolo[3,2-d]pyrimidin-4-yl}amino)phenoxy]phenyl}-2,2-dimethylpropan-1-ol,

1-[3-(2-chloro-4-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]-3,3-dimethylbutan-1-one,

N-(2-{4-[(3-methyl-4-{3-[(1E)-3-methylbut-1-en-1-yl]phenoxy}phenyl)amino]-5H-pyrrolo[3,2-d]pyrimidin-5-yl}ethyl)-2-(methylsulfonyl)acetamide, and

N-{2-[4-({3-chloro-4-[3-(1-cyanocyclopropyl)phenoxy]phenyl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethyl}-2-(methylsulfonyl)acetamide, or a salt thereof.

19. A compound represented by the formula:



(Ig)

wherein

W^g is $C(R^{1g})$ or N,

ring A^g is an optionally substituted benzene ring,

ring B^g is an optionally substituted nitrogen-containing heterocycle,

X^{1g} is $-NR^{3g}-Y^{1g}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-CHR^{3g}-$ wherein R^{3g} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3g} is optionally bonded to the carbon atom on the benzene ring for ring A^g to form an optionally substituted ring structure, and Y^{1g} is a bond, or a C_{1-4} alkylene or $-O-(C_{1-4}$ alkylene)-, each of which is optionally substituted, and

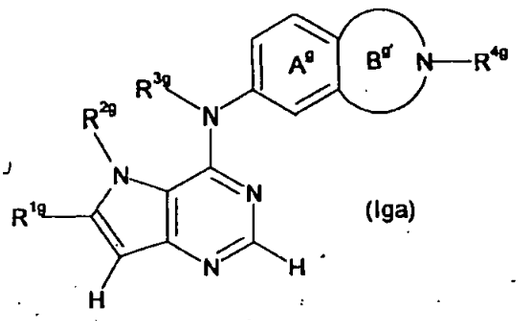
R^{1g} is a hydrogen atom, a halogen atom, or an optionally substituted group bonded via a carbon atom, a nitrogen atom or an oxygen atom,

R^{2g} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or R^{1g} and R^{2g}, or R^{2g} and R^{3g} are optionally bonded to form an optionally substituted ring structure,

or a salt thereof.

945

20. The compound of claim 19, which is a compound represented by the formula:



(Iga)

wherein R^{4g} is an optionally substituted hydrocarbon group, ring $B^{g'}$ is a 5 or 6-membered nitrogen-containing heterocycle optionally further substituted besides R^{4g}, and the other symbols are as defined in claim 19.

21. The compound of claim 20, wherein
R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2g} is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,
R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,
R^{4g} is (i) an optionally substituted C_{6-14} aryl-C_{1-8} alkyl group, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, (iii) a C_{1-8} alkyl group, or (iv) an optionally substituted C_{6-14} aryl group.

22. The compound of claim 20, wherein
R^{1g} is a hydrogen atom, a halogen atom, a cyano group or an optionally halogenated C_{1-6} alkyl group,
R^{2g} is
(i) a hydrogen atom,
(ii) a C_{1-6} alkyl group, or
(iii) a C_{1-6} alkyl group substituted by substituent(s) selected from the group consisting of
(a) $-O-(CH_2)_n-OH$,
(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

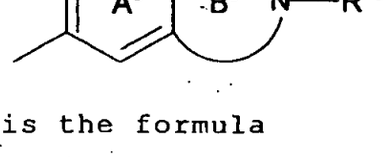
(c) $-NR^{5g}-CO-(CH_2)_n-SO_2-$optionally halogenated C_{1-4} alkyl,

(d) hydroxy, and

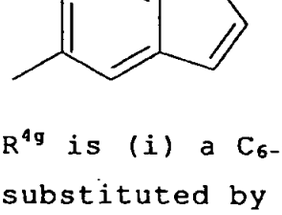
(e) amino

wherein n is an integer of 1 to 4, R^{5g} is a hydrogen atom or a C_{1-4} alkyl group, and $-(CH_2)_n-$ is optionally substituted by C_{1-4} alkyl,

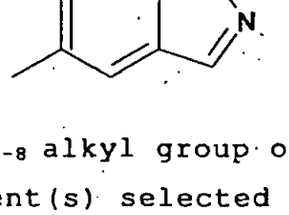
R^{3g} is a hydrogen atom or a C_{1-6} alkyl group,



is the formula



or



, and

R^{4g} is (i) a C_{6-14} aryl-C_{1-8} alkyl group optionally substituted by substituent(s) selected from the group consisting of halogen, C_{1-6} alkyl-carbamoyl and halo C_{1-6} alkoxy, (ii) an optionally substituted heterocyclyl-C_{1-8} alkyl group, or (iii) an optionally substituted C_{6-14} aryl group.

23. A compound selected from the following:

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indazol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-2-(methylsulfonyl)acetamide,

N-[2-(4-{[1-(3-fluorobenzyl)-1H-indol-5-yl]amino}-5H-pyrrolo[3,2-d]pyrimidin-5-yl)ethyl]-3-hydroxy-3-methylbutanamide,

N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]benzamide,

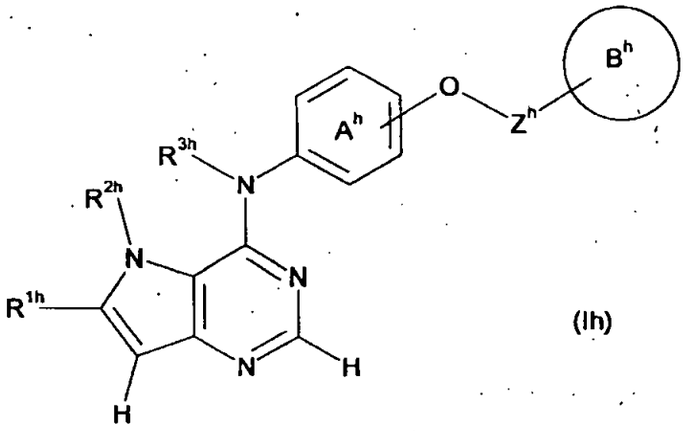
N-(tert-butyl)-3-[(5-{[5-(2-hydroxyethyl)-5H-

pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indazol-1-yl)methyl]benzamide, and

N-(tert-butyl)-6-[(5-{[5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}-1H-indol-1-yl)methyl]pyridine-2-carboxamide,

or a salt thereof.

24. A compound represented by the formula:



(Ih)

wherein

R^{1h} is a halogen atom or a halogenated C_{1-6} alkyl group,

R^{2h} is a hydrogen atom, or an optionally substituted group bonded via a carbon atom or a sulfur atom, or

R^{1h} and R^{2h}, or R^{2h} and R^{3h} are bonded to form an optionally substituted ring structure,

R^{3h} is a hydrogen atom or an optionally substituted aliphatic hydrocarbon group, or R^{3h} is optionally bonded to the carbon atom on the adjacent benzene ring to form an optionally substituted ring structure,

Z^h is a bond or an optionally substituted C_{1-3} alkylene,

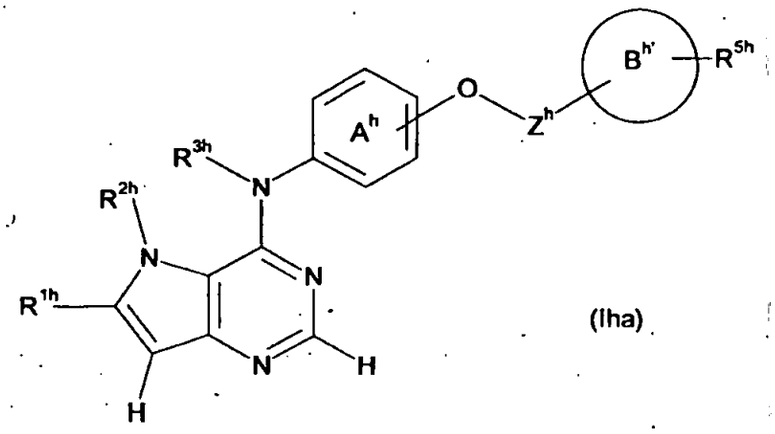
ring A^h is an optionally substituted benzene ring, and

ring B^h is (i) an optionally substituted C_{6-14} aryl group, (ii) an optionally substituted heterocyclic group, or (iii) an optionally substituted C_{5-8} cycloalkyl group,

or a salt thereof.

25. The compound of claim 24, which is a compound

represented by the formula:



(IIha)

wherein

R^{5h} is

(i) an optionally substituted amino group,
(ii) an optionally substituted carbamoyl group,
(iii) an optionally substituted ureido group,
(iv) an optionally substituted sulfamoyl group,
(v) an optionally substituted heterocyclic group,
(vi) an optionally substituted hydrocarbon group,
(vii) a halogen atom, or
(viii) an optionally substituted carboxyl group, and

ring $B^{h'}$ is (i) a C_{6-14} aryl group, (ii) a heterocyclic group, or (iii) a C_{5-8} cycloalkyl group, each of which is optionally further substituted besides R^{5h}, and the other symbols are as defined in claim 24.

26. A compound selected from the following:
N-(3-{2-chloro-4-[(6-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidin-4-yl)amino]phenoxy}phenyl)cyclopropanecarboxamide,
6-chloro-N-{3-chloro-4-[3-(trifluoromethyl)phenoxy]phenyl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-4-amine,
N-[3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)phenyl]cyclopropanecarboxamide, and

N-(tert-butyl)-3-(2-chloro-4-{[6-chloro-5-(2-hydroxyethyl)-5H-pyrrolo[3,2-d]pyrimidin-4-yl]amino}phenoxy)benzamide,
or a salt thereof.

27. A prodrug of the compound of any one of claims 1 to 26.

28. A pharmaceutical agent comprising any one of claims 1 to 26 or a salt thereof, or a prodrug thereof.

29. The pharmaceutical agent of claim 28, which is a tyrosine kinase inhibitor.

30. The pharmaceutical agent of claim 28, which is an agent for the prophylaxis or treatment of cancer.

31. The pharmaceutical agent of claim 30, wherein the cancer is breast cancer, ovarian cancer, colorectal cancer, gastric cancer, esophagus cancer, prostate cancer, lung cancer, pancreatic cancer or kidney cancer.

32. A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of any one of claims 1 to 26 or a salt thereof, or a prodrug thereof, to the mammal.

33. Use of the compound of any one of claims 1 to 26 or a salt thereof, or a prodrug thereof, for the production of an agent for the prophylaxis or treatment of cancer.

SEQUENCE LISTING

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<151> 2005-12-02

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348

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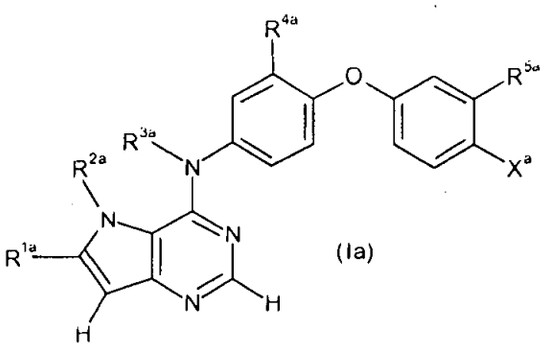
Para códigos de tres letras y otras abreviaturas, referirse a las "Notas de Instrucciones de Códigos y Abreviaturas" que aparecen en inicio de cada punto regular del Boletín Oficial PCT.

(54) Titulo: COMPUESTO HETEROCICLICO FUSIONADO



(Ia)

(57) Resumen: La presente invención proporciona un compuesto representado por la fórmula: en donde R^{1a} es un átomo de hidrógeno, R^{2a} es un grupo alquilo de C_{1-6} sustituido por un grupo representado por $-NR^{6a}-CO-(CH_2)_n-SO_2-$ opcionalmente alquilo de C_{1-4} halogenado en donde n es un número entero de 1 a 4, R^{6a} es un átomo de hidrógeno o grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido por alquilo de C_{1-4}, R^{3a} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, R^{4a} es un átomo de halógeno o un grupo alquilo de C_{1-4}, R^{5a} es un átomo de halógeno o un grupo alquilo de C_{1-4}, y X^a es un átomo de hidrógeno o un átomo de halógeno, o una sal del mismo. El compuesto de la presente invención tiene una acción inhibidora de tirosina cinasa superior, el altamente seguro, y es suficientemente satisfactorio como un producto farmacéutico.

COMPUESTO HETEROCICLICO FUSIONADO

CAMPO DE LA INVENCION

La presente invención se refiere a un compuesto fusionado de pirimidina con actividad inhibitoria de receptor de tirosina cinasa de factor de crecimiento, que es útil para la prevención o tratamiento de cáncer, uno de sus métodos de producción su uso.

ANTECEDENTES DE LA INVENCION

El gen de factor de crecimiento celular y de receptor de factor de crecimiento se denomina protooncogén y juega un papel clave en la patología de tumor humano. La familia de receptores de factor de crecimiento de células epiteliales (erbB) incluye EGFR, HER2, HER3 y HER4, que son de tipo tirosina cinasas del receptor de tipo I. Estas familias erbB se expresan en diversos grupos celulares e intervienen profundamente en el control del crecimiento y la diferenciación celular y el control de la supresión de la muerte celular (supresión de apoptosis). Por ejemplo, se sabe empíricamente que la elevada expresión de EGFR y HER2, y la activación homeostática de receptores transforma las células.

También se sabe que la expresión elevada y la expresión simultánea de cada uno de estos receptores son factores de mal pronóstico en diversos pacientes con cáncer.

Estos receptores se fijan a muchos ligandos peptídicos tales como EGF, TGFα y similares, y la fijación de

los ligandos favorece la homo- o heterodimerización de los receptores. Esto induce la actividad de cinasa por autofosforilación o transfosforilación de los receptores, y causa la activación de la trayectoria de señalización en corriente descendente (MAPK, Akt) a través de una proteína fijada a un residuo de tirosina fosforilada particular. Este es el mecanismo de actividad de receptor de los antes mencionados crecimiento celular, diferenciación, supresión de muerte celular y similares, que se consideran responsables de la elevada expresión de receptores en cáncer y degeneración maligna de cáncer debido al aumento tópico de la concentración de ligando.

Muchos tumores malignos se asocian con elevada expresión de EGFR o HER2. Por ejemplo, se pueden mencionar cáncer de mama (20-30%), cáncer de ovario (20-40%), cáncer de pulmón de células no pequeñas (30-60%), cáncer colorectal (40-80%), cáncer de próstata (10-60%), cáncer de vejiga (30-60%), cáncer de riñón (20-40%) y similares. Además, están correlacionados la expresión del receptor y el pronóstico, y la expresión del receptor es un factor de mal pronóstico en cáncer de mama, cáncer de pulmón de células no pequeñas y similares.

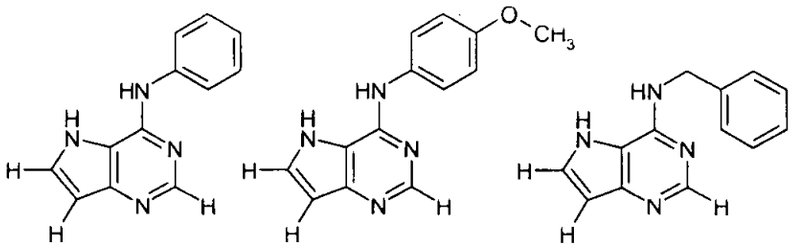
En años recientes, el uso clínico de un anticuerpo humanizado anti-HER2 (Trastuzumab) contra HER2 con elevada expresión en cáncer de mama, el estudio clínico de anticuerpo

anti-EGFR y estudios clínicos de varios inhibidores de receptores de enzimas de bajo peso molecular han demostrado un potencial de estos fármacos contra HER2 o EGFR para fármacos terapéuticos contra cáncer. Si bien estos fármacos muestran una acción inhibitoria de crecimiento de tumor en estudios clínicos y no clínicos, es sabido que inducen la inhibición de la actividad de receptores de enzimas y la supresión de la trayectoria de señalización en corriente descendente. En consecuencia, un compuesto inhibidor de EGFR o HER2 cinasa, o inhibidor de la activación de EGFR o HER2 cinasa es efectiva como fármaco terapéutico contra el cáncer.

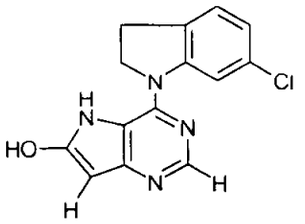
Como compuesto que inhibe el tipo de receptor de tirosina cinasas representado por HER2/EGFR cinasa, se conocen compuestos heterocíclicos fusionados (por ejemplo, WO97/13771, WO98/02437, WO00/44728), derivados de quinazolina (por ejemplo, WO02/02552, WO01/98277, WO03/049740, WO03/050108), derivados de tienopirimidina (por ejemplo, WO03/053446), derivados de azol aromático (por ejemplo, WO98/03648, WO01/77107, WO03/031442) y similares; sin embargo, hasta el momento no hay sustancia inhibidora de HER2 cinasa que se haya comercializado como fármaco terapéutico contra el cáncer.

Respecto de los derivados pirrolo[3,2-d]pirimidina, los siguientes compuestos se conocen como compuestos con actividad inhibitoria del crecimiento celular (Khim.-Farm.

Zh., 1982, 16, 1338-1343; Collect. Czech. Chem. Commun., 2003, 68, 779-791).



Como compuesto con actividad inhibitoria de receptor de tipo tirosina cinasa, se conoce el siguiente derivado pirrolo[3,2-d]pirimidina (WO96/40142, WO98/23613).



Además, respecto de derivados pirazolo[4,3-d]pirimidina, se conocen derivados 3,5,7-trisustituidos de pirazolo[4,3-d]pirimidina como compuestos con acción inhibitoria de CDK, se conoce una acción inhibitoria del crecimiento celular y/o una acción inductora de apoptosis (EP-A-1348707), y se conocen derivados de 3-isopropilpirazolo[4,3-d]pirimidina como compuestos con actividad inhibitoria de CDK1/ciclina B (Bioorganic & Medicinal Chemistry Letters, 2003, 13, 2989-2992). Además, se ha informado la síntesis de derivados 3-metilpirazolo[4,3-d]pirimidina (The Journal of Organic Chemistry, 1956, 21, 833-836)..

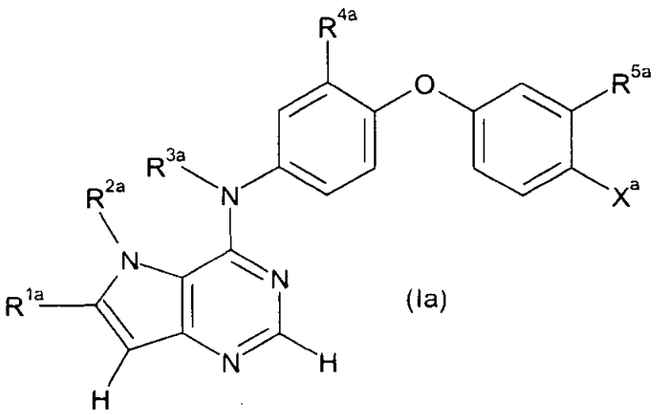
BREVE DESCRIPCION DE LA INVENCION

La presente invención está dirigida a proveer un compuesto con acción inhibitoria superior de tirosina cinasa, de baja toxicidad y altamente seguro como producto farmacéutico.

Los presentes inventores han realizado estudios intensivos en un intento por solucionar los problemas antes mencionados y hallaron que los compuestos representados por las siguientes fórmulas (Ia)-(Ih) y sus sales tienen una acción inhibitoria superior de tirosina cinasa. Otros estudios dieron por resultado la terminación de la presente invención.

Conforme a ello, la presente invención se refiere a lo siguiente.

[1a] Un compuesto representado por la fórmula:



(Ia)

en donde

R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} sustituido con un

grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6a}-CO-(CH_2)_n-SO_2-$

en donde n es un número entero de 1 a 4, R^{6a} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3a} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

R^{4a} es un átomo de halógeno o un grupo alquilo de C_{1-6},

R^{5a} es un átomo de halógeno o un grupo alquilo de C_{1-6}, y

X^a es un átomo de hidrógeno o un átomo de halógeno,

o una de sus sales,

con la condición de que se excluya N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida.

[2a] El compuesto del punto [1a] antes mencionado, en donde X^a es un átomo de hidrógeno.

[3a] El compuesto del punto [2a] antes mencionado, en donde

R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-$alquilo de C_{1-4}

en donde R^{6aa} es un átomo de hidrógeno o un grupo metilo, R^{7a} y R^{8a} son iguales o diferentes y cada uno es un

átomo de hidrógeno o un grupo metilo,

R^{3a} es un átomo de hidrógeno,

R^{4a} es un átomo de cloro o un grupo metilo, y

R^{5a} es un átomo de flúor, un átomo de cloro o un grupo metilo.

[4a] El compuesto del punto [3a] antes mencionado, en donde R^{7a} y R^{8a} son grupos metilo.

[5a] Un compuesto seleccionado de los siguientes:

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N,2-dimetil-2-(metilsulfonil)propanamida,

N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

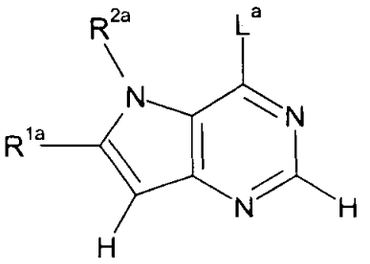
N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida, y

N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

o una de sus sales, o uno de sus hidratos.

[6a] Un profármaco del compuesto del punto [1a] antes mencionado.

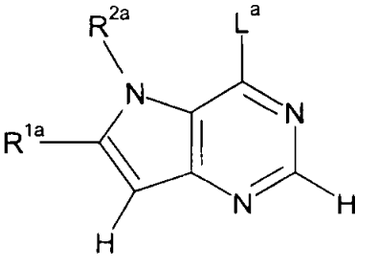
[7a] Un método de producción del compuesto del punto [1a] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIa)

en donde L^a es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIa)

en donde G^a es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[8a] Un agente farmacéutico que comprende el compuesto del punto [1a] antes mencionado o una de sus sales o uno de sus profármacos.

[9a] El agente farmacéutico del punto [8a] antes mencionado, que es un inhibidor de la tirosina cinasa.

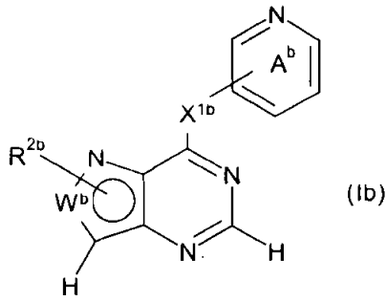
[10a] El agente farmacéutico del punto [8a] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[11a] El agente farmacéutico del punto [10a] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[12a] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto antes mencionado [1a] o una de sus sales o uno de sus profármacos, al mamífero.

[13a] Uso del compuesto del punto antes mencionado [1a] o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

[1b] Un compuesto representado por la fórmula:



(Ib)

en donde

W^b es $C(R^{1b})$ o N,

el anillo A^b es un anillo piridina opcionalmente sustituido,

X^{1b} es $-NR^{3b}-Y^{1b}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ o $-CHR^{3b}-$

en donde R^{3b} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3b} está opcionalmente unido al átomo de carbono en el anillo piridina para que el anillo A^b forme una estructura de anillo opcionalmente sustituida, e Y^{1b} es un enlace, o un alquileno de C_{1-4} u $-O-$(alquileno de C_{1-4})$-$, cada uno de los cuales está opcionalmente sustituido, y

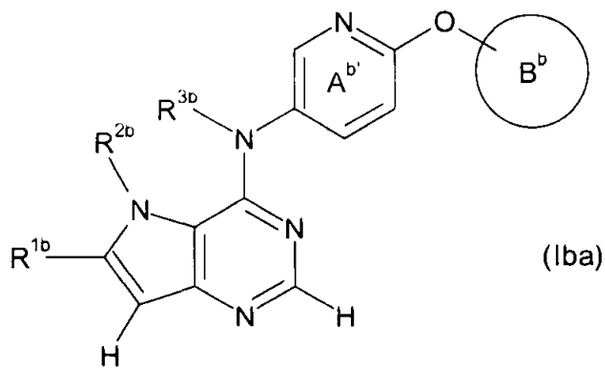
R^{1b} es un átomo de hidrógeno, un átomo de halógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2b} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1b} y R^{2b}, o R^{2b} y R^{3b} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

o una de sus sales.

[2b] El compuesto del punto [1b] antes mencionado, que es un compuesto representado por la fórmula:



(Iba)

en donde el anillo $A^{b'}$ es un anillo piridina también opcionalmente sustituido, el anillo B^b es un grupo arilo de C_{6-14} opcionalmente sustituido, y los otros símbolos son como se definieron con anterioridad.

[3b] El compuesto del punto [2b] antes mencionado, en donde

R^{1b} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2b} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-$alquilo de C_{1-4}

en donde R^{6ba} es un átomo de hidrógeno o un grupo metilo, n1 es un número entero de 1 a 4, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

en donde R^{6bb} es un átomo de hidrógeno o un grupo metilo, n2 es un número entero de 1 a 4, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4}, y

(iv) hidroxi,

R^{3b} es un átomo de hidrógeno,

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo, y

el anillo B^b es un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

[4b] El compuesto del punto [2b] antes mencionado, en donde

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con halógeno, y

el anillo B^b es un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

[5b] Un compuesto seleccionado de los siguientes:

2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-

d]pirimidin-5-il]etoxi}etanol,

N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

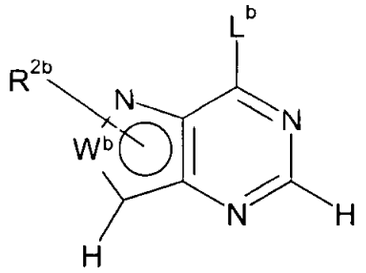
N-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida, y

N-(ter-butil)-3-[(3-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}piridin-2-il)oxi]benzamida,

o una de sus sales.

[6b] Un profármaco del compuesto del punto [1b] antes mencionado.

[7b] Un método de producción del compuesto del punto [1b] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIb)

en donde L^b es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

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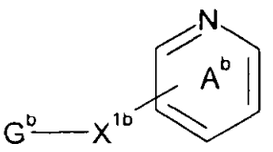
o una de sus sales y un compuesto representado por la fórmula:



(IIIb)

en donde G^b es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[8b] Un agente farmacéutico que comprende el compuesto del punto [1b] antes mencionado o una de sus sales o uno de sus profármacos.

[9b] El agente farmacéutico del punto [8b] antes mencionado, que es un inhibidor de la tirosina cinasa.

[10b] El agente farmacéutico del punto [8b] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

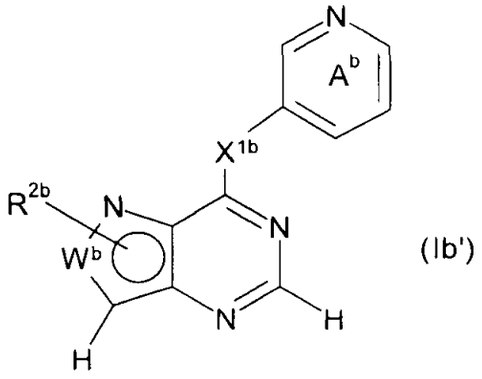
[11b] El agente farmacéutico del punto [10b] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[12b] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1b] antes

mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[13b] Uso del compuesto del punto [1b] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

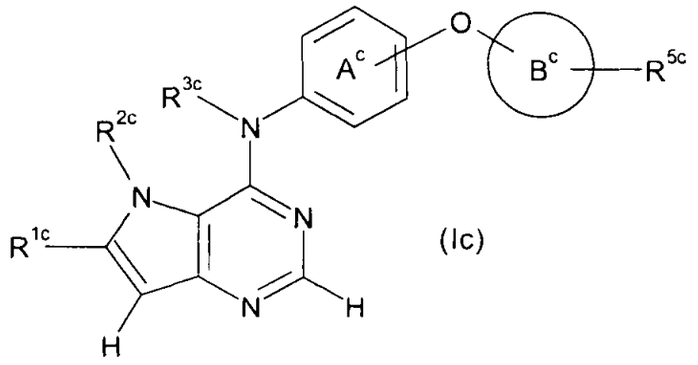
[14b] El compuesto del punto [1b] antes mencionado, que es un compuesto representado por la fórmula:



(Ib')

en donde cada símbolo es como se definió con anterioridad.

[1c] Un compuesto representado por la fórmula:



(Ic)

en donde

R^{1c} es un átomo de hidrógeno, o un grupo

opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxigeno,

R^{2c} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1c} y R^{2c}, o R^{2c} y R^{3c} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3c} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3c} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^c es un anillo benceno opcionalmente sustituido,

R^{5c} es

(i) un grupo amino opcionalmente sustituido,

(ii) un grupo carbamoilo opcionalmente sustituido,

(iii) un grupo ureido opcionalmente sustituido,

(iv) un grupo sulfamoilo opcionalmente sustituido,

(v) un grupo heterocíclico opcionalmente sustituido,

(vi) un grupo alcoxi de C_{2-6} opcionalmente sustituido,

(vii) un grupo aminometilo opcionalmente sustituido,

(viii) un grupo carbamoilmetilo opcionalmente sustituido,

(ix) un grupo alquilsulfonilo opcionalmente sustituido, o

(x) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido además de R^{5c},

o una de sus sales,

con la condición de que se excluyan

clorhidrato de N-(ter-butil)-4-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida,

4-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2,2-dimetilpropil)benzamida,

3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzonitrilo,

3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzonitrilo,

clorhidrato de 3-[2-cloro-4-(6,7-dihidro-9H-pirimido[4',5':4,5]pirrolo[2,1-c][1,4]oxazin-4-ilamino)fenoxi]benzonitrilo, y

(2E)-N-[(2E)-3-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5-metil-5H-pirrolo[3,2-d]pirimidin-6-il)prop-2-en-1-il]-4-(dimetilamino)but-2-enamida.

[2c] El compuesto del punto [1c] antes mencionado,

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en donde R^{1c} es un átomo de hidrógeno.

[3c] Un compuesto seleccionado de los siguientes:

2-{2-[4-({3-cloro-4-[3-(1,3-tiazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol,

N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida,

3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2-hidroxi-1,1-dimetiletil)benzamida,

N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

N-(3-{2-cloro-4-[(6-ciano-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida,

N-(ter-butil)-5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]acetamida,

N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-{2-[4-({3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida,

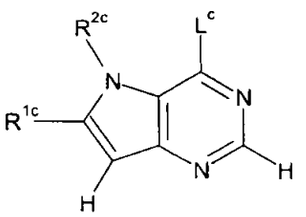
2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol, y

N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

o una de sus sales.

[4c] Un profármaco del compuesto del punto [1c] antes mencionado.

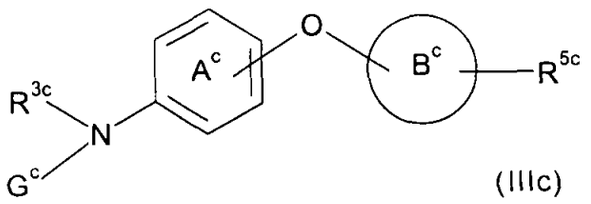
[5c] Un método de producción del compuesto del punto [1c] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIc)

en donde L^c es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIc)

en donde G^c es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[6c] Un agente farmacéutico que comprende el compuesto del punto [1c] antes mencionado o una de sus sales o uno de sus profármacos.

[7c] El agente farmacéutico del punto [6c] antes mencionado, que es un inhibidor de la tirosina cinasa.

[8c] El agente farmacéutico del punto [6c] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[9c] El agente farmacéutico del punto [8c] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

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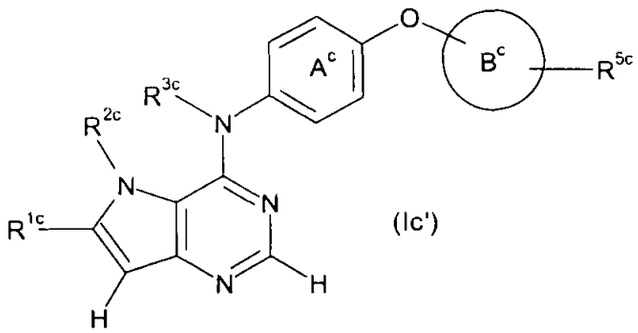
[10c] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1c] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[11c] Uso del compuesto del punto [1c] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

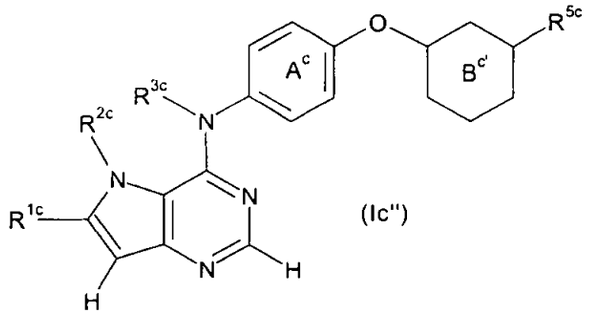
[12c] El compuesto del punto [1c] antes mencionado, que es un compuesto representado por la fórmula:



(Ic')

en donde cada símbolo es como se definió con anterioridad.

[13c] El compuesto del punto [1c] antes mencionado, que es un compuesto representado por la fórmula:



(Ic'')

en donde el anillo $B^{c'}$ es un grupo fenilo o un grupo ciclohexilo, cada uno de los cuales está también opcionalmente sustituido además de R^{5c}, y los otros símbolos son como se definieron con anterioridad.

[14c] El compuesto del punto [1c] antes mencionado, en donde

R^{2c} es un grupo alquilo de C_{1-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6c}-CO-$(CH_2)_n$-SO_2-,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4}o.

[15c] El compuesto del punto [1c] antes mencionado, en donde

R^{1c} es un átomo de hidrógeno o un grupo ciano,

R^{2c} es un grupo alquilo de C_{1-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo monoalquil de C_{1-6}-amino,

(iii) un grupo dialquil de C_{1-6}-amino,

(iv) un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado,

(v) un grupo hidroxi-alcanoil de C_{1-6}-amino,

(vi) un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno,

(vii) un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino,

(viii) un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(ix) un grupo alquilsulfonil de C_{1-6}-alcanoil de C_{1-6}-amino,

(x) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(xi) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xii) un grupo carbamoilo,

(xiii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiv) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xvi) un grupo aril de C_{6-14}-alquil de C_{1-6}-carbamoilo,

(xvii) un grupo alquinil C_{2-6}-carbamoilo,

(xviii) un grupo piperidil-alquil de C_{1-6}-carbamoilo,

(xix) un grupo morfolinil-alquil de C_{1-6}-carbamoilo,

(xx) un grupo cicloalquil de C_{3-7}-carbamoilo opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6},

(xxi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xxii) un grupo ureido,

(xxiii) un grupo alquil de C_{1-6}-ureido,

(xxiv) un grupo cicloalquil de C_{3-7}-ureido,

(xxv) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxvi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

(xxvii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

(xxviii) un grupo alcoxi de C_{2-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} y alquil de C_{1-6}-carbamoilo,

(xxix) un grupo carbamoilmetilo opcionalmente sustituido con alquilo de C_{1-6},

(xxx) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(xxxi) un grupo alquil de C_{1-6}-sulfonilo que opcionalmente contiene cicloalquilo de C_{3-7} o halógeno, o

(xxxii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[16c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{5c} es un grupo amino opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6},

(ii) alcanoilo de C_{1-6} opcionalmente halogenado,

(iii) hidroxi-alcanoilo de C_{1-6},

(iv) alcanoilo de C_{1-6} que tiene hidroxi y halógeno,

(v) cicloalquil de C_{3-7}-alcanoilo de C_{1-6},

(vi) alcanoilo de C_{1-6} que tiene cicloalquilo de C_{3-7} y halógeno,

(vii) alquil de C_{1-6}-sulfonil-alcanoilo de C_{1-6},

(viii) cicloalquil de C_{3-7}-carbonilo, y

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(ix) alcoxi de C_{1-6}-carbonilo,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6c}-CO-$(CH_2)_n$-SO_2,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente

sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[17c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{5c} es un grupo carbamoilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6} opcionalmente halogenado,

(ii) hidroxi-alquilo de C_{1-6},

(iii) alcoxi de C_{1-6}-alquilo de C_{1-6},

(iv) aril de C_{6-14}-alquilo de C_{1-6},

(v) alquinilo de C_{2-6},

(vi) piperidil-alquilo de C_{1-6},

(vii) morfolinil-alquilo de C_{1-6}, y

(viii) cicloalquilo de C_{3-7} opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6},

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

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(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO$-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) $-SO_2$-alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[18c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{5c} es un grupo ureido opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6},

(ii) cicloalquilo de C_{3-7}, y

(iii) grupo heterociclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de

nitrógeno, un átomo de oxígeno y un átomo de azufre,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino,

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente

sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[19c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{5c} es un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un

átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[20c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{5c} es un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -

NR^{6c}-CO-$(CH_2)_n$-SO_2-,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

(ix) amino,

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[21c] El compuesto de de cualquiera de los puntos [16c] a [20c] antes mencionados, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) -NH-CO-$CR^{7c}R^{8c}$-SO_2-alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) -NR^{6cb}-CO-$(CH_2)_{n2}$-OH

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en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino.

[22c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6ca}-CO-(CH_2)_{n1}-SO_2-$

en donde n1 es un número entero de 1 a 4, R^{6ca} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene alquil de C_{1-6}-sulfonilo, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6},

(iii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iv) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(v) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(vi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente sustituido con cicloalquilo de C_{3-7}, o

(vii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[23c] El compuesto del punto [22c] antes

mencionado, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por -NH-CO-$CR^{7c}R^{8c}$-SO_2-alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4}.

[24c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por -NR^{6cb}-CO-$(CH_2)_{n2}$-OH

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_{n2}$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene hidroxi, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6},

(iii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos

seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iv) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(v) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(vi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente sustituido con cicloalquilo de C_{3-7}, o

(vii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[25c] El compuesto del punto [24c] antes mencionado, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NH-CO-CH_2-CR^{9c}R^{10c}-OH$

en donde R^{9c} y R^{10c} son iguales o diferentes y cada uno es un grupo alquilo de C_{1-4}.

[26c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un

grupo representado por $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil de C_{1-6}-amino,

(v) un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino,

(vii) un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(viii) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(ix) un grupo alcoxi de C_{1-6}-carbonil-amino,

(x) un grupo carbamoilo,

(xi) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiii) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xv) un grupo ureido,

(xvi) un grupo alquil de C_{1-6}-ureido,

(xvii) un grupo cicloalquil de C_{3-7}-ureido,

(xviii) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xix) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xx) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con opcionalmente halogenado alquilo de C_{1-6} o alcoxi de C_{1-6}-carbonilo,

(xxi) un grupo alcoxi de C_{2-6} opcionalmente halogenado,

(xxii) un grupo alquil de C_{1-6}-sulfonilo, o

(xxiii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes

seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[27c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con hidroxi,

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene hidroxi, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iii) un grupo cicloalquil de C_{3-7}-carbamoilo opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6},

(iv) un grupo aril de C_{6-14}-alquil de C_{1-6}-carbamoilo,

(v) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(vi) un grupo morfolinil-alquil de C_{1-6}-carbamoilo,

(vii) un grupo alquinil C_{2-6}-carbamoilo,

(viii) un grupo carbamoilmetilo opcionalmente sustituido con alquilo de C_{1-6},

(ix) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(x) un grupo aminometilo opcionalmente sustituido con alcoxi de C_{1-6}-carbonilo, o

(xi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente sustituido con cicloalquilo de C_{3-7}, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[28c] El compuesto del punto [1c] o del punto [12c] antes mencionados, en donde

R^{1c} es un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2c} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6c}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil de C_{1-6}-amino,

(v) un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino,

(vii) un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(viii) un grupo alquilsulfonil de C_{1-6}-alcanoil de C_{1-6}-amino,

(ix) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(x) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xi) un grupo carbamoilo,

(xii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xvi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xvii) un grupo ureido,

(xviii) un grupo alquil de C_{1-6}-ureido,

(xix) un grupo cicloalquil de C_{3-7}-ureido,

(xx) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6}, o

(xxii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

[29c] El compuesto de cualquiera de los puntos [14c] a [20c] y [28c] antes mencionados, en donde el anillo B^c es un grupo fenilo o un grupo ciclohexilo, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno, y está sustituido con R^{5c} en la posición meta del grupo fenilo o la posición β del grupo ciclohexilo.

[30c] El compuesto de cualquiera de los puntos [22c] a [27c] antes mencionados, en donde el anillo B^c es un grupo fenilo también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno, cuyo fenilo está sustituido con R^{5c} en la posición meta del grupo fenilo.

[1d] Un compuesto representado por la fórmula:

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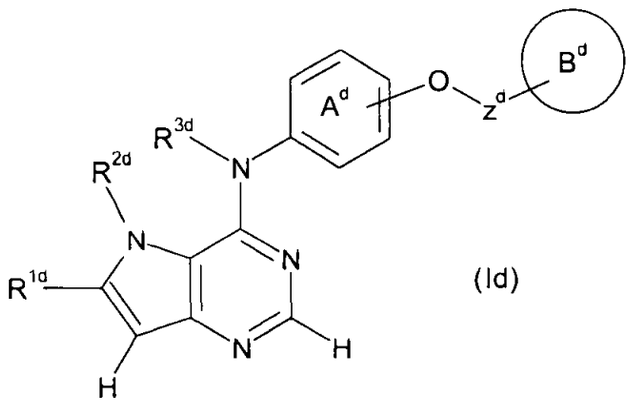

(Id)

en donde

R^{1d} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2d} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1d} y R^{2d}, o R^{2d} y R^{3d} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3d} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3d} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^d es un anillo benceno opcionalmente sustituido,

Z^d es un alquileno de C_{1-3} opcionalmente sustituido,

el anillo B^d es un grupo heterocíclico opcionalmente sustituido,

o una de sus sales,

con la condición de que se excluyan

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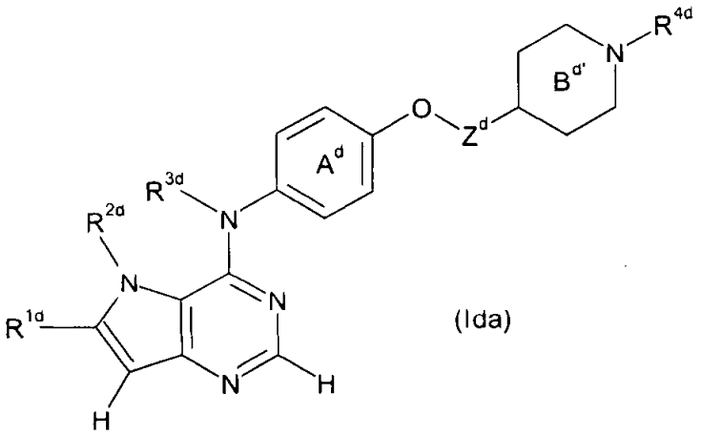
5-[(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)metil]-2-furoato de etilo,

ácido 5-[(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)metil]-2-furancarboxílico,

2-[2-(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol, y

N-[2-(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida.

[2d] El compuesto del punto [1d] antes mencionado, que es un compuesto representado por la fórmula:



(Ida)

en donde R^{4d} es un grupo acilo o un grupo ureido opcionalmente sustituido, el anillo $B^{d'}$ es un grupo piperidilo también opcionalmente sustituido además de R^{4d}, y los otros símbolos son como se definieron con anterioridad.

[3d] Un compuesto seleccionado de los siguientes:

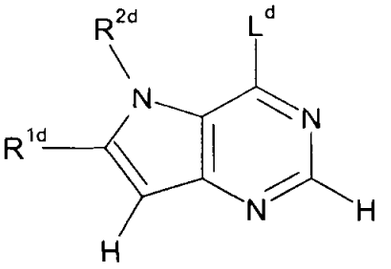
4-{[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]metil}piperidin-1-carboxilato de ter-butilo, y

4-[(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)metil]piperidin-1-carboxilato de ter-butilo,

o una de sus sales.

[4d] Un profármaco del compuesto del punto [1d] antes mencionado.

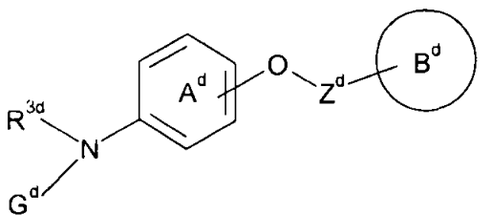
[5d] Un método de producción del compuesto del punto [1d] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IId)

en donde L^d es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIId)

en donde G^d es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con

anterioridad,

o una de sus sales.

[6d] Un agente farmacéutico que comprende el compuesto del punto [1d] antes mencionado o una de sus sales o uno de sus profármacos.

[7d] El agente farmacéutico del punto [6d] antes mencionado, que es un inhibidor de la tirosina cinasa.

[8d] El agente farmacéutico del punto [6d] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[9d] El agente farmacéutico del punto [8d] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[10d] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1d] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[11d] Uso del compuesto del punto [1d] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

[12d] El compuesto del punto [1d] antes mencionado,

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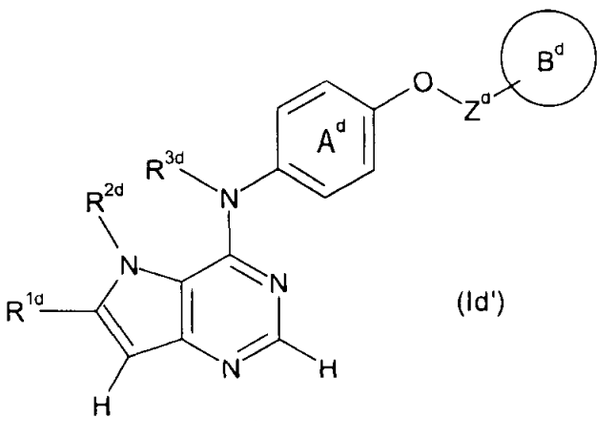
que es un compuesto representado por la fórmula:



(Id')

en donde cada símbolo es como se definió con anterioridad.

[13d] El compuesto del punto [2d] antes mencionado, en donde

R^{1d} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2d} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6d}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6d}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6d} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3d} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^d es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

Z^d es metileno,

el anillo $B^{d'}$ es un grupo piperidilo, y

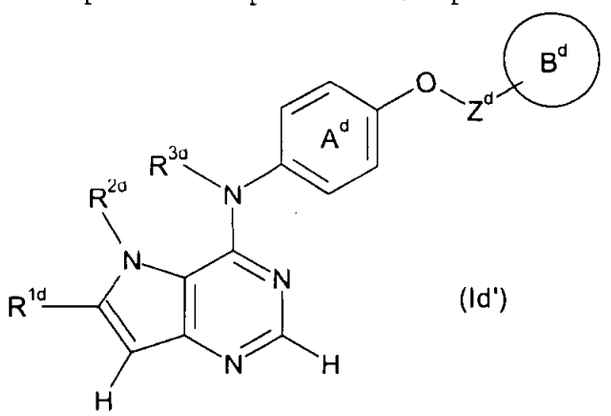
R^{4d} es un grupo alcoxi de C_{1-6}-carbonilo, un grupo cicloalquil de C_{5-8}-carbonilo, un grupo alquil de C_{1-6}-ureido o un grupo cicloalquil de C_{5-8}-ureido.

[14d] El compuesto del punto [2d] antes mencionado, en donde

R^{3d} es un átomo de hidrógeno, y

el anillo A^d es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[1e] Un compuesto representado por la fórmula:



(Id')

en donde

R^{1e} es un átomo de hidrógeno, o un grupo

opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2e} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1e} y R^{2e}, o R^{2e} y R^{3e} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3e} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3e} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^e es un anillo benceno opcionalmente sustituido,

R^{5e} es

(i) un grupo alquilo lineal sustituido con grupo heterocíclico opcionalmente sustituido,

(ii) un grupo alquilo lineal sustituido con imino opcionalmente sustituido,

(iii) un grupo alquilo lineal sustituido con arilo opcionalmente sustituido, que está también opcionalmente halogenado o hidroxilado,

(iv) un grupo alquilo ramificado opcionalmente sustituido,

(v) un grupo alquenilo opcionalmente sustituido,

(vi) un grupo hidroxi sustituido con arilo opcionalmente sustituido,

(vii) un grupo hidroxi sustituido con alquilo de C_{1-6},

(viii) un grupo hidroxi sustituido con alquilo de C_{2-6} halogenado,

(ix) un grupo alquilo de C_{2-6} halogenado,

(x) un grupo cicloalquilo opcionalmente sustituido, o

(xi) un grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con arilo opcionalmente sustituido, y

el anillo B^e es un grupo arilo de C_{6-14} también opcionalmente sustituido además de R^{5e},

o una de sus sales,

con la condición de que se excluyan

diclorhidrato de 2-(2-{4-[(3-cloro-4-{4-[3-(1H-imidazol-1-il)propil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol,

2-(2-{4-[(3-cloro-4-{4-[4-(1H-1,2,3-triazol-1-il)butil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol, y

1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}etanona.

[2e] El compuesto del punto [1e] antes mencionado, en donde el "grupo alquilo lineal sustituido con grupo heterocíclico opcionalmente sustituido" para R^{5e} es

(i) un grupo metilo sustituido con grupo

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heterocíclico opcionalmente sustituido, o

(ii) un grupo alquilo lineal sustituido con grupo heterocíclico sustituido.

[3e] Un compuesto seleccionado de los siguientes:

2-[4-({3-cloro-4-[3-(1,1-difluoroetil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol,

O-etiloxima de (1Z)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona,

1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ol,

1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona,

N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida, y

N-{2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

o una de sus sales.

[4e] Un profármaco del compuesto del punto [1e] antes mencionado.

[5e] Un método de producción del compuesto del

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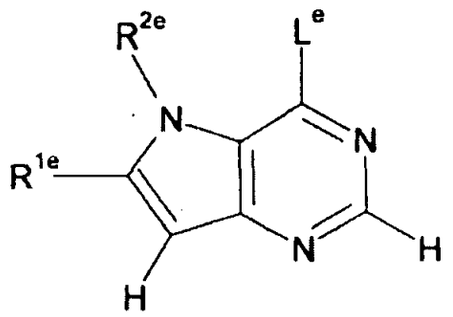
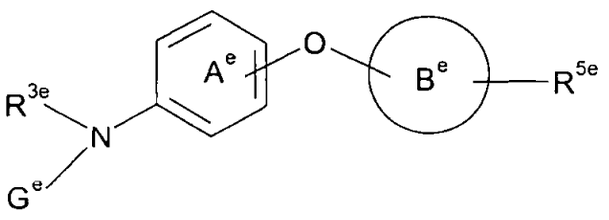
punto [1e] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIe)

en donde L^e es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIe)

en donde G^e es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[6e] Un agente farmacéutico que comprende el compuesto del punto [1e] antes mencionado o una de sus sales o uno de sus profármacos.

[7e] El agente farmacéutico del punto [6e] antes mencionado, que es un inhibidor de la tirosina cinasa.

[8e] El agente farmacéutico del punto [6e] antes

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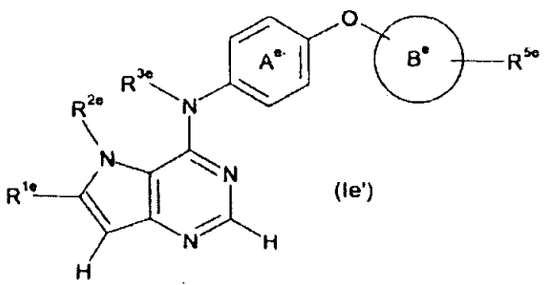
mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[9e] El agente farmacéutico del punto [8e] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[10e] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1e] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[11e] Uso del compuesto del punto [1e] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

[12e] El compuesto del punto [1e] antes mencionado, que es un compuesto representado por la fórmula:



(Ie')

en donde cada símbolo es como se definió con anterioridad.

[13e] El compuesto del punto [1e] antes mencionado,

en donde

R^{1e} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2e} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-NR^{6e}-CO-(CH_2)_n-SO_2$-alquilo de C_{1-4} opcionalmente halogenado,

(b) $-NR^{6e}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6e} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3e} es un átomo de hidrógeno,

el anillo A^e es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5e} es

(i) un grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6},

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(ii) un grupo alquilo de C_{1-6} lineal sustituido con hidroxiimino o alcoxi de C_{1-6}-imino,

(iii) un grupo alquilo de C_{1-6} lineal sustituido con arilo de C_{6-14}, que está también opcionalmente halogenado o hidroxilado,

(iv) un grupo alquilo de C_{3-6} ramificado opcionalmente halogenado,

(v) un grupo alquenilo C_{2-6},

(vi) un grupo hidroxi sustituido con arilo de C_{6-14},

(vii) un grupo hidroxi sustituido con alquilo de C_{1-6},

(viii) un grupo hidroxi sustituido con alquilo de C_{2-6} halogenado,

(ix) un grupo alquilo de C_{2-6} halogenado,

(x) un grupo cicloalquilo de C_{3-7} opcionalmente sustituido con ciano o carbamoilo, o

(xi) un grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con fenilo, y

el anillo B^e es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5e}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

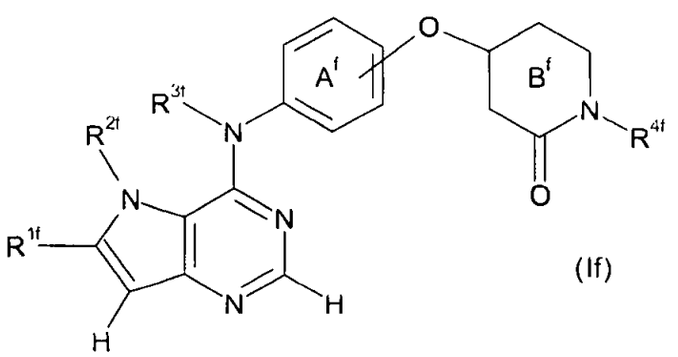
[14e] El compuesto del punto [13e] antes mencionado, en donde el "grupo alquilo de C_{1-6} heterociclilo- lineal de 5 a 8 miembros que contiene, además de átomos de

carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6}" para R^{5e} es

(i) un grupo heterociclil-metilo de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que tiene alquilo de C_{1-6}.

[1f] Un compuesto representado por la fórmula:



(If)

en donde

R^{1f} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2f} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1f} y R^{2f}, o R^{2f} y R^{3f} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3f} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3f} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^f es un anillo benceno opcionalmente sustituido,

el anillo B^f es un grupo piperidilo también opcionalmente sustituido además de R^{4f}, y

R^{4f} es (i) un grupo alquilo de C_{1-6} opcionalmente sustituido, o (ii) un grupo cicloalquilo de C_{5-8} opcionalmente sustituido,

o una de sus sales.

[2f] El compuesto del punto [1f] antes mencionado, en donde

R^{1f} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2f} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con

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$-NR^{6f}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6f} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3f} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^f es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

el anillo B^f es un grupo piperidilo, y

R^{4f} es (i) un grupo alquilo de C_{1-6} opcionalmente sustituido, o (ii) un grupo cicloalquilo de C_{5-8} opcionalmente sustituido.

[3f] El compuesto del punto [1f] antes mencionado, en donde

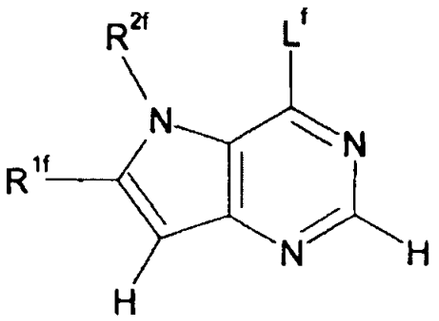
R^{3f} es un átomo de hidrógeno, y

el anillo A^f es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[4f] Un profármaco del compuesto del punto [1f] antes mencionado.

[5f] Un método de producción del compuesto del

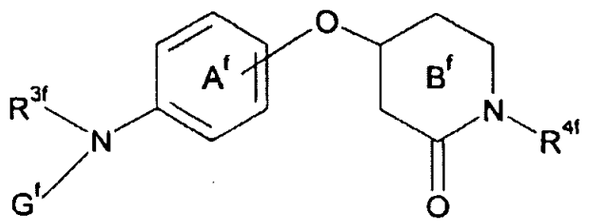
punto [1f] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIf)

en donde L^f es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIf)

en donde G^f es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[6f] Un agente farmacéutico que comprende el compuesto del punto [1f] antes mencionado o una de sus sales o uno de sus profármacos.

[7f] El agente farmacéutico del punto [6f] antes mencionado, que es un inhibidor de la tirosina cinasa.

[8f] El agente farmacéutico del punto [6f] antes

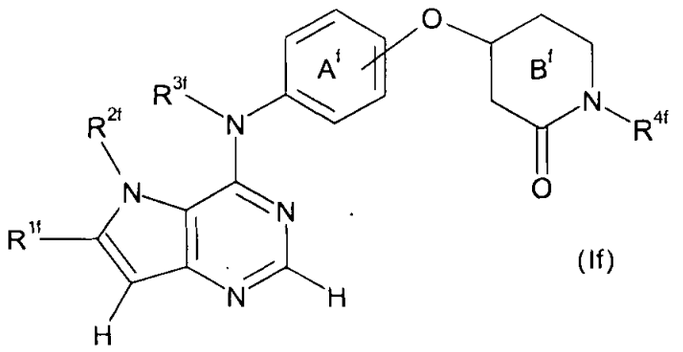
mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[9f] El agente farmacéutico del punto [8f] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[10f] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1f] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[11f] Uso del compuesto del punto [1f] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

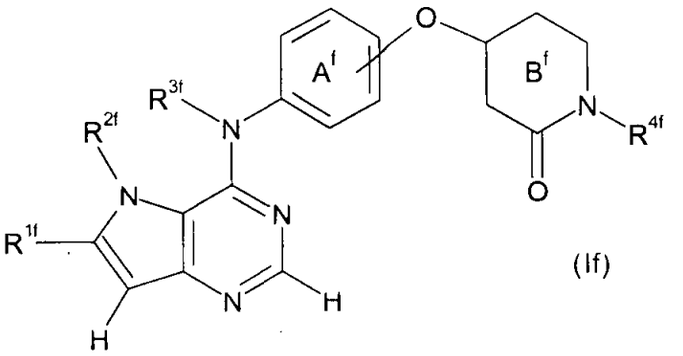
[12f] El compuesto del punto [1f] antes mencionado, que es un compuesto representado por la fórmula:



en donde cada símbolo es como se definió con

anterioridad.

[1g] Un compuesto representado por la fórmula:



(If)

en donde

W^g es $C(R^{1g})$ o N,

el anillo A^g es un anillo benceno opcionalmente sustituido,

el anillo B^g es un heterociclo con contenido de nitrógeno opcionalmente sustituido,

X^{1g} es $-NR^{3g}-Y^{1g}-$, -O-, -S-, -SO-, $-SO_2-$ o $-CHR^{3g}-$

en donde R^{3g} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3g} está opcionalmente unido al átomo de carbono en el anillo Benceno para el anillo A^g para formar una estructura de anillo opcionalmente sustituida, e Y^{1g} es un enlace, o un alquileno de C_{1-4} u -O-(alquileno de C_{1-4})-, cada uno de los cuales está opcionalmente sustituido, y

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de

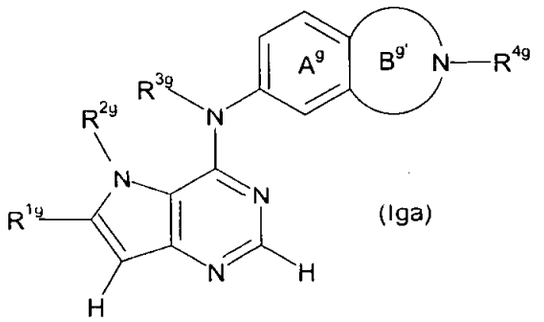
oxígeno,

R^{2g} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1g} y R^{2g}, o R^{2g} y R^{3g} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

o una de sus sales.

[2g] El compuesto del punto [1g] antes mencionado, que es un compuesto representado por la fórmula:



(Iga)

en donde R^{4g} es un grupo hidrocarburo opcionalmente sustituido, el anillo $B^{g'}$ es un heterociclo con contenido de nitrógeno de 5 ó 6 miembros también opcionalmente sustituido además de R^{4g}, y los otros símbolos son como se definieron con anterioridad.

[3g] El compuesto del punto [2g] antes mencionado, en donde

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es un átomo de hidrógeno o un grupo alquilo de

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C_{1-6} opcionalmente sustituido,

R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

R^{4g} es (i) un grupo aril de C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, (iii) un grupo alquilo de C_{1-8}, o (iv) un grupo arilo de C_{6-14} opcionalmente sustituido.

[4g] El compuesto del punto [2g] antes mencionado, en donde

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6}, o

(iii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) $-NR^{5g}-CO-(CH_2)_n-SO_2$-alquilo de C_{1-4} opcionalmente halogenado,

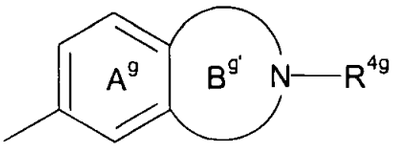
(d) hidroxi, y

(e) amino

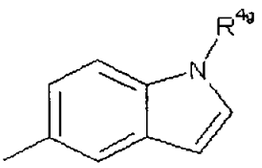
en donde n es un número entero de 1 a 4, R^{5g} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está

opcionalmente sustituido con alquilo de C_{1-4},

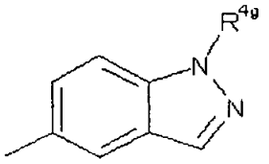
R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},



es la fórmula



o



y

R^{4g} es (i) un grupo aril de C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, alquil de C_{1-6}-carbamoilo y haloalcoxi de C_{1-6}, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, o (iii) un grupo arilo de C_{6-14} opcionalmente sustituido.

[5g] Un compuesto seleccionado de los siguientes:

N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

N-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida,

N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-

il)metil]benzamida,

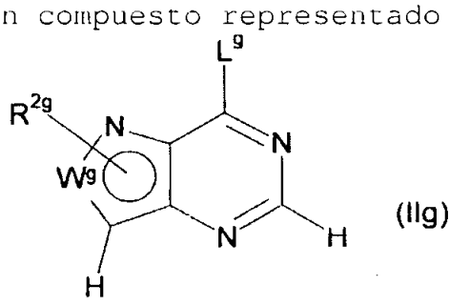
N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indazol-1-il)metil]benzamida, y

N-(ter-butil)-6-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piridin-2-carboxamida,

o una de sus sales.

[6g] Un profármaco del compuesto del punto [1g] antes mencionado.

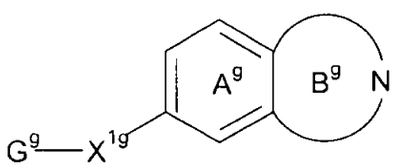
[7g] Un método de producción del compuesto del punto [1g] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:



(IIg)

en donde L^g es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIg)

en donde G^g es un átomo de hidrógeno o un átomo de

metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[8g] Un agente farmacéutico que comprende el compuesto del punto [1g] antes mencionado o una de sus sales o uno de sus profármacos.

[9g] El agente farmacéutico del punto [8g] antes mencionado, que es un inhibidor de la tirosina cinasa.

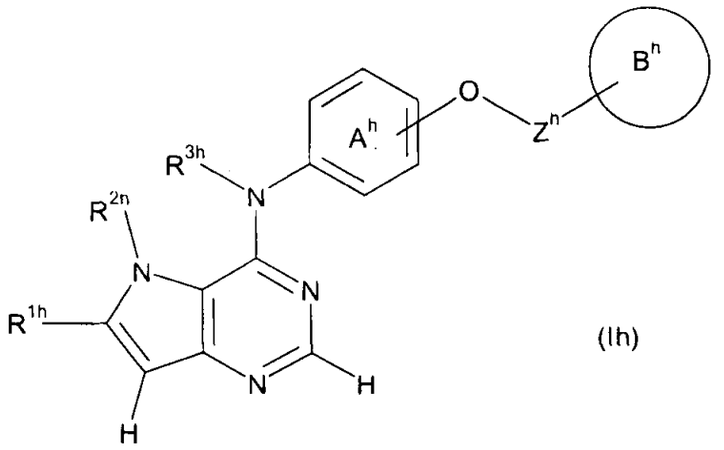
[10g] El agente farmacéutico del punto [8g] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[11g] El agente farmacéutico del punto [10g] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[12g] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1g] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[13g] Uso del compuesto del punto [1g] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

[1h] Un compuesto representado por la fórmula:



(Ih)

en donde

R^{1h} es un átomo de halógeno o un grupo alquilo de C_{1-6} halogenado,

R^{2h} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1h} y R^{2h}, o R^{2h} y R^{3h} están unidos para formar una estructura de anillo opcionalmente sustituida,

R^{3h} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3h} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

Z^h es un enlace o un alquileno de C_{1-3} opcionalmente sustituido,

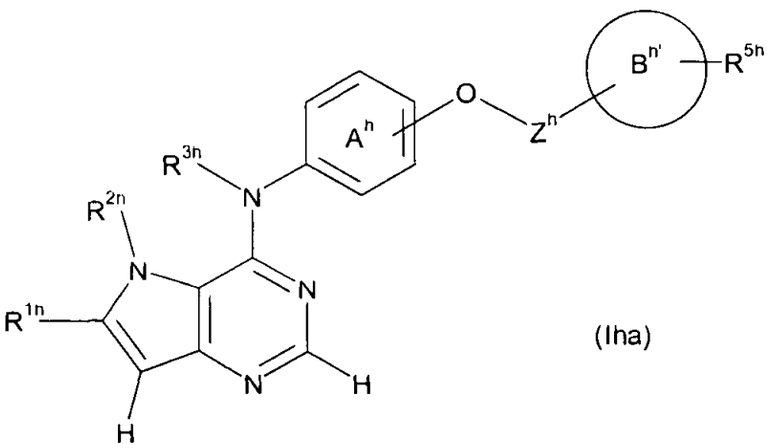
el anillo A^h es un anillo benceno opcionalmente sustituido, y

el anillo B^h es (i) un grupo arilo de C_{6-14}

opcionalmente sustituido, (ii) un grupo heterocíclico opcionalmente sustituido, o (iii) un grupo cicloalquilo de C_{5-8} opcionalmente sustituido,

o una de sus sales.

[2h] El compuesto del punto [1h] antes mencionado, que es un compuesto representado por la fórmula:



(Iha)

en donde

R^{5h} es

(i) un grupo amino opcionalmente sustituido,

(ii) un grupo carbamoilo opcionalmente sustituido,

(iii) un grupo ureido opcionalmente sustituido,

(iv) un grupo sulfamoilo opcionalmente sustituido,

(v) un grupo heterocíclico opcionalmente sustituido,

(vi) un grupo hidrocarburo opcionalmente sustituido,

(vii) un átomo de halógeno, o

(viii) un grupo carboxilo opcionalmente sustituido,

y

el anillo $B^{n'}$ es (i) un grupo arilo de C_{6-14}, (ii) un grupo heterocíclico, o (iii) un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido además de R^{5h}, y los otros símbolos son como se definieron con anterioridad.

[3h] Un compuesto seleccionado de los siguientes:

N-(3-{2-cloro-4-[(6-cloro-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida,

6-cloro-N-{3-cloro-4-[3-(trifluorometil)fenoxi]fenil}-5-metil-5H-pirrolo[3,2-d]pirimidin-4-amina,

N-[3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida, y

N-(ter-butil)-3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

o una de sus sales.

[4h] Un profármaco del compuesto del punto [1h] antes mencionado.

[5h] Un método de producción del compuesto del punto [1h] antes mencionado o una de sus sales, que comprende hacer reaccionar un compuesto representado por la fórmula:

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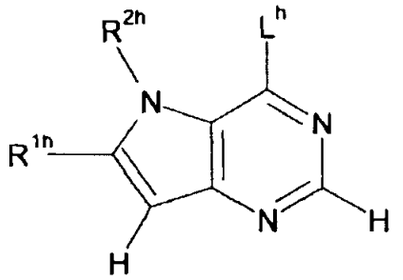
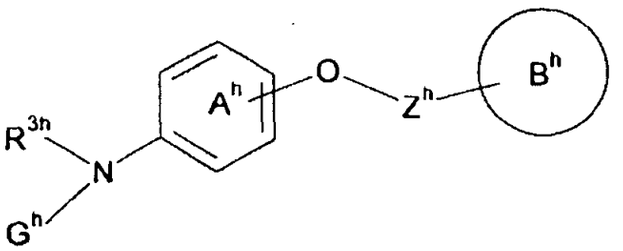


(IIh)

en donde L^h es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIh)

en donde G^h es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

[6h] Un agente farmacéutico que comprende el compuesto del punto [1h] antes mencionado o una de sus sales o uno de sus profármacos.

[7h] El agente farmacéutico del punto [6h] antes mencionado, que es un inhibidor de la tirosina cinasa.

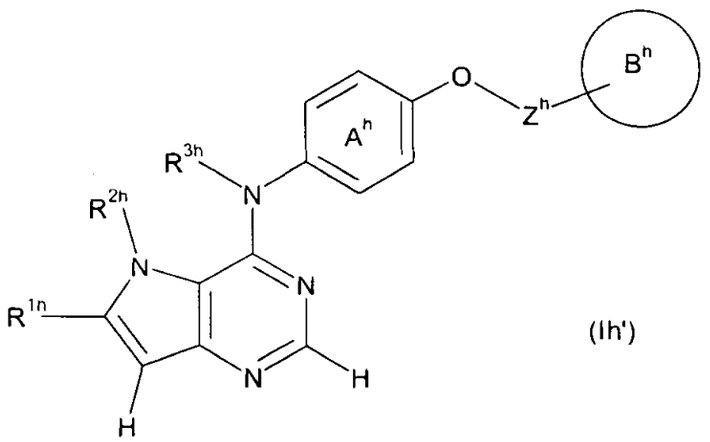
[8h] El agente farmacéutico del punto [6h] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[9h] El agente farmacéutico del punto [8h] antes mencionado, en donde el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

[10h] Un método para la prevención o el tratamiento de cáncer en un mamífero, que comprende la administración de una cantidad efectiva del compuesto del punto [1h] antes mencionado o una de sus sales o uno de sus profármacos, al mamífero.

[11h] Uso del compuesto del punto [1h] antes mencionado o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

[12h] El compuesto del punto [1h] antes mencionado, que es un compuesto representado por la fórmula:



(Ih')

en donde cada símbolo es como se definió con anterioridad.

[13h] El compuesto del punto [2h] antes mencionado, en donde

R^{1h} es un átomo de halógeno o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2h} es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6}, o

(iii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{6h}-CO-(CH_2)_n-OH$,

(c) $-NR^{6h}-CO-(CH_2)_n-SO_2$-alquilo de C_{1-4} opcionalmente halogenado, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6h} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3h} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

Z^h es un enlace o metileno,

el anillo A^h es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5h} es

(i) un grupo amino,

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(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil de C_{1-6}-amino,

(v) un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino,

(vii) un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(viii) un grupo alquilsulfonil de C_{1-6}-alcanoil de C_{1-6}-amino,

(ix) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(x) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xi) un grupo carbamoilo,

(xii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xvi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xvii) un grupo ureido,

(xviii) un grupo alquil de C_{1-6}-ureido,

(xix) un grupo cicloalquil de C_{3-7}-ureido,

(xx) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

(xxii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

(xxiii) un grupo alquilo de C_{1-6} opcionalmente halogenado,

(xxiv) un grupo alcoxi de C_{1-6}-carbonilo,

(xxv) un átomo de halógeno, o

(xxvi) un grupo carboxilo, y

el anillo $B^{h'}$ es un grupo fenilo, un grupo piridilo o un grupo piperidilo, cada uno de los cuales está también opcionalmente sustituido además de R^{5n}.

Cada símbolo usado en la presente especificación se describe en detalle a continuación.

En la presente especificación, salvo que se

especifique otra cosa, como "átomo de halógeno" (y "halógeno" en sustituyente), se pueden mencionar átomo de flúor, átomo de cloro, átomo de bromo y átomo de yodo.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo", se pueden mencionar un grupo alquilo de cadena lineal o ramificada con 1 a 10 (por ejemplo, 1 a 10, 1 a 8, 1 a 6, 2 a 6, 1 a 4) átomos de carbono, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo de C_{1-10}", se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo de C_{1-6}", se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo,

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isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo, heptilo, octilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo de C_{1-6}", se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo de C_{2-6}", se pueden mencionar, por ejemplo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquilo de C_{1-4}", se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquenilo", se puede mencionar un grupo alquenilo con 2 a 10 (por ejemplo, 2 a 10, 2 a 8, 2 a 6, 2 a 4) átomos de carbono, por ejemplo, etenilo,

1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquenilo C_{2-10}", se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquenilo C_{2-8}", se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquenilo C_{2-6}" se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-

hexenilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquenilo C_{2-4}" se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquinilo" se puede mencionar un grupo alquinilo de Con 2 a 10 (por ejemplo, 2 a 10, 2 a 8, 2 a 6, 2 a 4) átomos de carbono, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquinilo de C_{2-10}" se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquinilo de C_{2-8}" se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo,

2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquinilo de C_{2-6}" se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alquinilo de C_{2-4}" se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquilo" se puede mencionar un grupo cicloalquilo de Con 3 a 10 (por ejemplo, 3 a 10, 3 a 8, 3 a 7, 3 a 6, 5 a 8) átomos de carbono, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[2,2,1]heptilo, biciclo[2,2,2]octilo, biciclo[3,2,1]octilo, biciclo[3,2,2]nonilo, biciclo[3,3,1]nonilo, biciclo[4,2,1]nonilo, biciclo[4,3,1]decilo, adamantilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquilo de C_{3-10}" se

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pueden mencionar, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[2,2,1]heptilo, biciclo[2,2,2]octilo, biciclo[3,2,1]octilo, biciclo[3,2,2]nonilo, biciclo[3,3,1]nonilo, biciclo[4,2,1]nonilo, biciclo[4,3,1]decilo, adamantilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquilo de C_{3-8}" se pueden mencionar, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, biciclo[2,2,1]heptilo, biciclo[2,2,2]octilo, biciclo[3,2,1]octilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquilo de C_{3-7}" se pueden mencionar, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquilo de C_{5-8}" se pueden mencionar, por ejemplo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquenilo" se puede mencionar un grupo cicloalquenilo de Con 3 a 10 átomos de carbono, por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalquenilo de C_{3-10}" se pueden mencionar, por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalcadienilo" se puede mencionar un grupo cicloalcadienilo con 4 a 10 átomos de carbono, por ejemplo, 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2,5-ciclohexadien-1-ilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo cicloalcadienilo C_{4-10}" se pueden mencionar, por ejemplo, 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2,5-ciclohexadien-1-ilo y similares.

En la presente especificación, salvo que se especifique otra cosa, el término "grupo arilo" comprende un grupo arilo monocíclico y un grupo arilo policíclico fusionado. Como "grupo arilo" se puede mencionar un grupo arilo de Con 6 a 18 (por ejemplo, 6 a 18, 6 a 14, 6 a 10) átomos de carbono, por ejemplo, fenilo, naftilo, antrilo, fenantrilo, acenaftilo, bifenililo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo arilo de C_{6-18}" se pueden mencionar, por ejemplo, fenilo, naftilo, antrilo, fenantrilo, acenaftilo, bifenililo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo arilo de C_{6-14}" se pueden mencionar, por ejemplo, fenilo, naftilo, antrilo, fenantrilo, acenaftilo, bifenililo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo arilo de C_{6-10}" se pueden mencionar, por ejemplo, fenilo, naftilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo aralquilo" se puede mencionar un grupo aralquilo de Con 7 a 16 átomos de carbono, por ejemplo, bencilo, fenetilo, fenilpropilo, naftilmetilo, bifenililmetilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo aralquilo de C_{7-16}" se pueden mencionar, por ejemplo, bencilo, fenetilo, fenilpropilo, naftilmetilo, bifenililmetilo y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcanoilo" se puede mencionar un grupo alcanoilo de 1 a 7 (por ejemplo, 1 a 7, 1 a 6) átomos de carbono, por ejemplo, formilo, alquil de C_{1-6}-carbonilo (por ejemplo, acetilo, propionilo, butirilo, valerilo, pivaloilo) y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcanoilo de C_{1-6}" se pueden mencionar, por ejemplo, formilo, alquil de C_{1-6}-

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carbonilo (por ejemplo, acetilo, propionilo, butirilo, valerilo, pivaloilo) y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcoxi" se puede mencionar grupo alcoxi de Con 1 a 6 (por ejemplo, 1 a 6, 2 a 6, 1 a 4) átomos de carbono, por ejemplo, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, ter-butoxi, n-pentiloxi, n-hexiloxi y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcoxi de C_{1-6}" se pueden mencionar, por ejemplo, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, ter-butoxi, n-pentiloxi, n-hexiloxi y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcoxi de C_{2-6}" se pueden mencionar, por ejemplo, etoxi, n-propoxi, isopropoxi, n-butoxi, ter-butoxi, n-pentiloxi, n-hexiloxi y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo alcoxi de C_{1-4}" se pueden mencionar, por ejemplo, metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, ter-butoxi y similares.

En la presente especificación, salvo que se especifique otra cosa, como "alquileno" se puede mencionar un alquileno de Con 1 a 4 (por ejemplo, 1 a 4, 1 a 3) átomos de carbono, por ejemplo, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, -

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$CH_2C(CH_3)_2$- y similares.

En la presente especificación, salvo que se especifique otra cosa, como "alquileno de C_{1-4}" se pueden mencionar, por ejemplo, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2-$ y similares.

En la presente especificación, salvo que se especifique otra cosa, como "alquileno de C_{1-3}" se pueden mencionar, por ejemplo, $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$ y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" se pueden mencionar, por ejemplo, un grupo alquilo, un grupo alquenilo, un grupo alquinilo, un grupo cicloalquilo, un grupo cicloalquenilo, un grupo cicloalcadienilo, un grupo arilo, un grupo aralquilo, un grupo arilalquenilo, un grupo a cicloalquil-alquilo y similares. De ellos, se prefieren un grupo alquilo de C_{1-10}, un grupo alquenilo C_{2-10}, un grupo alquinilo de C_{2-10}, un grupo cicloalquilo de C_{3-10}, un grupo cicloalquenilo de C_{3-10}, un grupo cicloalcadienilo C_{4-10}, un grupo arilo de C_{6-14}, un grupo aralquilo de C_{7-16}, un grupo arilalquenilo de C_{8-13}, un grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} y similares.

El grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} antes mencionados

están cada uno opcionalmente condensados con un el anillo Benceno, y como tales se pueden mencionar un grupo de anillo fusionado, por ejemplo, indanilo, dihidronaftilo, tetrahidronaftilo, fluorenilo y similares. Además, como el grupo hidrocarburo antes mencionado, también se puede citar un grupo hidrocarburo de enlaces cruzados tales como norbornanilo, adamantilo y similares, y otros.

Como grupo arilalquenilo de C_{8-13} se pueden mencionar, por ejemplo, estirilo y similares.

Como grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} se pueden mencionar, por ejemplo, ciclopropilmetilo, ciclohexilmetilo y similares.

El grupo alquilo de C_{1-10}, grupo alquenilo C_{2-10} y grupo alquinilo de C_{2-10} antes mencionados, que se enuncian a modo de ejemplo como el "grupo hidrocarburo", tiene cada uno opcionalmente 1 a 3 sustituyentes en posiciones sustituibles.

Como tales sustituyentes se pueden mencionar, por ejemplo,

(1) un grupo cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo, ciclohexilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo que consiste en

halógeno;

hidroxi;

carboxilo;

sulfo;

ciano;

azido;

nitro;

nitroso;

alquilo de C_{1-4} opcionalmente halogenado;

alquenilo C_{2-4} opcionalmente halogenado;

alquinilo de C_{2-4} opcionalmente halogenado;

cicloalquilo de C_{3-7};

arilo de C_{6-14};

aralquilo de C_{7-16};

formilo;

alquil de C_{1-6}-carbonilo opcionalmente halogenado;

alcoxi de C_{1-6}-carbonilo opcionalmente halogenado;

alquil de C_{1-6}-sulfonilo opcionalmente halogenado;

carbamoilo;

carbamoilo mono- o disustituido con alquilo de C_{1-6} opcionalmente halogenado;

mono- o di-aril de C_{6-14}-carbamoilo;

tiocarbamoilo opcionalmente mono- o disustituido con alquilo de C_{1-6} opcionalmente halogenado;

ureido opcionalmente mono- o disustituido con alquilo de C_{1-6} opcionalmente halogenado;

mono- o di-aril de C_{6-14}-ureido;

sulfamoilo opcionalmente mono- o disustituido con alquilo de C_{1-6} opcionalmente halogenado;

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alcoxi de C_{1-6} opcionalmente halogenado;

alqueniloxi de C_{2-6} opcionalmente halogenado;

cicloalquiloxi de C_{3-10};

aralquiloxi de C_{7-16};

ariloxi de C_{6-14};

alquil de C_{1-6}-carboniloxi;

cicloalquil de C_{3-10}-alcoxi de C_{1-6};

alquilsulfoniloxi de C_{1-6};

mercapto;

alquiltio de C_{1-6} opcionalmente halogenado;

aralquiltio de C_{7-16};

ariltio de C_{6-14};

alquilsulfinilo de C_{1-6};

oxo;

alquilendioxi C_{1-3} (por ejemplo, metilendioxi, etilendioxi);

hidroxiimino opcionalmente sustituido con alquilo de C_{1-6};

y similares (grupo sustituyente S);

(2) un grupo arilo de C_{6-14} (por ejemplo, fenilo, naftilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo sustituyente S;

(3) un grupo heterocíclico opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo sustituyente S;

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(4) un grupo amino opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados del grupo que consiste en

alquilo de C_{1-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, cicloalquilo de C_{3-7}, alquil de C_{1-6}-sulfonilo, alcoxi de C_{1-6} y similares;

alquenilo C_{2-4} opcionalmente halogenado;

alquinilo de C_{2-4} opcionalmente halogenado;

cicloalquilo de C_{3-7};

arilo de C_{6-14};

aralquilo de C_{7-16};

grupo heterocíclico de 4 a 7 miembros (con preferencia de 5 ó 6 miembros) (por ejemplo, grupo heterocíclico no aromático como morfolinilo y similares) que contiene, como átomo constituyente del anillo, además de átomos de carbono, 1 a 4 heteroátomos seleccionados del grupo que consiste en un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno;

formilo;

alquil de C_{1-6}-carbonilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, cicloalquilo de C_{3-7}, alquil de C_{1-6}-sulfonilo, alcoxi de C_{1-6} y similares;

alcoxi de C_{1-6}-carbonilo;

aril de C_{6-14}-carbonilo (por ejemplo, benzoilo);

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aralquil de C_{7-16}-carbonilo (por ejemplo, bencilcarbonilo, fenetilcarbonilo);

cicloalquil de C_{3-7}-carbonilo;

alquil de C_{1-6}-carbamoilo (por ejemplo, metilaminocarbonilo, etilaminocarbonilo);

aril de C_{6-14}-carbamoilo (por ejemplo, fenilaminocarbonilo, 1-naftilaminocarbonilo, 2-naftilaminocarbonilo);

aralquil de C_{7-16}-carbamoilo (por ejemplo, bencilaminocarbonilo);

alquilsulfonilo de C_{1-6} (por ejemplo, metilsulfonilo, etilsulfonilo, isopropilsulfonilo);

arilsulfonilo de C_{6-14} (por ejemplo, bencensulfonilo, toluensulfonilo, 1-naftalensulfonilo, 2-naftalensulfonilo);

aralquilsulfonilo de C_{7-16} (por ejemplo, bencilsulfonilo);

y similares (grupo sustituyente T);

(5) un grupo amidino;

(6) un grupo alquil de C_{1-6}-carbonilo opcionalmente formilado o halogenado ;

(7) un grupo alcoxi de C_{1-6}-carbonilo opcionalmente halogenado;

(8) un alquilsulfonilo de C_{1-6} opcionalmente halogenado (por ejemplo, metilsulfonilo);

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(9) un grupo carbamoilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados del grupo sustituyente T;

(10) un grupo tiocarbamoilo opcionalmente mono- o disustituido con opcionalmente halogenado grupo alquilo de C_{1-6};

(11) un grupo ureido opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados del grupo sustituyente T;

(12) un grupo sulfamoilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados del grupo sustituyente T;

(13) un grupo carboxilo;

(14) un grupo hidroxi;

(15) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo que consiste en halógeno, carboxilo, alcoxi de C_{1-6} y alcoxi de C_{1-6}-carbonilo;

(16) un grupo alqueniloxi de C_{2-6} opcionalmente halogenado (por ejemplo, eteniloxi);

(17) un grupo cicloalquiloxi de C_{3-10} (por ejemplo, ciclohexiloxi);

(18) un grupo aralquiloxi de C_{7-16} (por ejemplo, benciloxi);

(19) un grupo ariloxi de C_{6-14} (por ejemplo, feniloxi, naftiloxi);

(20) un grupo alquil de C_{1-6}-carboniloxi (por ejemplo, acetiloxi, ter-butilcarboniloxi);

(21) un grupo mercapto;

(22) un grupo alquiltio de C_{1-6} opcionalmente halogenado (por ejemplo, metiltio, etiltio);

(23) un grupo aralquiltio de C_{7-16} (por ejemplo, benciltio);

(24) un grupo ariltio de C_{6-14} (por ejemplo, feniltio, naftiltio);

(25) un grupo sulfo;

(26) un grupo ciano;

(27) un grupo azido;

(28) un grupo nitro;

(29) un grupo nitroso;

(30) un átomo de halógeno;

(31) un grupo alquilsulfinilo de C_{1-6} (por ejemplo, metilsulfinilo);

(32) un grupo oxo;

(33) un grupo cicloalquil de C_{3-10}-alcoxi de C_{1-6} (por ejemplo, ciclopropilmetoxi);

(34) un grupo alquilendioxi C_{1-3} (por ejemplo, metilendioxi, etilendioxi);

(35) un grupo hidroxiimino opcionalmente sustituido con alquilo de C_{1-6};

y similares (grupo sustituyente U). Cuando el

número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

El grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10}, grupo cicloalcadienilo C_{4-10}, grupo arilo de C_{6-14}, grupo aralquilo de C_{7-16}, grupo aril de C_{8-13}-alquenilo y grupo cicloalquil de C_{3-10}-alquilo de C_{1-6} antes mencionados, que se enumeran a modo de ejemplo como el "grupo hidrocarburo", tienen cada uno opcionalmente 1 a 3 sustituyentes en posiciones sustituibles.

Como tales sustituyentes se pueden mencionar, por ejemplo,

(1) un sustituyente seleccionado del grupo sustituyente U;

(2) un grupo alquilo de C_{1-10} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo sustituyente U;

(3) un grupo alquenilo C_{2-10} (por ejemplo, etenilo, 1-propenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo sustituyente U;

(4) un grupo aralquilo de C_{7-16} (por ejemplo, bencilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo sustituyente U;

y similares (grupo sustituyente V). Cuando el número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

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En la presente especificación, salvo que se especifique otra cosa, como "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" se pueden mencionar un grupo heterocíclico aromático y un grupo heterocíclico no aromático.

Como grupo heterocíclico aromático se puede mencionar, por ejemplo, un grupo heterocíclico aromático monocíclico de 4 a 7 miembros (con preferencia de 5 ó 6 miembros) que contiene, como átomo constituyente del anillo Además de átomos de carbono, 1 a 4 heteroátomos seleccionados del grupo que consiste en un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno y un grupo heterocíclico aromático fusionado. Como grupo heterocíclico aromático fusionado se puede mencionar, por ejemplo, un grupo derivado de un anillo fusionado en donde están condensados un anillo correspondiente a tal grupo heterocíclico aromático monocíclico de 4 a 7 miembros, y 1 ó 2 anillos seleccionados del grupo que consiste en un anillo de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno, un anillo de 5 miembros que contiene un átomo de azufre, un el anillo Benceno y similares.

Como ejemplos preferidos del grupo heterocíclico aromático se pueden mencionar

grupos heterocíclicos aromáticos monocíclicos tales como

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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 (por ejemplo, 3-isotiazolilo, 4-isotiazolilo, 5-isotiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo), isoxazolilo (por ejemplo, 3-isoxazolilo, 4-isoxazolilo, 5-isoxazolilo), oxadiazolilo (por ejemplo, 1,2,4-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo), tiadiazolilo (por ejemplo, 1,3,4-tiadiazol-2-ilo), triazolilo (por ejemplo, 1,2,4-triazol-1-ilo, 1,2,4-triazol-3-ilo, 1,2,3-triazol-1-ilo, 1,2,3-triazol-2-ilo, 1,2,3-triazol-4-ilo), tetrazolilo (por ejemplo, tetrazol-1-ilo, tetrazol-5-ilo), triazinilo (por ejemplo, 1,2,4-triazin-1-ilo, 1,2,4-triazin-3-il) y similares;

grupos heterocíclicos aromáticos fusionados tales como

quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo,

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4-quinolilo, 6-quinolilo), isoquinolilo (por ejemplo, 3-isoquinolilo), quinazolilo (por ejemplo, 2-quinazolilo, 4-quinazolilo), quinoxalilo (por ejemplo, 2-quinoxalilo, 6-quinoxalilo), benzofurilo (por ejemplo, 2-benzofurilo, 3-benzofurilo), benzotienilo (por ejemplo, 2-benzotienilo, 3-benzotienilo), benzoxazolilo (por ejemplo, 2-benzoxazolilo), bencisoxazolilo (por ejemplo, 7-bencisoxazolilo), benzotiazolilo (por ejemplo, 2-benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol-1-ilo, bencimidazol-2-ilo, bencimidazol-5-ilo), benzotriazolilo (por ejemplo, 1H-1,2,3-benzotriazol-5-ilo), indolilo (por ejemplo, indol-1-ilo, indol-2-ilo, indol-3-ilo, indol-5-ilo), indazolilo (por ejemplo, 1H-indazol-3-ilo), pirrolopirazinilo (por ejemplo, 1H-pirrolo[2,3-b]pirazin-2-ilo, 1H-pirrolo[2,3-b]pirazin-6-ilo), imidazopiridinilo (por ejemplo, 1H-imidazo[4,5-b]piridin-2-ilo, 1H-imidazo[4,5-c]piridin-2-ilo, 2H-imidazo[1,2-a]piridin-3-ilo), imidazopirazinilo (por ejemplo, 1H-imidazo[4,5-b]pirazin-2-ilo), pirazolopiridinilo (por ejemplo, 1H-pirazolo[4,3-c]piridin-3-ilo), pirazolotienilo (por ejemplo, 2H-pirazolo[3,4-b]tiofen-2-ilo), pirazolotriazinilo (por ejemplo, pirazolo[5,1-c][1,2,4]triazin-3-il) y similares;

y similares.

Como el grupo heterocíclico no aromático se puede mencionar, por ejemplo, un grupo heterocíclico no aromático

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monocíclico de 4 a 7 miembros (con preferencia de 5 ó 6 miembros) que contiene, como átomo constituyente del anillo Además de átomos de carbono, 1 a 4 heteroátomos seleccionados del grupo que consiste en un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno y un grupo heterocíclico no aromático fusionado. Como grupo heterocíclico no aromático fusionado se puede mencionar, por ejemplo, un grupo derivado de un anillo fusionado en donde están condensados un anillo correspondiente a tal grupo heterocíclico no aromático monocíclico de 4 a 7 miembros, y 1 ó 2 anillos seleccionados del grupo que consiste en un anillo de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno, un anillo de 5 miembros que contiene un átomo de azufre, un el anillo Benceno y similares, y otros.

Como ejemplos preferidos de grupo heterocíclico no aromático se pueden mencionar,

grupos heterocíclicos no aromáticos monocíclicos tales como

oxetanilo (por ejemplo, 2-oxetanilo, 3-oxetanilo), pirrolidinilo (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo), piperidinilo (por ejemplo, piperidino, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo), morfolinilo (por ejemplo, morfolino), tiomorfolinilo (por ejemplo, tiomorfolino), piperazinilo (por ejemplo, 1-piperazinilo, 2-piperazinilo, 3-piperazinilo), hexametileniminilo (por

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ejemplo, hexametilenimin-1-ilo), oxazolidinilo (por ejemplo, oxazolidin-2-ilo), tiazolidinilo (por ejemplo, tiazolidin-2-ilo), imidazolidinilo (por ejemplo, imidazolidin-2-ilo, imidazolidin-3-ilo), oxazolinilo (por ejemplo, oxazolin-2-ilo), tiazolinilo (por ejemplo, tiazolin-2-ilo), imidazolinilo (por ejemplo, imidazolin-2-ilo, imidazolin-3-ilo), dioxolilo (por ejemplo, 1,3-dioxol-4-ilo), dioxolanilo (por ejemplo, 1,3-dioxolan-4-ilo), dihidrooxadiazolilo (por ejemplo, 4,5-dihidro-1,2,4-oxadiazol-3-ilo), 2-tioxo-1,3-oxazolidin-5-ilo, piranilo (por ejemplo, 4-piranilo), tetrahidropiranilo (por ejemplo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo), tiopiranilo (por ejemplo, 4-tiopiranilo), tetrahidrotiopiranilo (por ejemplo, 2-tetrahidrotiopiranilo, 3-tetrahidrotiopiranilo, 4-tetrahidrotiopiranilo), 1-oxidotetrahidrotiopiranilo (por ejemplo, 1-oxidotetrahidrotiopiran-4-ilo), 1,1-dioxidotetrahidrotiopiranilo (por ejemplo, 1,1-dioxidotetrahidrotiopiran-4-ilo), tetrahidrofurilo (por ejemplo, tetrahidrofurano-3-ilo, tetrahidrofurano-2-ilo), pirazolidinilo (por ejemplo, pirazolidin-1-ilo, pirazolidin-3-ilo), pirazolinilo (por ejemplo, pirazolin-1-ilo), tetrahidropirimidinilo (por ejemplo, tetrahidropirimidin-1-ilo), dihidrotriazolilo (por ejemplo, 2,3-dihidro-1H-1,2,3-triazol-1-ilo), tetrahidrotriazolilo (por ejemplo, 2,3,4,5-tetrahidro-1H-1,2,3-triazol-1-il) y similares;

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grupos heterocíclicos no aromáticos fusionados tales como

dihidroindolilo (por ejemplo, 2,3-dihidro-1H-indol-1-ilo), dihidroisoindolilo (por ejemplo, 1,3-dihidro-2H-isoindol-2-ilo), dihidrobenzofuranilo (por ejemplo, 2,3-dihidro-1-benzofuran-5-ilo), dihidrobenzodioxinilo (por ejemplo, 2,3-dihidro-1,4-benzodioxinilo), dihidrobenzodioxepinilo (por ejemplo, 3,4-dihidro-2H-1,5-benzodioxepinilo), tetrahidrobenzofuranilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzofuran-3-ilo), cromenilo (por ejemplo, 4H-cromen-2-ilo, 2H-cromen-3-ilo), dihidroquinolinilo (por ejemplo, 1,2-dihidroquinolin-4-ilo), tetrahidroquinolinilo (por ejemplo, 1,2,3,4-tetrahidroquinolin-4-ilo), dihidroisoquinolinilo (por ejemplo, 1,2-dihidroisoquinolin-4-ilo), tetrahidroisoquinolinilo (por ejemplo, 1,2,3,4-tetrahidroisoquinolin-4-ilo), dihidroftalazinilo (por ejemplo, 1,4-dihidroftalazin-4-il) y similares.

El "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como tales sustituyentes se pueden mencionar, por ejemplo, sustituyentes seleccionados del grupo sustituyente V. Cuando el número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente especificación, salvo que se especifique otra cosa, como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" se puede mencionar un grupo hidrocarburo alifático lineal o ramificado que tiene 1 a 10 átomos de carbono (con preferencia, 1 a 8 átomos de carbono). Como "grupo hidrocarburo alifático" se pueden mencionar, por ejemplo, un grupo alquilo de C_{1-10}, un grupo alquenilo C_{2-10}, un grupo alquinilo de C_{2-10} y un grupo cicloalquilo de C_{3-10} (cada grupo es como se definió con anterioridad).

El "grupo hidrocarburo alifático" está opcionalmente sustituido con sustituyentes seleccionados del grupo sustituyente V, en particular, 1 a 3 sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, alcoxi de C_{1-4}, alquilo de C_{1-4}-carbonilo, carboxi, alcoxi de C_{1-4}-carbonilo, ciano, carbamoilo, sulfamoilo, nitro, amino, alquilo de C_{1-4}-carbonilamino, alcoxi de C_{1-4}-carbonilamino y alquil de C_{1-4}-sulfonilamino. Cuando el número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente especificación, salvo que se especifique otra cosa, como "grupo acilo" se pueden mencionar, por ejemplo, $-COR^{Y1}$, $-CO-OR^{Y1}$, $-SO_2R^{Y1}$, $-SOR^{Y1}$, $-PO(OR^{Y1})(OR^{Y2})$ (en donde R^{Y1} y R^{Y2} son iguales o diferentes y cada uno es un átomo de hidrógeno, un grupo hidrocarburo

opcionalmente sustituido, o un grupo heterocíclico opcionalmente sustituido), y similares.

En la presente especificación, salvo que se especifique otra cosa, el "grupo amino" del "grupo amino opcionalmente sustituido", el "grupo carbamoilo" del "grupo carbamoilo opcionalmente sustituido", el "grupo ureido" del "grupo ureido opcionalmente sustituido" y el "grupo sulfamoilo" del "grupo sulfamoilo opcionalmente sustituido" tienen opcionalmente 1 ó 2 sustituyentes en posiciones sustituibles. Como tales sustituyentes se pueden mencionar, por ejemplo, un grupo hidrocarburo opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituido, un grupo acilo y similares. De ellos, se prefieren 1 ó 2 sustituyentes seleccionados del grupo sustituyente T. Cuando el número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

Cuando el átomo de nitrógeno que constituye el grupo amino, grupo carbamoilo, grupo ureido o grupo sulfamoilo antes mencionados está sustituido con dos sustituyentes, estos sustituyentes pueden formar combinados, junto con el átomo de nitrógeno adyacente, un heterociclo que contiene nitrógeno. Como "heterociclo que contiene nitrógeno" se pueden mencionar, por ejemplo, un heterociclo de 3 a 8 miembros con nitrógeno que contiene, como átomo constituyente del anillo, además de átomos de carbono, al menos un átomo de

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nitrógeno y también opcionalmente contiene uno o dos heteroátomos seleccionados del grupo que consiste en un átomo de oxígeno, un átomo de azufre y un átomo de nitrógeno. Como ejemplos preferidos del heterociclo que contiene nitrógeno, se pueden mencionar una amina cíclica de 5 ó 6 miembros que contiene opcionalmente un átomo de oxígeno (por ejemplo, 1-pirrolidina, piperidina, 1-piperazina, morfolina).

En la presente especificación, salvo que se especifique otra cosa, el "grupo imino" del "grupo imino opcionalmente sustituido" tiene opcionalmente 1 ó 2 sustituyentes en posiciones sustituibles. Como tales sustituyentes se pueden mencionar, por ejemplo, un grupo hidrocarburo opcionalmente sustituido, un grupo heterocíclico opcionalmente sustituido, un grupo acilo y similares. De ellos, se prefieren sustituyentes seleccionados del grupo sustituyente T. Cuando el número de sustituyentes no es inferior a 2, los respectivos sustituyentes pueden ser iguales o diferentes.

En la presente especificación, salvo que se especifique otra cosa, como "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno", se puede mencionar un grupo representado por la fórmula: $-X^x-R^x$, un grupo amino y un grupo hidroxi.

En la fórmula antes mencionada, X^x es un enlace,

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$-NR^Y-$ (en donde R^Y es un átomo de hidrógeno o un grupo alquilo de C_{1-6}) u -O-.

En la fórmula antes mencionada, R^X es un grupo ciano, o un grupo alquilo de C_{1-8}, un grupo alquenilo C_{2-8}, un grupo alquinilo de C_{2-8}, un grupo carbamoilo, un grupo alquil de C_{1-8}-carbonilo, un grupo cicloalquilo de C_{3-8}, un grupo arilo de C_{6-18}, un grupo aril de C_{6-18}-alquilo de C_{1-4}, un grupo aril de C_{6-18}-carbonilo, un grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo, un grupo heterocíclico, un grupo heterociclil-alquilo de C_{1-4}, un grupo heterociclilcarbonilo o un grupo heterociclil-alquilo de C_{1-4}-carbonilo, cada uno de los cuales está opcionalmente sustituido.

En la fórmula antes mencionada, el "grupo alquilo de C_{1-8}", "grupo alquenilo C_{2-8}", "grupo alquinilo de C_{2-8}", "grupo carbamoilo", "grupo alquil de C_{1-8}-carbonilo", "grupo cicloalquilo de C_{3-8}", "grupo arilo de C_{6-18}", "grupo aril de C_{6-18}-alquilo de C_{1-4}", "grupo aril de C_{6-18}-carbonilo", "grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo", "grupo heterocíclico", "grupo heterociclil-alquilo de C_{1-4}", "grupo heterociclilcarbonilo" y "grupo heterociclil-alquilo de C_{1-4}-carbonilo" para R^X están opcionalmente sustituidos con uno o varios (con preferencia 1 a 5, con mayor preferencia 1 a 3) sustituyentes seleccionados, por ejemplo, del siguiente grupo (grupo sustituyente X)

(a) un átomo de halógeno,

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(b) un grupo oxo,

(c) un grupo alquilo de C_{1-4} opcionalmente halogenado,

(d) grupo $-(CH_2)_m-Q^x$,

(e) grupo alquilo de C_{1-4} opcionalmente halogenado con $-(CH_2)_m-Z^{1x}-$,

(f) grupo $-(CH_2)_m-Z^{1x}-$cicloalquilo de C_{3-8},

(g) grupo $-(CH_2)_m-Z^{2x}-(CH_2)_n-Q^x$,

(h) grupo alquilo de C_{1-4} opcionalmente halogenado con $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-$,

(i) grupo $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-$ cicloalquilo de C_{3-8},

(j) grupo $-(CH_2)_m-Z^{1x}-$heterocíclico opcionalmente sustituido (con preferencia, el grupo heterocíclico es un grupo heterocíclico de 5 a 8 miembros que contiene 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y átomo de azufre opcionalmente oxidado),

(k) grupo $-(CH_2)_m-Z^{2x}-$alcoxi de C_{1-4}, y

(l) grupo $-(CH_2)_m-Z^{2x}-(CH_2)_n-Z^{1x}-(CH_2)_n-Z^{1x}-$alquilo de C_{1-4}.

R^Y es con preferencia un átomo de hidrógeno o metilo, con particular preferencia un átomo de hidrógeno.

En la fórmula antes mencionada,

m es un número entero de 0 a 4,

n es un número entero de 1 a 4,

Q^x es hidroxi, carboxi, ciano, nitro, $-NR^{1x}R^{2x}$, $-CONR^{1x}R^{2x}$ o $-SO_2NR^{1x}R^{2x}$,

Z^{1x} es $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-SO_2-$ o $-NR^{3x}-C(=NH)-NH-$,

Z^{2x} es $-O-$, $-CO-$, $-C(OH)R^{3x}-$, $-C(=N-OR^{3x})-$, $-S-$, $-SO-$, $-SO_2-$, $-NR^{3x}-$, $-N(COR^{3x})-$, $-N(CO_2R^{4x})-$, $-N(SO_2R^{4x})-$, $-CO-O-$, $-O-CO-$, $-CO-NR^{3x}-$, $-NR^{3x}-CO-$, $-NR^{3x}-CO_2-$, $-NR^{3x}-CO-NH-$, $-NR^{3x}-C(=NH)-NH-$, $-NR^{3x}-SO_2-$ o $-SO_2-NR^{3x}-$.

En la fórmula antes mencionada, $-(CH_2)_m-$ y $-(CH_2)_n-$ están opcionalmente sustituidos con uno o varios (con preferencia 1 a 5, con mayor preferencia 1 a 3) sustituyentes seleccionados, por ejemplo, del grupo que consiste en halógeno, alquilo de C_{1-4} opcionalmente halogenado e hidroxi, y cuando m o n no es inferior a 2, un subgrupo $-CH_2CH_2-$ de $-(CH_2)_m-$ o $-(CH_2)_n-$ está opcionalmente reemplazado por $-CH=CH-$ o $-C\equiv C-$.

En la fórmula antes mencionada, R^{1x} y R^{2x} son iguales o diferentes y cada uno es un átomo de hidrógeno o un alquilo de C_{1-4}, o R^{1x} y R^{2x} se unen opcionalmente para formar un anillo junto con el átomo de nitrógeno. En la fórmula antes mencionada, R^{3x} es un átomo de hidrógeno o un alquilo de C_{1-4}, y R^{4x} es un alquilo de C_{1-4}.

Cuando R^{1x} y R^{2x} están unidos para formar un anillo

junto con el átomo de nitrógeno, como heterociclo que contiene nitrógeno se pueden mencionar, por ejemplo, grupos heterocíclicos alifáticos de 3 a 8 miembros (con preferencia de 5 ó 6 miembros) saturados o insaturados (con preferencia saturados) tales como azetidina, pirrolidina, piperidina, homopiperidina, heptametilenimina, morfolina, tiomorfolina, piperazina, homopiperazina y similares.

En la presente especificación, salvo que se especifique otra cosa, como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" se pueden mencionar un grupo alquilo de C_{1-8}, un grupo alquenilo C_{2-8}, un grupo alquinilo de C_{2-8}, un grupo carbamoilo, un grupo alquil de C_{1-8}-carbonilo, un grupo alquil de C_{1-8}-tio, un grupo alquil de C_{1-8}-sulfonilo, un grupo cicloalquilo de C_{3-8}, un grupo arilo de C_{6-18}, un grupo aril de C_{6-18}-alquilo de C_{1-4}, un grupo aril de C_{6-18}-carbonilo, un grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo, un grupo aril de C_{6-18}-tio, un grupo aril de C_{6-18}-sulfonilo, un grupo heterocíclico, un grupo heterociclil-alquilo de C_{1-4}, un grupo heterociclilcarbonilo, un grupo heterociclil-alquilo de C_{1-4}-carbonilo, un grupo heterocicliltio y un grupo heterociclil-alquil de C_{1-4}-tio, cada uno de los cuales está opcionalmente sustituido, y similares.

El "grupo alquilo de C_{1-8}", "grupo alquenilo C_{2-8}", "grupo alquinilo de C_{2-8}", "grupo carbamoilo", "grupo alquil

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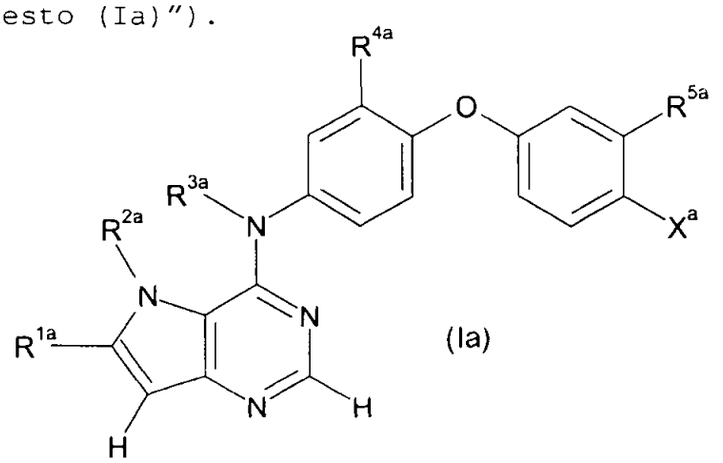
de C_{1-8}-carbonilo", "grupo alquiltio de C_{1-8}", "grupo alquilsulfonilo de C_{1-8}", "grupo cicloalquilo de C_{3-8}", "grupo arilo de C_{6-18}", "grupo aril de C_{6-18}-alquilo de C_{1-4}", "grupo aril de C_{6-18}-carbonilo", "grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo", "grupo ariltio de C_{6-18}", "grupo arilsulfonilo de C_{6-18}", "grupo heterocíclico", "grupo heterociclil-alquilo de C_{1-4}", "grupo heterociclilcarbonilo", "grupo heterociclil-alquilo de C_{1-4}-carbonilo", "grupo heterociclíltio" y "grupo heterociclil-alquiltio de C_{1-4}" están opcionalmente sustituidos con uno o varios (con preferencia 1 a 5, con mayor preferencia 1 a 3) sustituyentes seleccionados, por ejemplo, de grupo sustituyente X.

DESCRIPCION DETALLADA DE LA INVENCION

[compuesto (Ia)]

La presente invención provee un compuesto representado por la fórmula (Ia) o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Ia)").



en donde cada símbolo es como se definió con

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anterioridad.

R^{2a} es con preferencia un grupo alquilo de C_{1-6} (en particular, un grupo etilo) sustituido con un grupo representado por la fórmula "$-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2$-alquilo de C_{1-4}".

En la fórmula, R^{6aa} es un átomo de hidrógeno o un grupo metilo, y R^{7a} y R^{8a} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo metilo. R^{7a} y R^{8a} son con preferencia grupos metilo.

R^{3a} es con preferencia un átomo de hidrógeno.

Como "átomo de halógeno" para R^{4a}, se prefiere un átomo de cloro. Como "grupo alquilo de C_{1-6}" para R^{4a}, se prefiere un grupo metilo. R^{4a} es con preferencia un átomo de cloro o un grupo metilo.

Como "átomo de halógeno" para R^{5a}, se prefieren un átomo de flúor y un átomo de cloro. Como "grupo alquilo de C_{1-6}" para R^{5a}, se prefiere un grupo metilo. R^{5a} es con preferencia un átomo de flúor, un átomo de cloro o un grupo metilo.

Como "átomo de halógeno" para X^a, se prefiere un átomo de flúor. X^a es con preferencia un átomo de hidrógeno o un átomo de flúor, con mayor preferencia un átomo de hidrógeno.

Como modalidad preferida del compuesto (Ia), se puede mencionar el compuesto (Ia) en donde

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R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} (en particular, un grupo etilo) sustituido con un grupo representado por $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2$-alquilo de C_{1-4}

en donde R^{6aa} es un átomo de hidrógeno o un grupo metilo, R^{7a} y R^{8a} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo metilo,

R^{3a} es un átomo de hidrógeno,

R^{4a} es un átomo de cloro o un grupo metilo,

R^{5a} es un átomo de flúor, un átomo de cloro o un grupo metilo, y

X^a es un átomo de hidrógeno o átomo de flúor (con preferencia, un átomo de hidrógeno).

Como modalidad más preferida del compuesto (Ia), se puede mencionar el compuesto (Ia) en donde

R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} (en particular, un grupo etilo) sustituido con un grupo representado por $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2$-alquilo de C_{1-4}

en donde R^{6aa} es un átomo de hidrógeno o un grupo metilo, R^{7a} y R^{8a} son grupos metilo,

R^{3a} es un átomo de hidrógeno,

R^{4a} es un átomo de cloro o un grupo metilo,

R^{5a} es un átomo de flúor, un átomo de cloro o un grupo metilo, y

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X^a es un átomo de hidrógeno o átomo de flúor (con preferencia, un átomo de hidrógeno).

Como compuesto (Ia), se pueden mencionar con preferencia particular

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N,2-dimetil-2-(metilsulfonil)propanamida,

N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida, y

N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

y sus sales e hidratos.

[compuesto (Ib)]

La presente invención provee también un compuesto representado por la fórmula (Ib) o una de sus sales (en la

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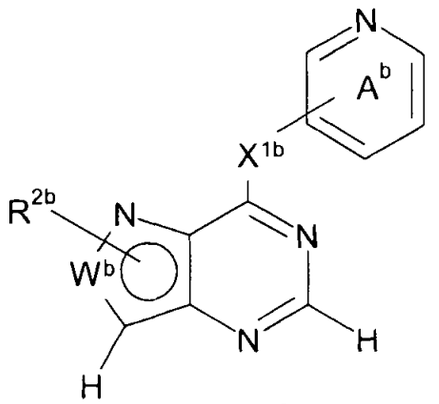
presente especificación, de ahora en más abreviado a veces como "compuesto (Ib)").



(Ib)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (Ib), el "anillo piridina" del "anillo piridina opcionalmente sustituido" para el anillo A^b está opcionalmente sustituido, por ejemplo, por un grupo representado por la fórmula: $-Y^{2b}-B^{b'}$. Y^{2b} es un enlace, -O-, -O-(alquileno de C_{1-3})-, $-NR^{2b}-$ (en donde R^{2b} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}), o -S-, y $B^{b'}$ es un grupo arilo de C_{6-18} (con preferencia, un grupo arilo de C_{6-14}, con mayor preferencia un grupo fenilo), un grupo heterocíclico (con preferencia, un grupo heterocíclico de 5 ó 6 miembros, con mayor preferencia un grupo piridilo o un grupo piperidilo), un grupo cicloalquilo de C_{3-8} (con preferencia, un grupo ciclohexilo), un grupo carbamoilo, un grupo ureido, un grupo aril de C_{6-18}-carbonilo o un grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo, cada uno de los cuales está opcionalmente sustituido.

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Y^{2b} es con preferencia un enlace, -O- u $-OCH_2-$, con mayor preferencia -O- u $-OCH_2-$, con particular preferencia -O-.

El "grupo arilo de C_{6-18}", "grupo heterocíclico", "grupo cicloalquilo de C_{3-8}", "grupo carbamoilo", "grupo ureido", "grupo aril de C_{6-18}-carbonilo" y "grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo" del "grupo arilo de C_{6-18}, grupo heterocíclico, grupo cicloalquilo de C_{3-8}, grupo carbamoilo, grupo ureido, grupo aril de C_{6-18}-carbonilo o grupo aril de C_{6-18}-alquilo de C_{1-4}-carbonilo, cada uno de los cuales está opcionalmente sustituido" para $B^{b'}$ tienen cada uno opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

$B^{b'}$ es con preferencia un grupo arilo de C_{6-14} opcionalmente sustituido, con mayor preferencia un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno (con preferencia un grupo fenilo opcionalmente sustituido con

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sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado y alquil de C_{1-6}-carbamoilo), con particular preferencia un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno (con preferencia, un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado y alquil de C_{1-6}-carbamoilo).

El "anillo piridina" del "anillo piridina opcionalmente sustituido" para el anillo A^b también tiene opcionalmente, además del grupo representado por la fórmula: $-Y^{2b}-B^{b'}$, 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^b es con preferencia un anillo piridina también opcionalmente sustituido, además del grupo representado por la fórmula: $-Y^{2b}-B^{b'}$, con sustituyentes seleccionados del grupo que consiste en halógeno y metilo, con mayor preferencia un anillo piridina también

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opcionalmente sustituido, además del grupo representado por la fórmula: $-Y^{2b}-B^{b'}$, por halógeno.

Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3b}, se prefiere un grupo alquilo de C_{1-6}.

El "alquileno de C_{1-4}" y "-O-(alquileno de C_{1-4})-" del "alquileno de C_{1-4} u -O-(alquileno de C_{1-4})-, cada uno de los cuales está opcionalmente sustituido" para Y^{1b} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, alcoxi de C_{1-4}, alquilo de C_{1-4}-carbonilo, carboxi, alcoxi de C_{1-4}-carbonilo, ciano, carbamoilo, sulfamoilo, nitro, amino, alquilo de C_{1-4}-carbonilamino, alcoxi de C_{1-4}-carbonilamino y alquil de C_{1-4}-sulfonilamino.

X^{1b} es con preferencia $-NR^{3b}-$. En la fórmula, R^{3b} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

W^b es con preferencia $C(R^{1b})$.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para R^{1b}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo

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sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1b} es con preferencia un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2b}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-$alquilo de C_{1-4}

en donde R^{6ba} es un átomo de hidrógeno o un grupo metilo, n1 es un número entero de 1 a 4, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

en donde R^{6bb} es un átomo de hidrógeno o un grupo metilo, n2 es un número entero de 1 a 4, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y -

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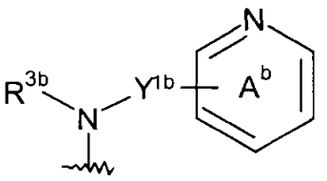
$(CH_2)_{n3}$- está opcionalmente sustituido con alquilo de C_{1-4}, y

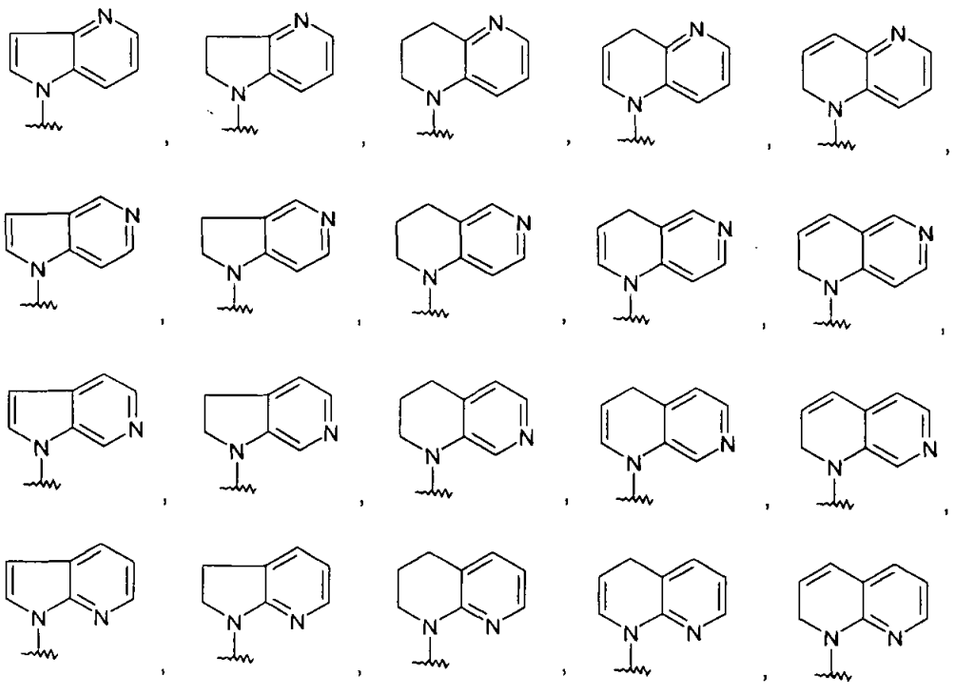
(iv) hidroxi.

Como "estructura del anillo" de la "estructura del anillo opcionalmente sustituida" formada por R^{3b} unido al átomo de carbono en el anillo piridina para el anillo A^b, se puede mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,

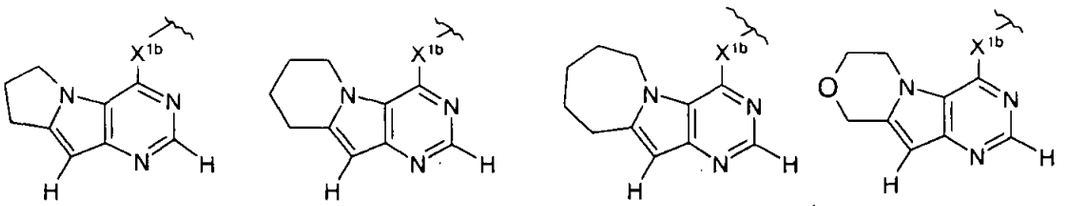


y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1b} y R^{2b} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1b} y R^{2b} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2b} y R^{3b} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo

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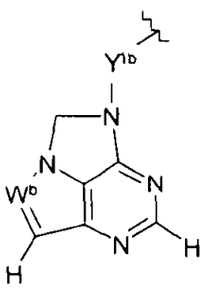
saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2b} y R^{3b} unidas entre sí se pueden mencionar, por ejemplo,



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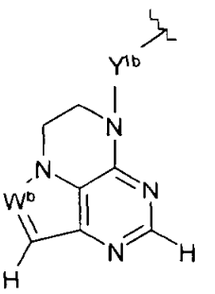

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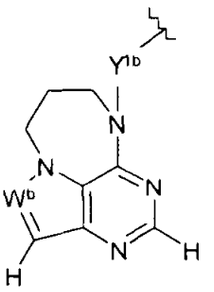

en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1b} y R^{2b}, o R^{2b} y R^{3b} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Cuando W^b es $C(R^{1b})$, el compuesto (Ib) está representado por la siguiente fórmula (IbA):

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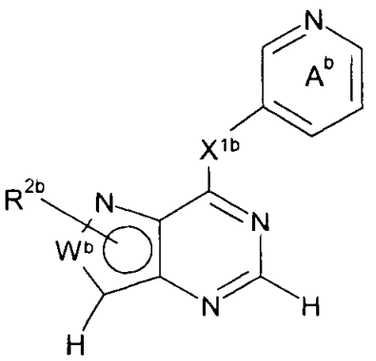
en donde cada símbolo es como se definió con anterioridad.

Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (Ib') o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Ib')"):

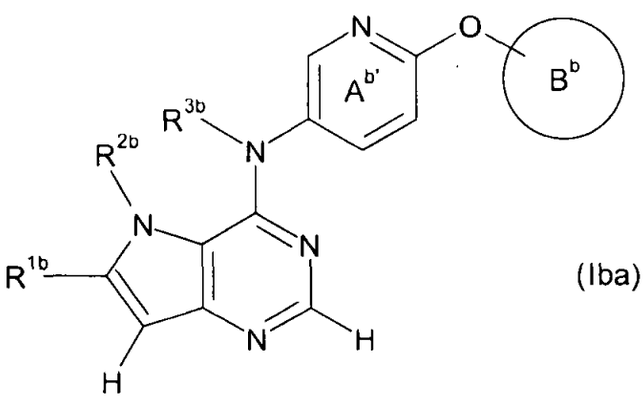


(Ib')

en donde cada símbolo es como se definió con anterioridad.

[compuesto (Iba)]

Como modalidad preferida de compuesto (Ib), se puede mencionar un compuesto representado por la siguiente fórmula (Iba) o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Iba)"):



(Iba)

en donde el anillo $A^{b'}$ es un anillo piridina también opcionalmente sustituido, el anillo B^b es un grupo arilo de C_{6-14} opcionalmente sustituido, y los otros símbolos son como se definieron con anterioridad.

En la fórmula antes mencionada (Iba), el "anillo piridina" del "también opcionalmente sustituido anillo piridina" para el anillo $A^{b'}$ también tiene opcionalmente, además del grupo representado por la fórmula: $-O-B^b$, 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^b es con preferencia un anillo piridina también opcionalmente sustituido, además del grupo representado por la fórmula: $-O-B^b$, con sustituyentes seleccionados del grupo que consiste en halógeno y metilo, con mayor preferencia un anillo piridina también opcionalmente sustituido, además del grupo representado por

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la fórmula: -O-B^b, por halógeno.

El "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^b tiene opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

El anillo B^b es con preferencia un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno (con preferencia un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado y alquil de C_{1-6}-carbamoilo), con mayor preferencia un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno (con preferencia, un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que

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consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado y alquil de C_{1-6}-carbamoilo).

Como modalidad más preferida del compuesto (Ib), se puede mencionar el compuesto (Iba) en donde la fórmula antes mencionada (Iba)

R^{1b} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2b} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2$-alquilo de C_{1-4}

en donde R^{6ba} es un átomo de hidrógeno o un grupo metilo, n1 es un número entero de 1 a 4, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

en donde R^{6bb} es un átomo de hidrógeno o un grupo metilo, n2 es un número entero de 1 a 4, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4}, y

(iv) hidroxi,

R^{3b} es un átomo de hidrógeno,

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con sustituyentes seleccionados del grupo que

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consiste en halógeno y metilo, y

el anillo B^b es un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

Como otra modalidad de mayor preferencia del compuesto (Ib), se puede mencionar el compuesto (Iba) en donde se puede mencionar la fórmula antes mencionada (Iba),

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con halógeno, y

el anillo B^b es un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

Como compuesto (Ib), se pueden mencionar con preferencia particular

2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol,

N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-{2-[4-({5-cloro-6-[3-

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(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

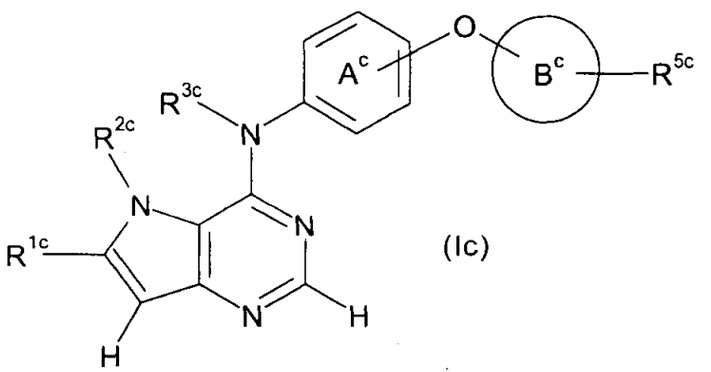
N-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida, y

N-(ter-butil)-3-[(3-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}piridin-2-il)oxi]benzamida,

y sus sales.

[compuesto (Ic)]

La presente invención también provee un compuesto representado por la fórmula (Ic) o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Ic)").



(Ic)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (Ic), como el "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para

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R^{1c}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1c} es con preferencia un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno o un grupo ciano, con particular preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2c}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

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(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

y con mayor preferencia, sustituyentes seleccionados del grupo que consiste en

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-$alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

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(viii) $-SO_2$-alquilo de C_{1-4}, y

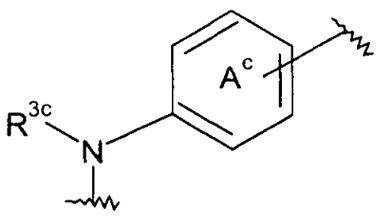
(ix) amino.

Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3c}, se prefiere un grupo alquilo de C_{1-6}.

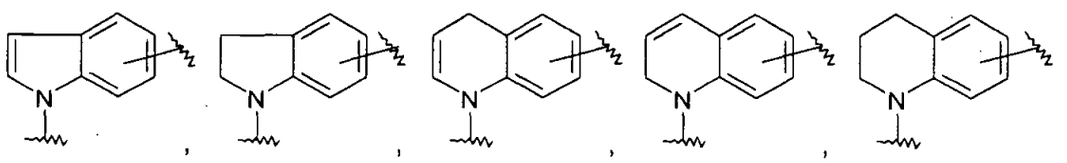
R^{3c} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3c} unido al átomo de carbono en el anillo Benceno adyacente se puede mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,



y similares.

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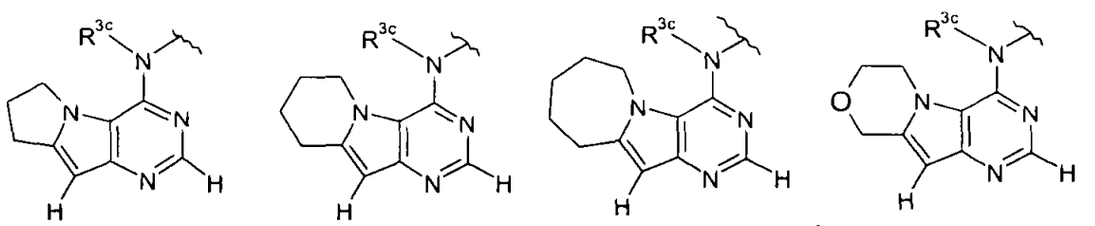
La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1c} y R^{2c} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1c} y R^{2c} unidas entre sí se puede mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2c} y R^{3c} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8

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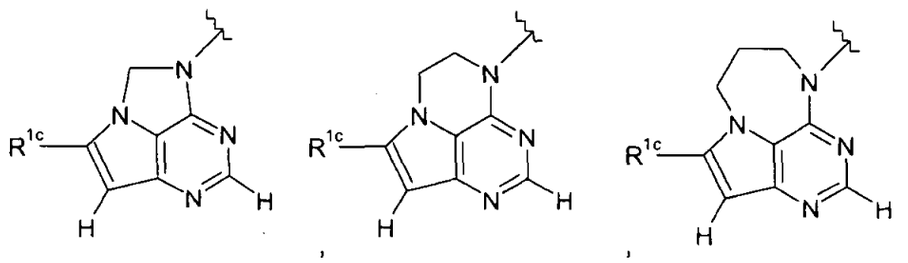
miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2c} y R^{3c} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1c} y R^{2c}, o R^{2c} y R^{3c} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^c tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

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El anillo A^c es con preferencia un el anillo Benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

Como "grupo amino opcionalmente sustituido" para R^{5c}, se prefieren un grupo amino, un grupo mono- o di-alquil de C_{1-6}-amino, un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado, un grupo hidroxi-alcanoil de C_{1-6}-amino, un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno, un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino, un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno, un grupo alquilsulfonil de C_{1-6}-alcanoil de C_{1-6}-amino, un grupo cicloalquil de C_{3-7}-carbonil-amino y un grupo alcoxi de C_{1-6}-carbonil-amino.

Como "grupo carbamoilo opcionalmente sustituido" para R^{5c}, se prefieren un grupo carbamoilo, un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado, un grupo hidroxi-alquil de C_{1-6}-carbamoilo, un grupo alquil de C_{1-6}-oxi-alquil de C_{1-6}-carbamoilo, un grupo aril de C_{6-14}-alquil de C_{1-6}-carbamoilo, un grupo alquinil C_{2-6}-carbamoilo, un grupo piperidil-alquil de C_{1-6}-carbamoilo, un grupo morfolinil-alquil de C_{1-6}-carbamoilo, un grupo cicloalquil de C_{3-7}-carbamoilo opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6}, y un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno.

Como "grupo ureido opcionalmente sustituido" para

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R^{5c}, son preferibles un grupo ureido, un grupo alquil de C_{1-6}-ureido, un grupo cicloalquil de C_{3-7}-ureido, y un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

Como "grupo sulfamoilo opcionalmente sustituido" para R^{5c}, se prefiere un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6}.

Como "grupo heterocíclico opcionalmente sustituido" para R^{5c}, es preferible un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo.

Como "grupo alcoxi de C_{2-6} opcionalmente sustituido" para R^{5c}, se prefiere un grupo alcoxi de C_{2-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} y alquil de C_{1-6}-carbamoilo.

Como "grupo aminometilo opcionalmente sustituido" para R^{5c}, se prefiere un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo.

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Como "grupo carbamoilmetilo opcionalmente sustituido" para R^{5c}, se prefiere un grupo carbamoilmetilo opcionalmente sustituido con alquilo de C_{1-6}.

Como "grupo alquilsulfonilo opcionalmente sustituido" para R^{5c}, se prefiere un grupo alquil de C_{1-6}-sulfonilo que opcionalmente contiene cicloalquilo de C_{3-7} o halógeno.

Como "grupo arilo de C_{6-14}" del "también grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^c, se prefiere un grupo fenilo.

Como "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo de C_{5-8} también opcionalmente sustituido" para el anillo B^c, se prefiere un grupo ciclohexilo.

El "grupo arilo de C_{6-14}" del "también grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^c y el "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo de C_{5-8} también opcionalmente sustituido" para el anillo B^c, tiene cada uno opcionalmente, además de R^{5c}, 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren alquilo de C_{1-6} opcionalmente halogenado y halógeno.

En la fórmula antes mencionada, la fórmula estructural parcial

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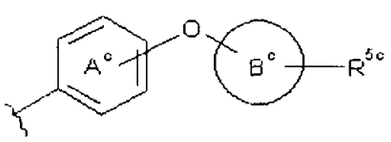
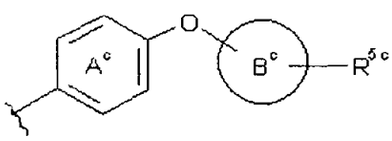


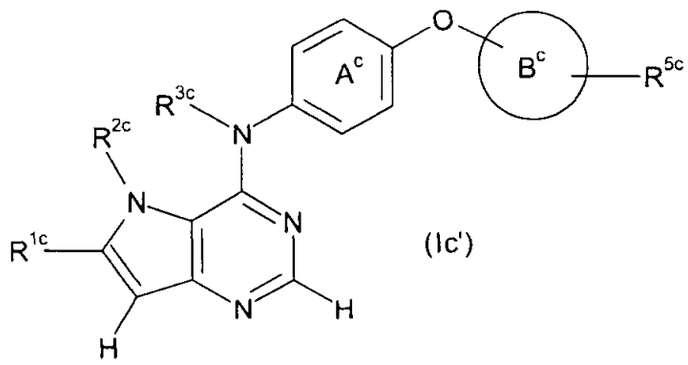


es preferentemente

en donde cada símbolo es como se definió con anterioridad.

Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (Ic') o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Ic')"), y se puede mencionar un compuesto representado por la siguiente fórmula (Ic'') o una de sus sales (en la presente especificación, de ahora en más abreviado a veces como "compuesto (Ic'')"):

[compuesto (Ic')]



(Ic')

en donde cada símbolo es como se definió con anterioridad.

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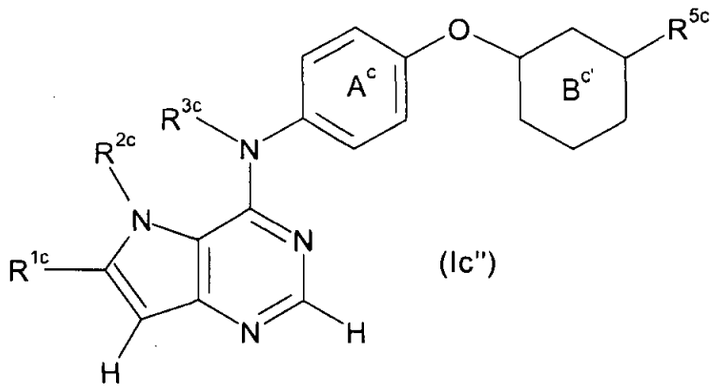
[compuesto (Ic'')]



(Ic'')

en donde el anillo $B^{c'}$ es un grupo fenilo o un grupo ciclohexilo, cada uno de los cuales está también opcionalmente sustituido además de R^{5c}, y los otros símbolos son como se definieron con anterioridad.

Como modalidad preferida de compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{2c} es un grupo alquilo de C_{1-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6c}-CO-$(CH_2)_n$-SO_2-,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

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(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4}.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{1c} es un átomo de hidrógeno o un grupo ciano,

R^{2c} es un grupo alquilo de C_{1-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo monoalquil de C_{1-6}-amino,

(iii) un grupo dialquil de C_{1-6}-amino,

(iv) un grupo alcanoil de C_{1-6}-amino opcionalmente halogenado,

(v) un grupo hidroxi-alcanoil de C_{1-6}-amino,

(vi) un grupo alcanoil de C_{1-6}-amino con hidroxi y halógeno,

(vii) un grupo cicloalquil de C_{3-7}-alcanoil de C_{1-6}-amino,

(viii) un grupo alcanoil de C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(ix) un grupo alquilsulfonil de C_{1-6}-alcanoil de C_{1-6}-amino,

(x) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(xi) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xii) un grupo carbamoilo,

(xiii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiv) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-

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carbamoilo,

(xvi) un grupo aril de C_{6-14}-alquil de C_{1-6}-carbamoilo,

(xvii) un grupo alquinil C_{2-6}-carbamoilo,

(xviii) un grupo piperidil-alquil de C_{1-6}-carbamoilo,

(xix) un grupo morfolinil-alquil de C_{1-6}-carbamoilo,

(xx) un grupo cicloalquil de C_{3-7}-carbamoilo opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6},

(xxi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xxii) un grupo ureido,

(xxiii) un grupo alquil de C_{1-6}-ureido,

(xxiv) un grupo cicloalquil de C_{3-7}-ureido,

(xxv) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxvi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

(xxvii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está

opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

(xxviii) un grupo alcoxi de C_{2-6} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} y alquil de C_{1-6}-carbamoilo,

(xxix) un grupo carbamoilmetilo opcionalmente sustituido con alquilo de C_{1-6},

(xxx) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(xxxi) un grupo alquil de C_{1-6}-sulfonilo que opcionalmente contiene cicloalquilo de C_{3-7} o halógeno, o

(xxxii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{5c} es un grupo amino opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6},

(ii) alcanoilo de C_{1-6} opcionalmente halogenado,

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(iii) hidroxi-alcanoilo de C_{1-6},

(iv) alcanoilo de C_{1-6} que tiene hidroxi y halógeno,

(v) cicloalquil de C_{3-7}-alcanoilo de C_{1-6},

(vi) alcanoilo de C_{1-6} que tiene cicloalquilo de C_{3-7} y halógeno,

(vii) alquil de C_{1-6}-sulfonil-alcanoilo de C_{1-6},

(viii) cicloalquil de C_{3-7}-carbonilo, y

(ix) alcoxi de C_{1-6}-carbonilo,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

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(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

En la modalidad antes mencionada, con mayor preferencia, R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-$alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

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(vii) -S-alquilo de C_{1-4},

(viii) $-SO_2$-alquilo de C_{1-4}, y

(ix) amino.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{5c} es un grupo carbamoilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6} opcionalmente halogenado,

(ii) hidroxi-alquilo de C_{1-6},

(iii) alcoxi de C_{1-6}-alquilo de C_{1-6},

(iv) aril de C_{6-14}-alquilo de C_{1-6},

(v) alquinilo de C_{2-6},

(vi) piperidil-alquilo de C_{1-6},

(vii) morfolinil-alquilo de C_{1-6}, y

(viii) cicloalquilo de C_{3-7} opcionalmente sustituido con alquilo de C_{1-6} o alquinilo de C_{2-6},

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -

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NR^{6c}-CO-$(CH_2)_n$-SO_2-,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

(ix) amino,

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

En la modalidad antes mencionada, con mayor preferencia, R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) -NH-CO-$CR^{7c}R^{8c}$-SO_2-alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) -NR^{6cb}-CO-$(CH_2)_{n2}$-OH

en donde n2 es un número entero de 1 a 4, R^{6cb} es un

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átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{5c} es un grupo ureido opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-6},

(ii) cicloalquilo de C_{3-7}, y

(iii) grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6}

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opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

En la modalidad antes mencionada, con mayor preferencia, R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

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(i) $-NH-CO-CR^{7c}R^{8c}-SO_2$-alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO$-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) $-SO_2$-alquilo de C_{1-4}, y

(ix) amino.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{5c} es un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6c}-CO-$(CH_2)_n$-SO_2-,

(ii) -NR^{6c}-CO-$(CH_2)_n$-OH,

(iii) -O-$(CH_2)_n$-OH,

(iv) hidroxi,

(v) -NR^{6c}-CO-alquilo de C_{1-4},

(vi) -O-alquilo de C_{1-4},

(vii) -S-alquilo de C_{1-4},

(viii) -SO_2-alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

En la modalidad antes mencionada, con mayor preferencia, R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) -NH-CO-$CR^{7c}R^{8c}$-SO_2-alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{5c} es un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

el anillo B^c es un grupo arilo de C_{6-14} o un grupo

cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno,

R^{1c} es un átomo de hidrógeno,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(ii) $-NR^{6c}-CO-(CH_2)_n-OH$,

(iii) $-O-(CH_2)_n-OH$,

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, y

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

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En la modalidad antes mencionada, con mayor preferencia, R^{2c} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) $-NH-CO-CR^{7c}R^{8c}-SO_2-$alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4},

(ii) $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(iv) hidroxi,

(v) $-NR^{6c}-CO-$alquilo de C_{1-4},

(vi) $-O-$alquilo de C_{1-4},

(vii) $-S-$alquilo de C_{1-4},

(viii) $-SO_2-$alquilo de C_{1-4}, y

(ix) amino.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6ca}-CO-(CH_2)_{n1}-SO_2-$

en donde n1 es un número entero de 1 a 4, R^{6ca} es un

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átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene alquil de C_{1-6}-sulfonilo, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6},

(iii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iv) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(v) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(vi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente

sustituido con cicloalquilo de C_{3-7}, o

(vii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

En la modalidad antes mencionada, con mayor preferencia,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NH-CO-CR^{7c}R^{8c}-SO_2-$alquilo de C_{1-4}

en donde R^{7c} y R^{8c} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-4}.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NR^{6cb}-CO-(CH_2)_{n2}-OH$

en donde n2 es un número entero de 1 a 4, R^{6cb} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene hidroxi, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6},

(iii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iv) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(v) un grupo aminometilo opcionalmente sustituido con alquil de C_{1-6}-carbonilo,

(vi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente sustituido con cicloalquilo de C_{3-7}, o

(vii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

En la modalidad antes mencionada, con mayor preferencia,

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NH-CO-CH_2-CR^{9c}R^{10c}-OH$

en donde R^{9c} y R^{10c} son iguales o diferentes y cada uno es un grupo alquilo de C_{1-4}.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil C_{1-6}-amino,

(v) un grupo alcanoil C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil C_{1-6}-amino,

(vii) un grupo alcanoil C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(viii) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(ix) un grupo alcoxi de C_{1-6}-carbonil-amino,

(x) un grupo carbamoilo,

(xi) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiii) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xv) un grupo ureido,

(xvi) un grupo alquil de C_{1-6}-ureido,

(xvii) un grupo cicloalquil de C_{3-7}-ureido,

(xviii) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xix) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xx) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con opcionalmente halogenado alquilo

de C_{1-6} o alcoxi de C_{1-6}-carbonilo,

(xxi) un grupo alcoxi de C_{2-6} opcionalmente halogenado,

(xxii) un grupo alquil de C_{1-6}-sulfonilo, o

(xxiii) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{2c} es un grupo alquilo de C_{1-6} sustituido con hidroxi,

R^{1c} es un átomo de hidrógeno,

R^{3c} es un átomo de hidrógeno,

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino opcionalmente (a) monosustituido con alcanoilo de C_{1-6} que opcionalmente tiene hidroxi, o (b) mono- o disustituido con alquilo de C_{1-6},

(ii) un grupo carbamoilo opcionalmente sustituido con alquilo de C_{1-6} opcionalmente halogenado,

(iii) un grupo cicloalquil de C_{3-7}-carbamoilo

opcionalmente sustituido con alquilo de C_{1-6} o alquinilo C_{2-6},

(iv) un grupo aril C_{6-14}-alquil de C_{1-6}-carbamoilo,

(v) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(vi) un grupo morfolinil-alquil de C_{1-6}-carbamoilo,

(vii) un grupo alquinil C_{2-6}-carbamoilo,

(viii) un grupo carbamoilmetilo opcionalmente sustituido con alquilo de C_{1-6},

(ix) un grupo alcoxi de C_{2-6} opcionalmente sustituido con cicloalquilo de C_{3-7}, halógeno, alcoxi de C_{1-6} o alquil de C_{1-6}-carbamoilo,

(x) un grupo aminometilo opcionalmente sustituido con alcoxi de C_{1-6}-carbonilo, o

(xi) un grupo alquil de C_{1-6}-sulfonilo opcionalmente sustituido con cicloalquilo de C_{3-7}, y

el anillo B^c es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

Como otra modalidad preferida del compuesto (Ic), se puede mencionar el compuesto (Ic) en donde

R^{1c} es un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2c} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con

sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6c}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6c}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6c} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^c es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5c} es

(i) un grupo amino,

(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil C_{1-6}-amino,

(v) un grupo alcanoil C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil C_{1-6}-amino,

(vii) un grupo alcanoil C_{1-6}-amino con cicloalquilo

de C_{3-7} y halógeno,

(viii) un grupo alquilsulfonil C_{1-6}-alcanoil C_{1-6}-amino,

(ix) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(x) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xi) un grupo carbamoilo,

(xii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xvi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xvii) un grupo ureido,

(xviii) un grupo alquil de C_{1-6}-ureido,

(xix) un grupo cicloalquil de C_{3-7}-ureido,

(xx) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6}, o

(xxii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos

seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

De las modalidades preferidas antes mencionadas del compuesto (Ic), se prefiere en particular un compuesto correspondiente al compuesto (Ic''). Es decir, se prefieren en particular

(i) un compuesto en donde el anillo B^c es un grupo fenilo o un grupo ciclohexilo, cada uno de los cuales está también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno, y está sustituido con R^{5c} en la posición meta del grupo fenilo o la posición β del grupo ciclohexilo, y

(ii) un compuesto en donde el anillo B^c es un grupo fenilo también opcionalmente sustituido, además de R^{5c}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno, cuyo fenilo está

sustituido con R^{5c} en la posición meta del grupo fenilo.

Como compuesto (Ic), se puede mencionar, con preferencia particular,

2-{2-[4-({3-cloro-4-[3-(1,3-tiazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol,

N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida,

3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2-hidroxi-1,1-dimetiletil)benzamida,

N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

N-(3-{2-cloro-4-[(6-ciano-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida,

N-(ter-butil)-5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-

5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]acetamida,

N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-{2-[4-({3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida,

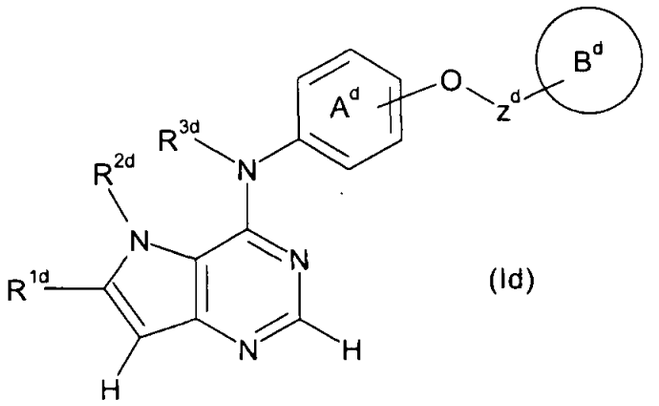
2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol, y

N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

y sus sales.

[compuesto (Id)]

La presente invención también provee un compuesto representado por la fórmula (Id) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Id)").



(Id)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (Id), como el "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para R^{1d}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1d} es con preferencia un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2d}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido.

Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6d}-CO-$(CH_2)_n$-SO_2-,

(b) -NR^{6d}-CO-$(CH_2)_n$-OH,

(c) -O-$(CH_2)_n$-OH, y

(d) hidroxi

en donde n es un número entero de 1 a 4, R^{6d} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4}.

Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3d}, se prefiere un grupo alquilo de C_{1-6}.

R^{3d} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3d} unido al átomo de carbono en el anillo Benceno adyacente, se puede mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con

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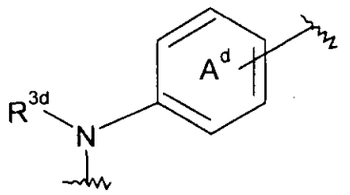
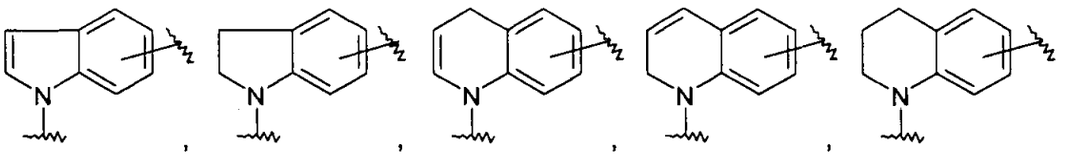
preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,

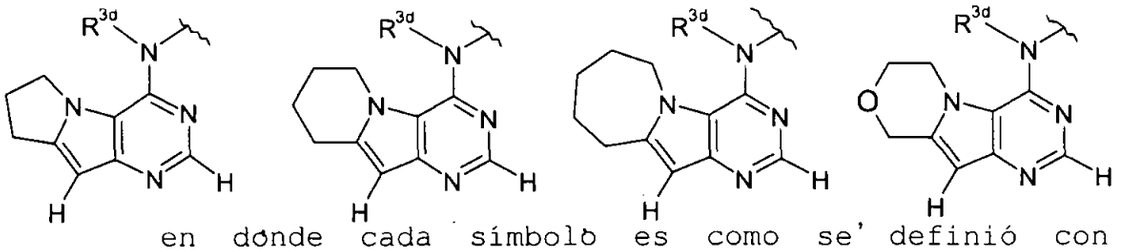


y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1d} y R^{2d} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1d} y R^{2d} unidas entre sí se pueden mencionar, por ejemplo,

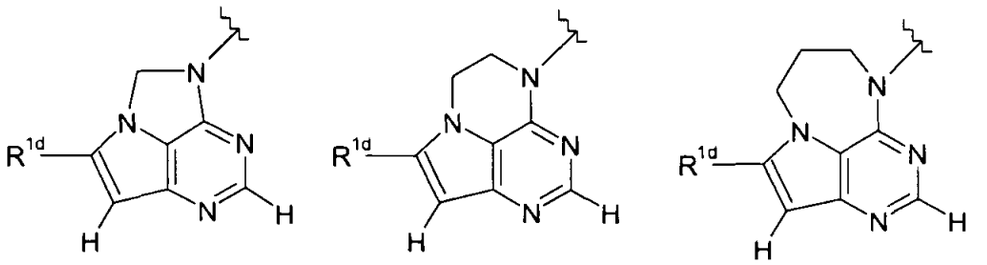


en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2d} y R^{3d} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2d} y R^{3d} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1d} y R^{2d}, o R^{2d} y R^{3d} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes

en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^d tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^d es con preferencia un el anillo Benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo, con mayor preferencia un el anillo Benceno opcionalmente sustituido con halógeno.

Como "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo B^d, se prefiere un grupo heterocíclico monocíclico de 5 ó 6 miembros, y se prefiere aún más un grupo piperidilo.

El "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo B^d tiene opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar acilo y sustituyentes similares a los del grupo sustituyente antes mencionado V. De ellos, se prefieren acilo

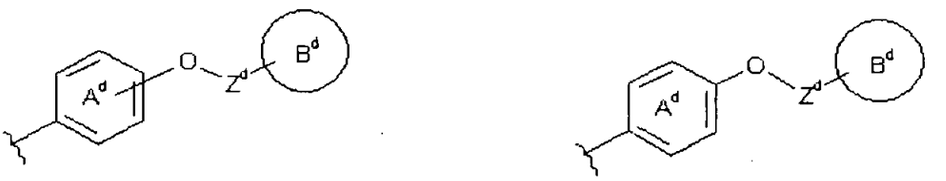
y ureido opcionalmente sustituido, y se prefieren aún más alcoxi de C_{1-6}-carbonilo, cicloalquil de C_{5-8}-carbonilo, alquil de C_{1-6}-ureido y cicloalquil de C_{5-8}-ureido.

El anillo B^d es con preferencia un grupo heterocíclico (con preferencia, un grupo heterocíclico monocíclico 5 ó 6 miembros, con mayor preferencia, un grupo piperidilo) opcionalmente sustituido con acilo o ureido opcionalmente sustituido, con mayor preferencia un grupo heterocíclico (con preferencia, un grupo heterocíclico monocíclico 5 ó 6 miembros, con mayor preferencia, un grupo piperidilo) opcionalmente sustituido con alcoxi de C_{1-6}-carbonilo, cicloalquil de C_{5-8}-carbonilo, alquil de C_{1-6}-ureido o cicloalquil de C_{5-8}-ureido.

Como "alquileno de C_{1-3}" del "alquileno de C_{1-3} opcionalmente sustituido" para Z^d, se prefiere metileno.

El "alquileno de C_{1-3}" del "alquileno de C_{1-3} opcionalmente sustituido" para Z^d está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, alcoxi de C_{1-4}, alquilo de C_{1-4}-carbonilo, carboxi, alcoxi de C_{1-4}-carbonilo, ciano, carbamoilo, sulfamoilo, nitro, amino, alquilo de C_{1-4}-carbonilamino, alcoxi de C_{1-4}-carbonilamino y alquil de C_{1-4}-sulfonilamino.

En la fórmula antes mencionada, la fórmula estructural parcial

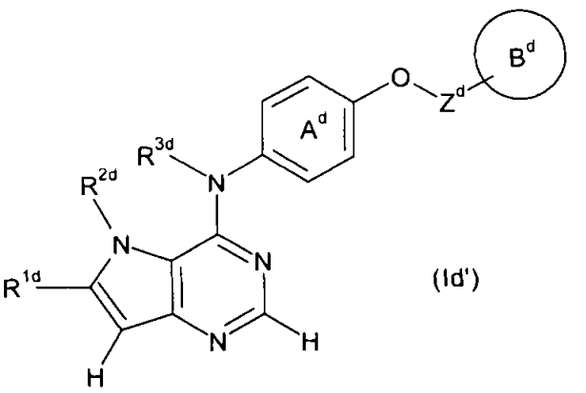


es preferentemente

en donde cada símbolo es como se definió con anterioridad.

Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (Id') o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Id')"):

[compuesto (Id')]



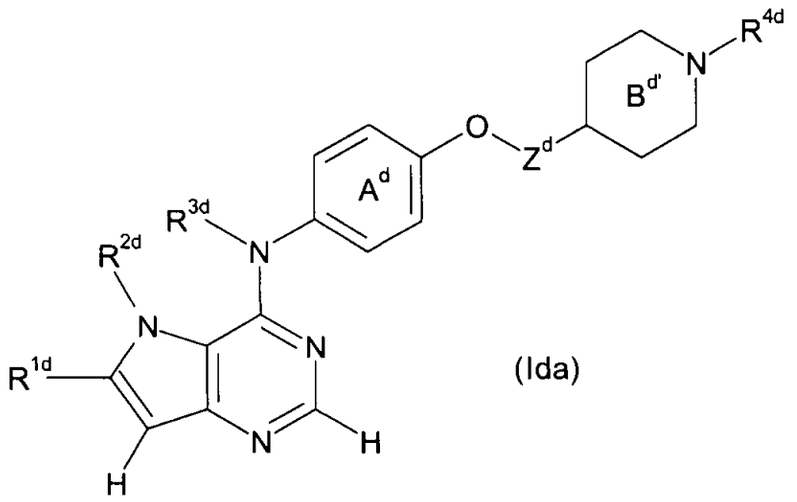
(Id')

en donde cada símbolo es como se definió con anterioridad.

Como modalidad preferida de compuesto (Id), se puede mencionar un compuesto representado por la siguiente fórmula (Ida) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como

"compuesto (Ida)"):

[compuesto (Ida)]



(Ida)

en donde R^{4d} es un grupo acilo o un grupo ureido opcionalmente sustituido, el anillo $B^{d'}$ es un grupo piperidilo también opcionalmente sustituido además de R^{4d}, y los otros símbolos son como se definieron con anterioridad.

En la fórmula antes mencionada (Ida), como el "grupo acilo" para R^{4d}, son preferibles un grupo alcoxi de C_{1-6}-carbonilo y un grupo cicloalquil de C_{5-8}-carbonilo.

En la fórmula antes mencionada (Ida), como el "grupo ureido opcionalmente sustituido" para R^{4d}, se prefieren un grupo alquil de C_{1-6}-ureido y un grupo cicloalquil de C_{5-8}-ureido.

El "grupo piperidilo" del "grupo piperidilo también opcionalmente sustituido" para el anillo $B^{d'}$ opcionalmente tiene, además de R^{4d}, 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se

pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Como modalidad más preferida del compuesto (Id), se puede mencionar el compuesto (Ida) en donde, en la fórmula antes citada (Ida),

R^{1d} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2d} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6d}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6d}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6d} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3d} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^d es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

Z^d es metileno,

el anillo $B^{d'}$ es un grupo piperidilo, y

R^{4d} es un grupo alcoxi de C_{1-6}-carbonilo, un grupo cicloalquil de C_{5-8}-carbonilo, un grupo alquil de C_{1-6}-ureido o un grupo cicloalquil de C_{5-8}-ureido.

Como otra modalidad de mayor preferencia de compuesto (Id), se puede mencionar el compuesto (Ida) en donde la fórmula antes mencionada (Ida),

R^{3d} es un átomo de hidrógeno, y

el anillo A^d es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

Como compuesto (Id), se pueden mencionar con preferencia particular,

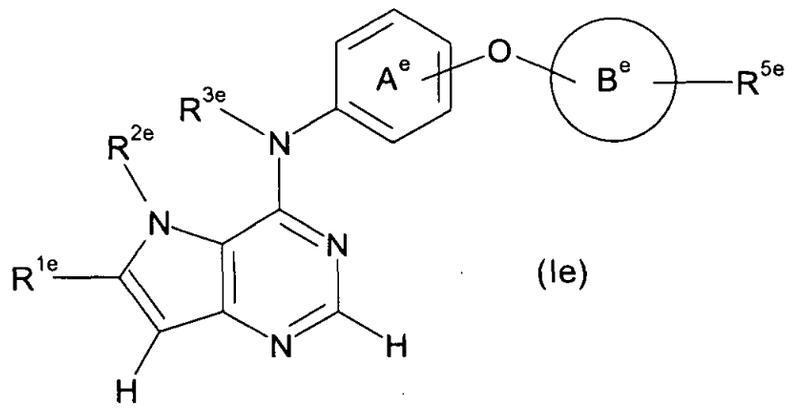
4-{[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]metil}piperidin-1-carboxilato de ter-butilo, y

4-[(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)metil]piperidin-1-carboxilato de ter-butilo,

y sus sales.

[compuesto (Ie)]

La presente invención también provee un compuesto representado por la fórmula (Ie) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Ie)").



(Ie)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (Ie), como el "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para R^{1e}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1e} es con preferencia un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno o un grupo ciano, con particular preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través

de un átomo de carbono o un átomo de azufre" para R^{2e}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6e}-CO-$(CH_2)_n$-SO_2-,

(b) -NR^{6e}-CO-$(CH_2)_n$-OH,

(c) -O-$(CH_2)_n$-OH, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6e} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4}.

Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3e}, se prefiere un grupo alquilo de C_{1-6}.

R^{3e} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3e} unido al átomo de carbono en el anillo Benceno adyacente, se puede

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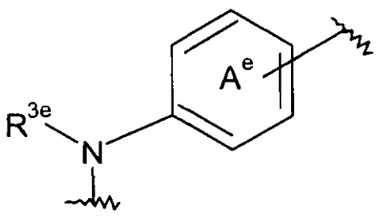
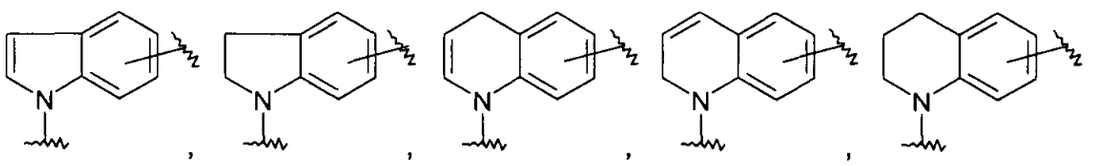
mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,



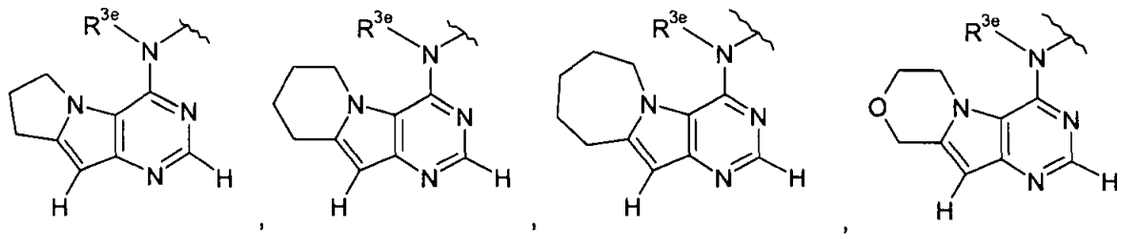
y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1e} y R^{2e} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del

anillo opcionalmente sustituida" formada por R^{1e} y R^{2e} unidas entre sí se pueden mencionar, por ejemplo,

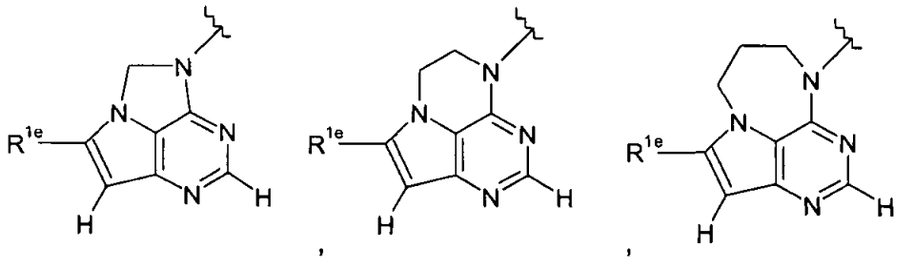


en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2e} y R^{3e} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2e} y R^{3e} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del

anillo opcionalmente sustituida" formada por R^{1e} y R^{2e}, o R^{2e} y R^{3e} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^e tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^e es con preferencia un el anillo Benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

Como grupo alquilo lineal en R^{5e}, se puede mencionar un grupo alquilo lineal con 1 a 10 (con preferencia 1 a 8, con mayor preferencia 1 a 6) átomos de carbono. Específicamente, se pueden mencionar metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo y decilo.

Como grupo alquilo ramificado en R^{5e}, se puede mencionar un grupo alquilo ramificado con 3 a 10 (con preferencia 3 a 8, con mayor preferencia 3 a 6) átomos de carbono. Específicamente, se pueden mencionar isopropilo,

isobutilo, sec-butilo, ter-butilo, isopentilo, neopentilo, 1-etilpropilo, isohexilo, 1,1-dimetilbutilo, 2,2-dimetilbutilo, 3,3-dimetilbutilo, 2-etilbutilo y similares.

Como sustituyente para el "arilo" del "grupo alquilo lineal sustituido con arilo opcionalmente sustituido, que está también opcionalmente halogenado o hidroxilado", "grupo hidroxi sustituido con arilo opcionalmente sustituido" y "grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con arilo opcionalmente sustituido" para R^{5e}, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Como sustituyente de "grupo alquilo ramificado opcionalmente sustituido", "grupo alquenilo opcionalmente sustituido" y "grupo cicloalquilo opcionalmente sustituido" para R^{5e}, se pueden mencionar sustituyentes similares a los del grupo sustituyente U antes mencionado.

Como "grupo alquilo lineal sustituido con grupo heterocíclico opcionalmente sustituido" para R^{5e}, se prefiere un grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6}.

Como "grupo alquilo lineal sustituido con imino opcionalmente sustituido" para R^{5e}, se prefiere un grupo

alquilo de C_{1-6} lineal sustituido con hidroxiimino o alcoxi de C_{1-6}-imino.

Como "grupo alquilo lineal sustituido con arilo opcionalmente sustituido, que está también opcionalmente halogenado o hidroxilado" para R^{5e}, se prefiere un grupo alquilo de C_{1-6} lineal sustituido con arilo de C_{6-14}, que está también opcionalmente halogenado o hidroxilado.

Como "grupo alquilo ramificado opcionalmente sustituido" para R^{5e}, se prefiere un grupo alquilo de C_{3-6} ramificado opcionalmente halogenado.

Como "grupo alquenilo opcionalmente sustituido" para R^{5e}, se prefiere un grupo alquenilo C_{2-6}.

Como "grupo hidroxi sustituido con arilo opcionalmente sustituido" para R^{5e}, se prefiere un grupo hidroxi sustituido con arilo de C_{6-14}.

Como "alquilo de C_{2-6} halogenado" del "grupo hidroxi sustituido con alquilo de C_{2-6} halogenado" para R^{5e} y "grupo alquilo de C_{2-6} halogenado" para R^{5e}, se pueden mencionar etilo, propilo, isopropilo, butilo, isobutilo, t-butilo, pentilo, isopentilo, neopentilo, hexilo y similares, cada uno de los cuales está halogenado. De ellos, se prefiere etilo halogenado.

Como "grupo cicloalquilo opcionalmente sustituido" para R^{5e}, se prefiere un grupo cicloalquilo de C_{3-7} opcionalmente sustituido con ciano o carbamoilo.

Como "grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con arilo opcionalmente sustituido" para R^{5e}, se prefiere grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con fenilo.

Como "grupo alquilo lineal sustituido con grupo heterocíclico opcionalmente sustituido" para R^{5e}, se prefieren

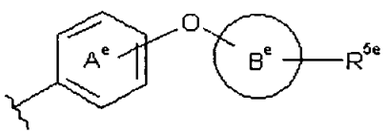
(i) un grupo metilo sustituido con grupo heterocíclico opcionalmente sustituido, y

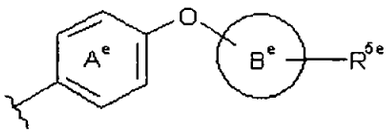
(ii) un grupo alquilo lineal sustituido con grupo heterocíclico sustituido.

El "grupo arilo de C_{6-14}" del "también grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^e opcionalmente tiene, además de R^{5c}, 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren alquilo de C_{1-6} opcionalmente halogenado y halógeno.

El anillo B^e es con preferencia un grupo arilo de C_{6-14} (con preferencia, un grupo fenilo) también opcionalmente sustituido, además de R^{5e}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

En la fórmula antes mencionada, la fórmula estructural parcial



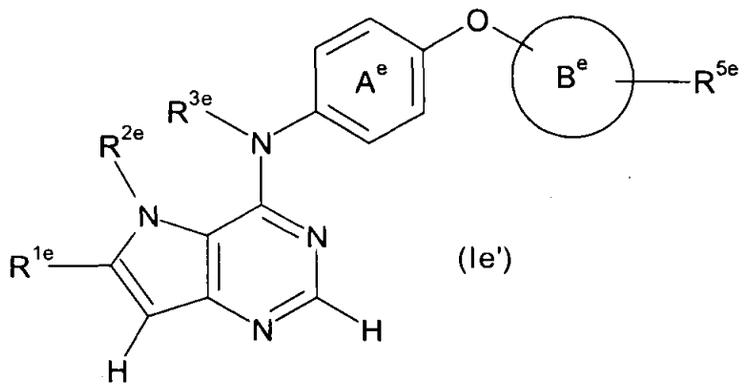


es preferentemente

en donde cada símbolo es como se definió con anterioridad.

Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (Ie') o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Ie')"):

[compuesto (Ie')]



(Ie')

en donde cada símbolo es como se definió con anterioridad.

Como modalidad preferida de compuesto (Ie), se puede mencionar el compuesto (Ie) en donde

R^{1e} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2e} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con

sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con -NR^{6e}-CO-$(CH_2)_n$-SO_2-,

(b) -NR^{6e}-CO-$(CH_2)_n$-OH,

(c) -O-$(CH_2)_n$-OH, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6e} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y -$(CH_2)_n$- está opcionalmente sustituido con alquilo de C_{1-4},

R^{3e} es un átomo de hidrógeno,

el anillo A^e es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5e} es

(i) un grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6},

(ii) un grupo alquilo de C_{1-6} lineal sustituido con hidroxiimino o alcoxi de C_{1-6}-imino,

(iii) un grupo alquilo de C_{1-6} lineal sustituido con arilo de C_{6-14}, que está también opcionalmente halogenado o hidroxilado,

(iv) un grupo alquilo de C_{3-6} ramificado

opcionalmente halogenado,

(v) un grupo alquenilo C_{2-6},

(vi) un grupo hidroxi sustituido con arilo de C_{6-14},

(vii) un grupo hidroxi sustituido con alquilo de C_{1-6},

(viii) un grupo hidroxi sustituido con alquilo de C_{2-6} halogenado,

(ix) un grupo alquilo de C_{2-6} halogenado,

(x) un grupo cicloalquilo de C_{3-7} opcionalmente sustituido con ciano o carbamoilo, o

(xi) un grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con fenilo, y

el anillo B^e es un grupo arilo de C_{6-14} también opcionalmente sustituido, además de R^{5e}, con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y halógeno.

En la modalidad preferida antes mencionada del compuesto (Ie), se prefiere un compuesto en donde

el "grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6}" para R^{5e} es

(i) un grupo heterociclil-metilo de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos

seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que opcionalmente tiene alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} heterociclilo-lineal de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, y que tiene alquilo de C_{1-6}.

Como compuesto (Ie), se pueden mencionar, con preferencia particular,

2-[4-({3-cloro-4-[3-(1,1-difluoroetil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol,

O-etiloxima de (1Z)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona,

1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ol,

1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona,

N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida, y

N-{2-[4-({3-cloro-4-[3-(1-

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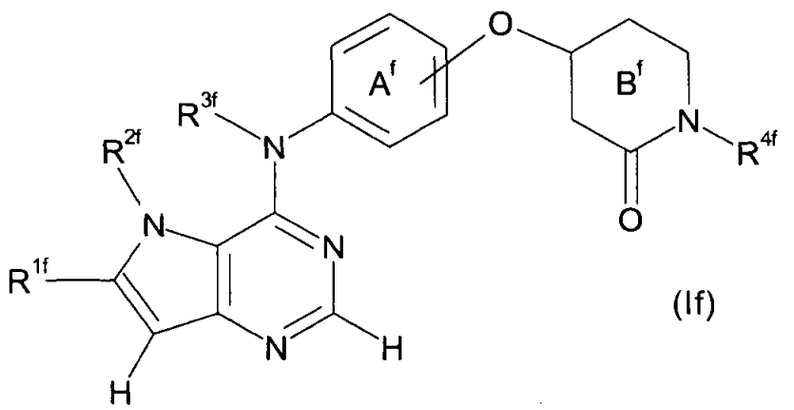
cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

y sus sales.

[compuesto (If)]

La presente invención también provee un compuesto representado por la fórmula (If) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (If)").



(If)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (If), como el "grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para R^{1f}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo

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sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1f} es con preferencia un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno o un grupo ciano, con particular preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2f}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6f}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6f} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4}.

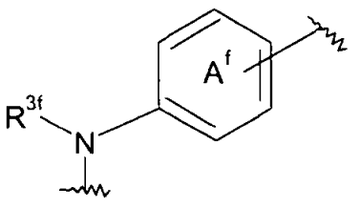
Como "grupo hidrocarburo alifático" del "grupo

hidrocarburo alifático opcionalmente sustituido" para R^{3f}, se prefiere un grupo alquilo de C_{1-6}.

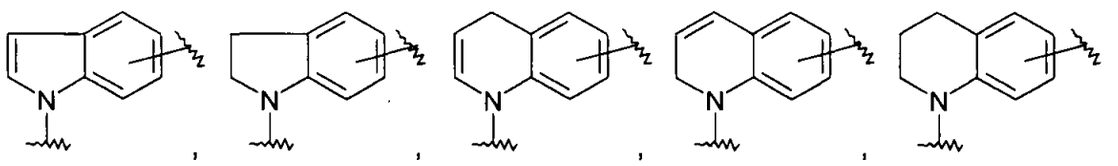
R^{3f} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3f} unido al átomo de carbono en el anillo Benceno adyacente, se puede mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,



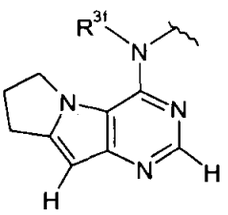
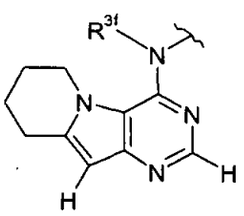
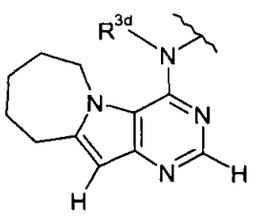
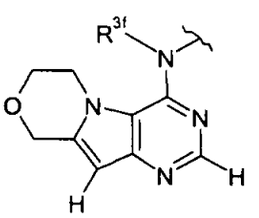
y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar

sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1f} y R^{2f} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1f} y R^{2f} unidas entre sí se pueden mencionar, por ejemplo,

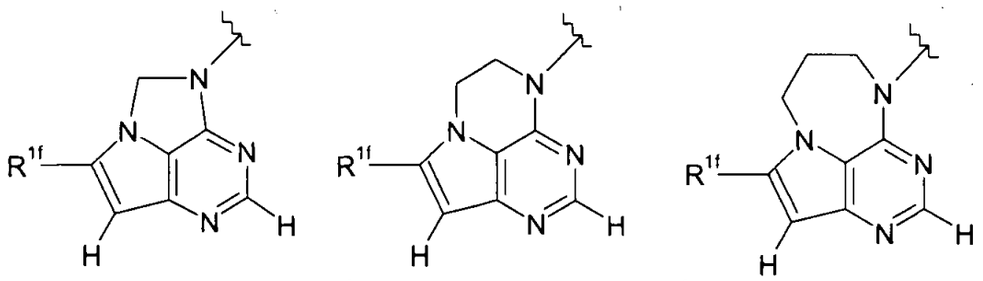





en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2f} y R^{3f} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2f} y R^{3f} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1f} y R^{2f}, o R^{2f} y R^{3f} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^f tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^f es con preferencia un el anillo Benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

El "grupo piperidilo" del "grupo piperidilo también

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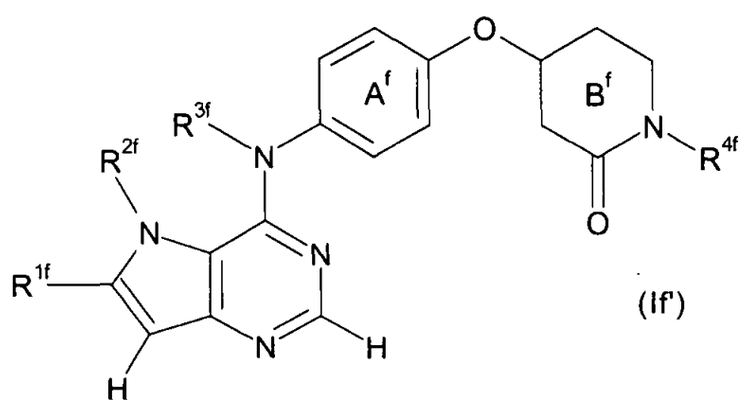
Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (If') o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (If')"):

[compuesto (If')]



(If')

en donde cada símbolo es como se definió con anterioridad.

Como modalidad preferida de compuesto (If), se puede mencionar el compuesto (If) en donde

R^{1f} es un átomo de hidrógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2f} es

(i) un grupo alquilo de C_{1-6}, o

(ii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6f}-CO-(CH_2)_n-SO_2-$,

(b) $-NR^{6f}-CO-(CH_2)_n-OH$,

(c) $-O-(CH_2)_n-OH$, y

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(d) hidroxi

en donde n es un número entero de 1 a 4, R^{6f} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3f} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

el anillo A^f es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

el anillo B^f es un grupo piperidilo, y

R^{4f} es (i) un grupo alquilo de C_{1-6} opcionalmente sustituido, o (ii) un grupo cicloalquilo de C_{5-8} opcionalmente sustituido.

Como otra modalidad preferida del compuesto (If), se puede mencionar el compuesto (If) en donde

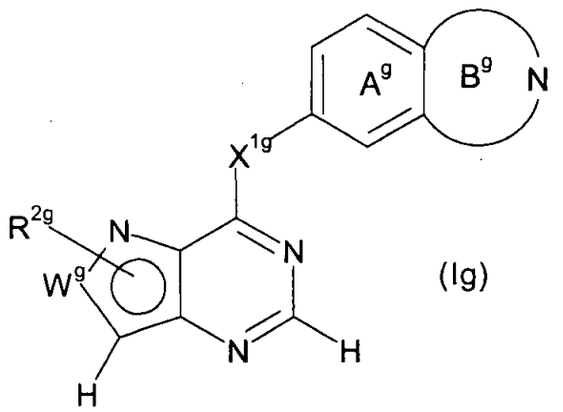
R^{3f} es un átomo de hidrógeno, y

el anillo A^f es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

[compuesto (Ig)]

La presente invención también provee un compuesto representado por la fórmula (Ig) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Ig)").

S42



(Ig)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula (Ig), el "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^g tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Como "heterociclo que contiene nitrógeno" del "heterociclo con contenido de nitrógeno opcionalmente sustituido" para el anillo B^g, se puede mencionar, por ejemplo, un heterociclo aromático de 3 a 8 miembros (con preferencia de 5 ó 6 miembros) o un heterociclo alifático insaturado (con preferencia saturado). De ellos, se pueden usar preferentemente grupos heterocíclicos alifáticos de 3 a 8 miembros (con preferencia de 5 ó 6 miembros) saturados o insaturados (con preferencia saturados) tales como azetidina,

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pirrolidina, piperidina, homopiperidina, heptametilenimina, morfolina, tiomorfolina, piperazina, homopiperazina y similares, y otros.

El "heterociclo que contiene nitrógeno" tiene opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyente, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3g}, se prefiere un grupo alquilo de C_{1-6}.

El "alquileno de C_{1-4}" y "-O-(alquileno de C_{1-4})-" del "alquileno de C_{1-4} u -O-(alquileno de C_{1-4})-, cada uno de los cuales está opcionalmente sustituido," para Y^{1g} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de halógeno, hidroxi, alcoxi de C_{1-4}, alquilo de C_{1-4}-carbonilo, carboxi, alcoxi de C_{1-4}-carbonilo, ciano, carbamoilo, sulfamoilo, nitro, amino, alquilo de C_{1-4}-carbonilamino, alcoxi de C_{1-4}-carbonilamino y alquil de C_{1-4}-sulfonilamino.

X^{1g} es con preferencia $-NR^{3g}-$. En la fórmula, R^{3g} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

W^g es con preferencia $C(R^{1g})$.

Como "grupo opcionalmente sustituido unido a través

de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno" para R^{1g}, se prefieren un grupo ciano y un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden mencionar sustituyentes similares a los del grupo sustituyente X antes mencionado. De ellos, se prefiere halógeno.

R^{1g} es con preferencia un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado, con mayor preferencia un átomo de hidrógeno.

Como "grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2g}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{5g}-CO-(CH_2)_n-SO_2-$,

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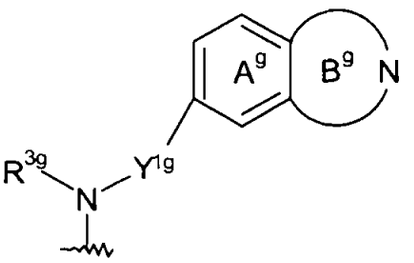
(d) hidroxi, y

(e) amino

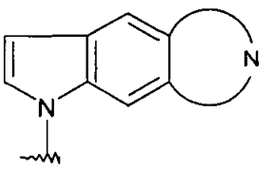
en donde n es un número entero de 1 a 4, R^{5g} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4}.

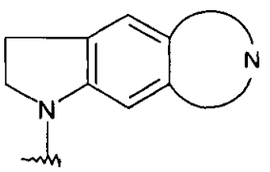
Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3g} unido al átomo de carbono en el anillo Benceno para el anillo A^g, se puede mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

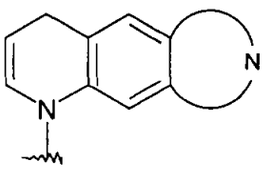
Específicamente,

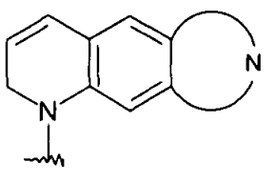


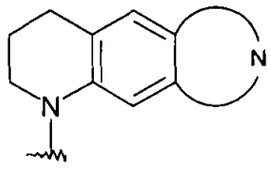
en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,









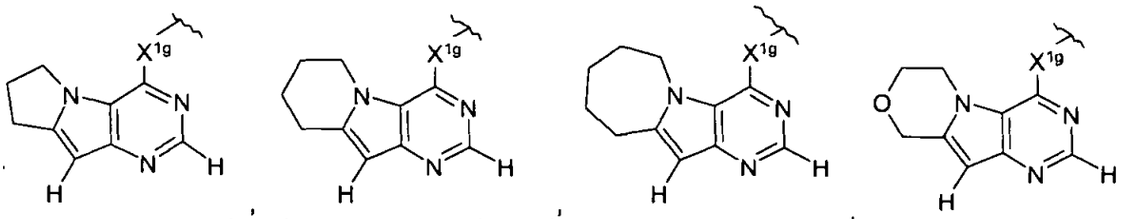


y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1g} y R^{2g} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1g} y R^{2g} unidas entre sí se pueden mencionar, por ejemplo,

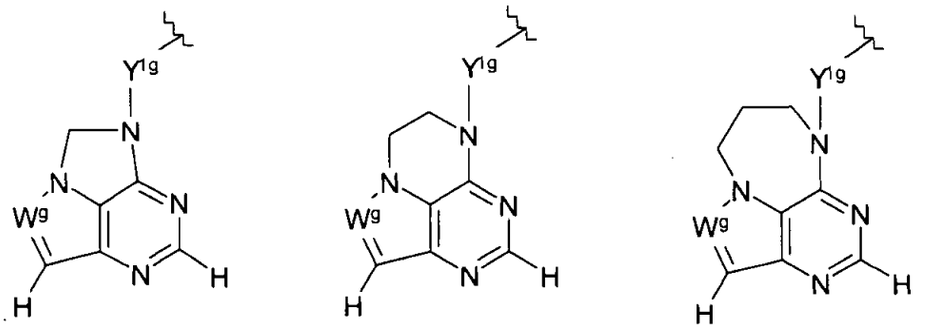


en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2g} y R^{3g} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2g} y R^{3g} unidas entre sí se pueden mencionar, por ejemplo,

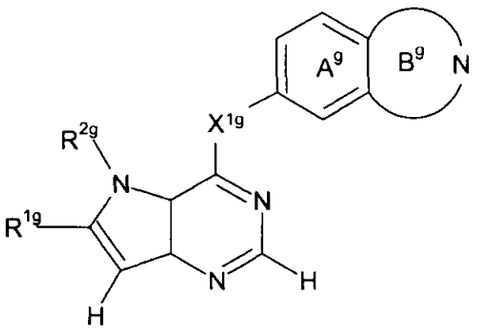


en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1g} y R^{2g}, o R^{2g} y R^{3g} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

Cuando W^g es $C(R^{1g})$, el compuesto (Ig) está representado por la siguiente fórmula (IgA):



(IgA)

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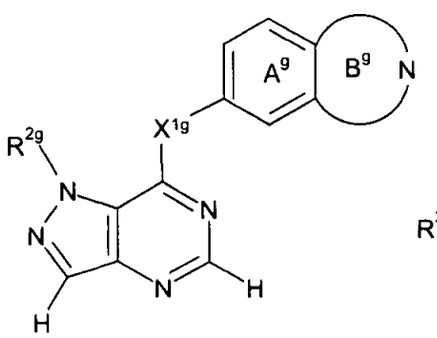
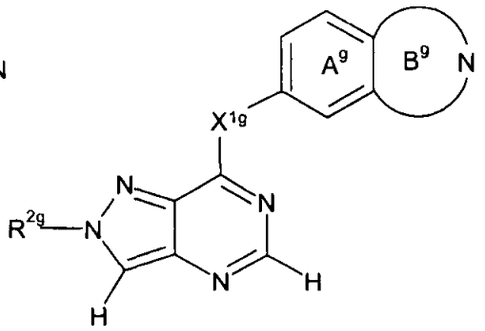
en donde cada símbolo es como se definió con anterioridad.

Cuando W^g es N, el compuesto (Ig) está representado por la siguiente fórmula (IgB) o (IgC):



(IgB)

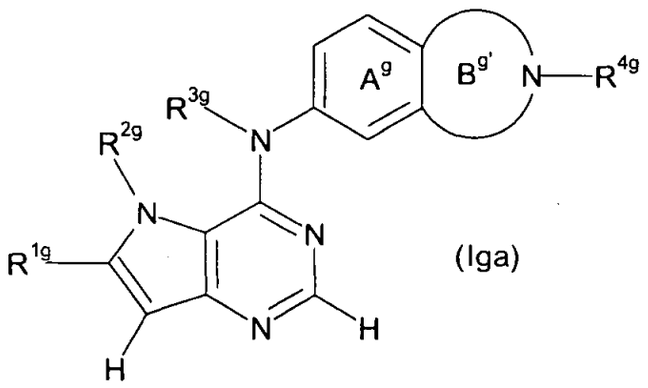


(IgC)

en donde cada símbolo es como se definió con anterioridad.

[compuesto (Iga)]

Como modalidad preferida de compuesto (Ig), se puede mencionar un compuesto representado por la siguiente fórmula (Iga) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Iga)"):



(Iga)

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en donde R^{4g} es un grupo hidrocarburo opcionalmente sustituido, el anillo $B^{g'}$ es un heterociclo con contenido de nitrógeno de 5 ó 6 miembros también opcionalmente sustituido además de R^{4g}, y los otros símbolos son como se definieron con anterioridad.

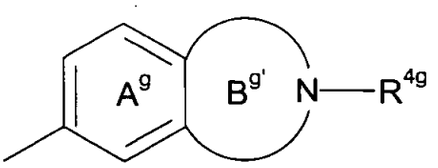
En la fórmula antes mencionada (Iga), como "heterociclo con contenido de nitrógeno de 5 ó 6 miembros" del "también opcionalmente sustituido heterociclo con contenido de nitrógeno de 5 ó 6 miembros" para el anillo $B^{g'}$, se puede mencionar un "heterociclo que contiene nitrógeno" de 5 ó 6 miembros del "heterociclo que contiene nitrógeno" del "heterociclo con contenido de nitrógeno opcionalmente sustituido" para el anillo B^{g}.

R^{4g} es con preferencia (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, (iii) un grupo alquilo de C_{1-8}, o (iv) un grupo arilo de C_{6-14} opcionalmente sustituido, con mayor preferencia (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, alquil de C_{1-6}-carbamoilo y haloalcoxi de C_{1-6}, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, o (iii) un grupo arilo de C_{6-14} opcionalmente sustituido.

El "grupo aril C_{6-14}-alquilo de C_{1-8}" del

"opcionalmente sustituido grupo aril C_{6-14}-alquilo de C_{1-8}" para R^{4g}, "grupo heterociclil-alquilo de C_{1-8}" del "grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido" para R^{4g} y "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para R^{4g} tienen opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

En la fórmula antes mencionada, la fórmula estructural parcial



es con preferencia

en donde cada símbolo es como se definió con anterioridad.

Como modalidad preferida de compuesto (Ig), se puede mencionar el compuesto (Iga) en donde, en la fórmula antes mencionada (Iga),

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6} opcionalmente sustituido,

R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

R^{4g} es (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, (iii) un grupo alquilo de C_{1-8}, o (iv) un grupo arilo de C_{6-14} opcionalmente sustituido.

Como otra modalidad de mayor preferencia de compuesto (Ig), compuesto (Iga) en donde, en la fórmula antes mencionada (Iga),

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6}, o

(iii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

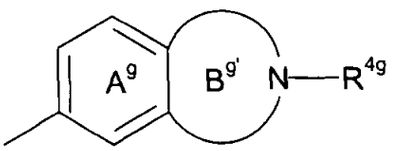
(c) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{5g}-CO-(CH_2)_n-SO_2-$,

(d) hidroxi, y

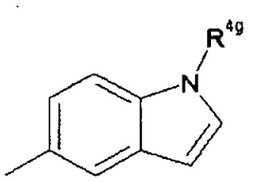
(e) amino

en donde n es un número entero de 1 a 4, R^{5g} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

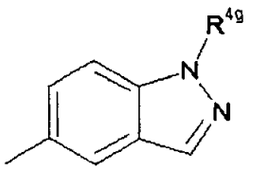
R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},



es la fórmula



o



y

R^{4g} es (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, alquil de C_{1-6}-carbamoilo y haloalcoxi de C_{1-6}, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, o (iii) un grupo arilo de C_{6-14} opcionalmente sustituido.

Como compuesto (Ig), se pueden mencionar con preferencia particular

N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

N-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida,

N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida,

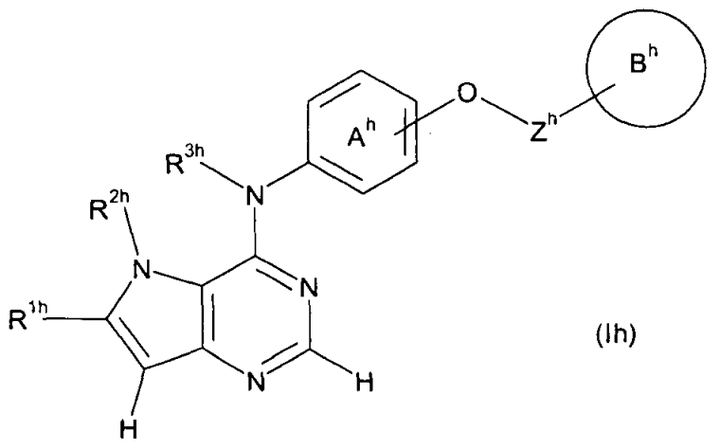
N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indazol-1-il)metil]benzamida, y

N-(ter-butil)-6-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piridin-2-carboxamida,

y sus sales.

[compuesto (Ih)]

La presente invención también provee un compuesto representado por la fórmula (Ih) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Ih)").



(Ih)

en donde cada símbolo es como se definió con anterioridad.

En la fórmula antes mencionada (Ih), como el "grupo

opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre" para R^{2h}, se prefiere un grupo alquilo de C_{1-8} opcionalmente sustituido. Como grupo alquilo de C_{1-8}, se prefiere un grupo alquilo de C_{1-6}.

Como sustituyentes para el grupo alquilo, se pueden usar sustituyentes similares a los del grupo sustituyente X antes mencionado, con preferencia, sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{5g}-CO-(CH_2)_n-SO_2-$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6h} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4}.

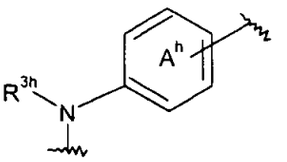
Como "grupo hidrocarburo alifático" del "grupo hidrocarburo alifático opcionalmente sustituido" para R^{3h}, se prefiere un grupo alquilo de C_{1-6}.

R^{3h} es con preferencia un átomo de hidrógeno o un grupo alquilo de C_{1-6}, con mayor preferencia un átomo de hidrógeno.

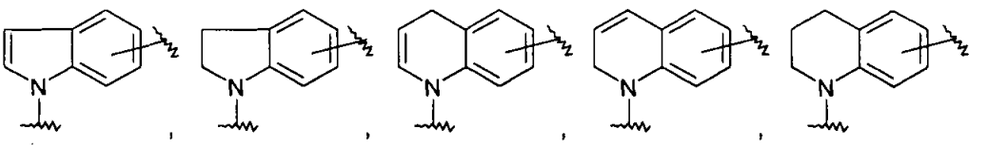
Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{3h} unido al átomo de carbono en el anillo Benceno adyacente, se puede

mencionar un heterociclo que contiene nitrógeno saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 ó 6 miembros).

Específicamente,



en donde cada símbolo es como se definió con anterioridad, es, por ejemplo,



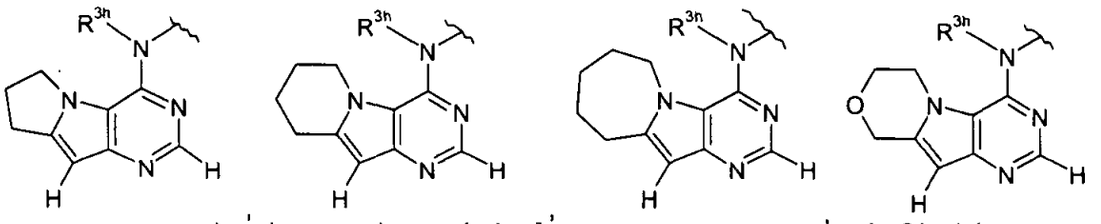
y similares.

La "estructura del anillo" tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

R^{1h} y R^{2h} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del

anillo opcionalmente sustituida" formada por R^{1h} y R^{2h} unidas entre sí se pueden mencionar, por ejemplo,

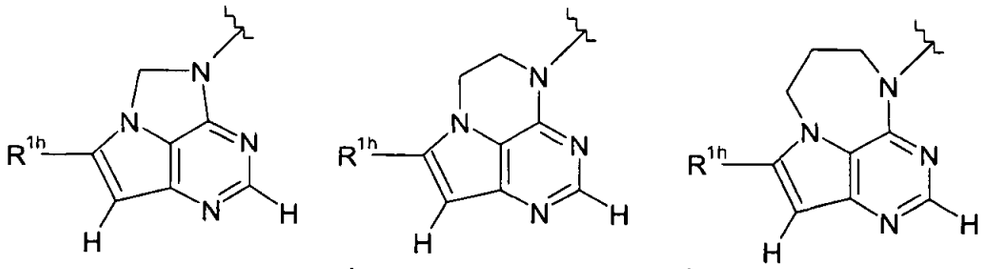


en donde cada símbolo es como se definió con anterioridad,

y similares.

R^{2h} y R^{3h} se unen opcionalmente entre sí para formar una estructura de anillo opcionalmente sustituida. Como "estructura del anillo", se puede mencionar un heterociclo saturado o insaturado (con preferencia saturado) de 4 a 8 miembros (con preferencia de 5 a 7 miembros).

Como "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{2h} y R^{3h} unidas entre sí se pueden mencionar, por ejemplo,



en donde cada símbolo es como se definió con anterioridad,

y similares.

La "estructura del anillo" del "estructura del anillo opcionalmente sustituida" formada por R^{1h} y R^{2h}, o R^{2h} y

R^{3h} tiene opcionalmente 1 a 5 (con preferencia 1 a 3, con mayor preferencia 1 ó 2), sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El "el anillo Benceno" del "el anillo Benceno opcionalmente sustituido" para el anillo A^h tiene opcionalmente 1 a 3 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado. De ellos, se prefieren halógeno y metilo.

El anillo A^h es con preferencia un el anillo Benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo.

Como "alquileno de C_{1-3}" del "alquileno de C_{1-3} opcionalmente sustituido" para Z^h, se prefiere metileno.

El "alquileno de C_{1-3}" del "alquileno de C_{1-3} opcionalmente sustituido" para Z^h está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo que consiste en halógeno, hidroxi, alcoxi de C_{1-4}, alquilo de C_{1-4}-carbonilo, carboxi, alcoxi de C_{1-4}-carbonilo, ciano, carbamoilo, sulfamoilo, nitro, amino, alquilo de C_{1-4}-carbonilamino, alcoxi de C_{1-4}-carbonilamino y alquil de C_{1-4}-sulfonilamino.

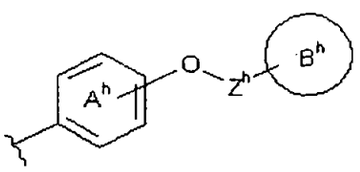
Como "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^h, se prefiere un grupo fenilo.

Como "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo B^h, se prefieren un grupo piridilo y un grupo piperidilo.

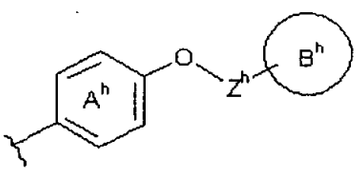
Como "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo opcionalmente sustituido C_{5-8}" para el anillo B^h, se prefiere un grupo ciclohexilo.

El "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo B^h, el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo B^h y el "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo opcionalmente sustituido C_{5-8}" para el anillo B^h tienen opcionalmente 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

En la fórmula antes mencionada, la fórmula estructural parcial



es preferentemente



en donde cada símbolo es como se definió con

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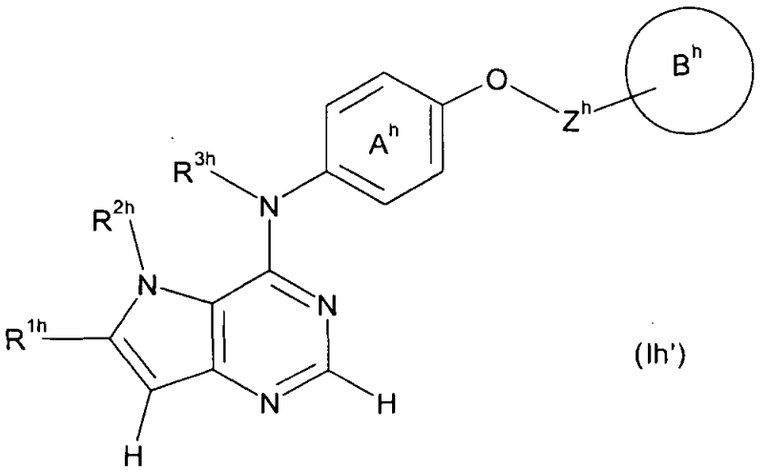
anterioridad.

Como ejemplos específicos, se puede mencionar un compuesto representado por la siguiente fórmula (Ih') o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Ih')"):

[compuesto (Ih')]



(Ih')

en donde cada símbolo es como se definió con anterioridad.

Como modalidad preferida de compuesto (Ih), se puede mencionar un compuesto representado por la siguiente fórmula (Iha) o una de sus sales (en la presente memoria descriptiva, de ahora en más abreviado a veces como "compuesto (Iha)"):

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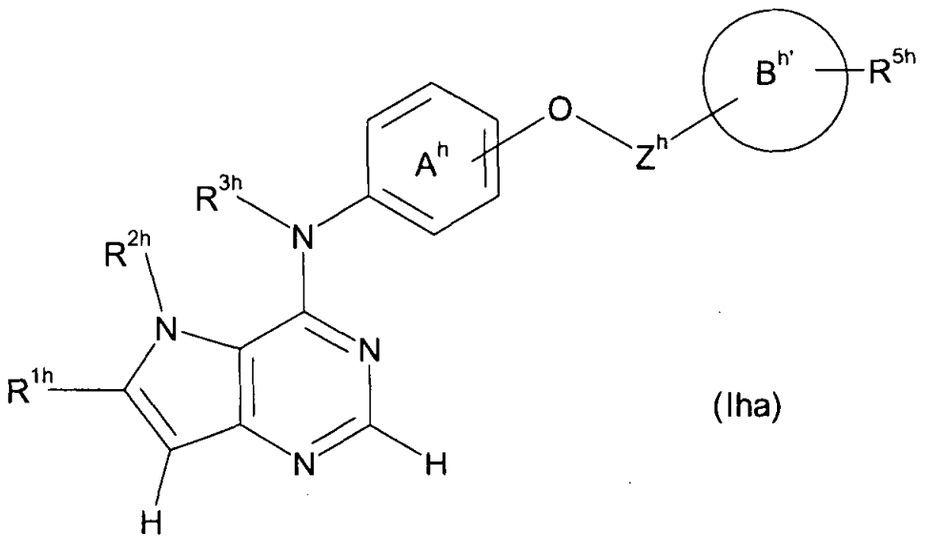

(Iha)

en donde

R^{5h} es

(i) un grupo amino opcionalmente sustituido,

(ii) un grupo carbamoilo opcionalmente sustituido,

(iii) un grupo ureido opcionalmente sustituido,

(iv) un grupo sulfamoilo opcionalmente sustituido,

(v) un grupo heterocíclico opcionalmente sustituido,

(vi) un grupo hidrocarburo opcionalmente sustituido,

(vii) un átomo de halógeno, o

(viii) un grupo carboxilo opcionalmente sustituido,

y

el anillo $B^{h'}$ es (i) un grupo arilo de C_{6-14}, (ii) un grupo heterocíclico, o (iii) un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido además de R^{5h}, y los otros símbolos son como se definieron con

anterioridad.

En la fórmula antes mencionada (Iha), como el "grupo amino opcionalmente sustituido" para R^{5h}, se prefieren un grupo amino, un grupo alquil de C_{1-6}-amino, un grupo alcanoil C_{1-6}-amino opcionalmente halogenado, un grupo hidroxi-alcanoil C_{1-6}-amino, un grupo alcanoil C_{1-6}-amino con hidroxi y halógeno, un grupo cicloalquil de C_{3-7}-alcanoil C_{1-6}-amino, un grupo alcanoil C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno, un grupo alquilsulfonil C_{1-6}-alcanoil C_{1-6}-amino, un grupo cicloalquil de C_{3-7}-carbonil-amino y un grupo alcoxi de C_{1-6}-carbonil-amino.

Como "grupo carbamoilo opcionalmente sustituido" para R^{5h}, se prefieren un grupo carbamoilo, un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado, un grupo hidroxi-alquil de C_{1-6}-carbamoilo, un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo, un grupo cicloalquil de C_{3-7}-carbamoilo, y un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno.

Como "grupo ureido opcionalmente sustituido" para R^{5h}, se prefieren un grupo ureido, un grupo alquil de C_{1-6}-ureido, un grupo cicloalquil de C_{3-7}-ureido, y un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre.

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Como "grupo sulfamoilo opcionalmente sustituido" para R^{5h}, se prefiere un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6}.

Como "grupo heterocíclico opcionalmente sustituido" para R^{5h}, se prefiere un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo.

Como "grupo hidrocarburo opcionalmente sustituido" para R^{5h}, se prefieren un grupo alquilo de C_{1-6} opcionalmente halogenado y un grupo alcoxi de C_{1-6}-carbonilo.

Como "grupo carboxilo opcionalmente sustituido" para R^{5h}, se prefiere un grupo carboxilo.

En la fórmula antes mencionada (Iha), como el "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo $B^{h'}$, se prefiere un grupo fenilo.

Como "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo $B^{h'}$, se prefieren un grupo piridilo y un grupo piperidilo.

Como "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo opcionalmente sustituido C_{5-8}" para el anillo $B^{h'}$, se prefiere un grupo ciclohexilo.

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El "grupo arilo de C_{6-14}" del "grupo arilo de C_{6-14} opcionalmente sustituido" para el anillo $B^{h'}$, el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para el anillo $B^{h'}$ y el "grupo cicloalquilo de C_{5-8}" del "grupo cicloalquilo opcionalmente sustituido C_{5-8}" para el anillo $B^{h'}$ tienen opcionalmente, además de R^{5h}, 1 a 5 sustituyentes iguales o diferentes en cualquier posición sustituible. Como sustituyentes, se pueden mencionar sustituyentes similares a los del grupo sustituyente V antes mencionado.

El anillo $B^{h'}$ es con preferencia un grupo fenilo, un grupo piridilo o un grupo piperidilo, cada uno de los cuales está también opcionalmente sustituido además de R^{5h}.

Como modalidad más preferida del compuesto (Ih), se puede mencionar el compuesto (Iha) en donde, en la fórmula antes mencionada (Iha),

R^{1h} es un átomo de halógeno o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2h} es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6}, o

(iii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{6h}-CO-(CH_2)_n-OH$,

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(c) alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6h}-CO-(CH_2)_n-SO_2-$, y

(d) hidroxi,

en donde n es un número entero de 1 a 4, R^{6h} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3h} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

Z^h es un enlace o metileno,

el anillo A^h es un anillo benceno opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo,

R^{5h} es

(i) un grupo amino,

(ii) un grupo alquil de C_{1-6}-amino,

(iii) un grupo alcanoil C_{1-6}-amino opcionalmente halogenado,

(iv) un grupo hidroxi-alcanoil C_{1-6}-amino,

(v) un grupo alcanoil C_{1-6}-amino con hidroxi y halógeno,

(vi) un grupo cicloalquil de C_{3-7}-alcanoil C_{1-6}-amino,

(vii) un grupo alcanoil C_{1-6}-amino con cicloalquilo de C_{3-7} y halógeno,

(viii) un grupo alquilsulfonil C_{1-6}-alcanoil C_{1-6}-

amino,

(ix) un grupo cicloalquil de C_{3-7}-carbonil-amino,

(x) un grupo alcoxi de C_{1-6}-carbonil-amino,

(xi) un grupo carbamoilo,

(xii) un grupo alquil de C_{1-6}-carbamoilo opcionalmente halogenado,

(xiii) un grupo hidroxi-alquil de C_{1-6}-carbamoilo,

(xiv) un grupo alcoxi de C_{1-6}-alquil de C_{1-6}-carbamoilo,

(xv) un grupo cicloalquil de C_{3-7}-carbamoilo,

(xvi) un grupo amino-carbonilo cíclico de 5 ó 6 miembros que opcionalmente contiene un átomo de oxígeno,

(xvii) un grupo ureido,

(xviii) un grupo alquil de C_{1-6}-ureido,

(xix) un grupo cicloalquil de C_{3-7}-ureido,

(xx) un grupo heterociclil-ureido de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre,

(xxi) un grupo sulfamoilo opcionalmente sustituido con alquilo de C_{1-6},

(xxii) un grupo heterocíclico de 5 a 8 miembros que contiene, además de átomos de carbono, 1 a 3 heteroátomos seleccionados del grupo que consiste en un átomo de nitrógeno, un átomo de oxígeno y un átomo de azufre, que está

opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado y alcoxi de C_{1-6}-carbonilo,

(xxiii) un grupo alquilo de C_{1-6} opcionalmente halogenado,

(xxiv) un grupo alcoxi de C_{1-6}-carbonilo,

(xxv) un átomo de halógeno, o

(xxvi) un grupo carboxilo, y

el anillo $B^{h'}$ es un grupo fenilo, un grupo piridilo o un grupo piperidilo, cada uno de los cuales está también opcionalmente sustituido además de R^{5h}.

Como compuesto (Ih), se pueden mencionar, con preferencia particular,

N-(3-{2-cloro-4-[(6-cloro-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil) ciclopropancarboxamida,

6-cloro-N-{3-cloro-4-[3-(trifluorometil)fenoxi]fenil}-5-metil-5H-pirrolo[3,2-d]pirimidin-4-amina,

N-[3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida, y

N-(ter-butil)-3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

y sus sales.

Como sales de los compuestos representados por las fórmulas, se pueden mencionar, por ejemplo, sales de metales, sales de amonio, sales con base orgánica, sales con ácido inorgánico, sales con ácido orgánico, sales con aminoácido básico o ácido y similares.

Como ejemplos preferidos de la sal de metales, se pueden mencionar, por ejemplo, sales de metales alcalinos tales como sal de sodio, sal de potasio y similares; sales de metales alcalinotérreos tales como sal de calcio, sal de magnesio, sal de bario y similares; sal de aluminio y similares.

Como ejemplos preferidos del sales con base orgánica, se pueden mencionar, por ejemplo, sales con trimetilamina, trietilamina, piridina, picolina, 2,6-lutidina, etanolamina, dietanolamina, trietanolamina, trometamin[tris(hidroximetil)metilamina], t-butilamina, ciclohexilamina, diciclohexilamina, N,N'-dibenciletilendiamina y similares.

Como ejemplos preferidos de sales con ácido inorgánico, se pueden mencionar, por ejemplo, sales con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, y similares.

Como ejemplos preferidos de sales con ácido orgánico, se pueden mencionar, por ejemplo, sales con ácido fórmico, ácido acético, ácido trifluoroacético, ácido

ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido málico, ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico y similares.

Como ejemplos preferidos de sales con aminoácido básico, se pueden mencionar, por ejemplo, sales con arginina, lisina, ornitina y similares.

Como ejemplos preferidos del sales con aminoácido ácido, se pueden mencionar, por ejemplo, sales con ácido aspártico, ácido glutámico y similares.

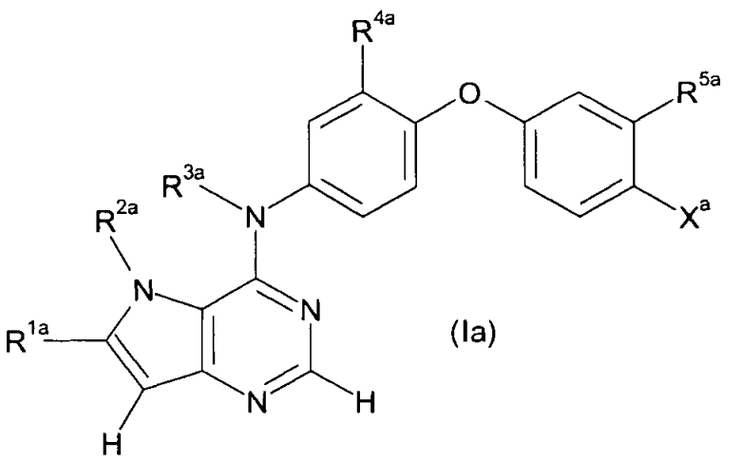
De ellos, se prefieren las sales farmacéuticamente aceptables. Cuando un compuesto contiene un grupo funcional ácido, se pueden mencionar, por ejemplo, sales inorgánicas tales como sales de metales alcalinos (por ejemplo, sal de sodio, sal de potasio etc.), sales de metales alcalinotérreos (por ejemplo, sal de calcio, sal de magnesio, sal de bario etc.) y similares, sal de amonio y similares. Y cuando un compuesto contiene un grupo funcional básico, se pueden mencionar, por ejemplo, sales con ácido inorgánico tales como ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico y similares, y sales con ácido orgánico tales como ácido acético, ácido ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico y similares.

[Métodos de producción]

De ahora en adelante, se explican los métodos de producción de los compuestos (Ia) a (Ih) de la presente invención.

[Método de producción A]

El compuesto (Ia) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



en donde cada símbolo es como se definió con anterioridad.

Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto (Ia) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de

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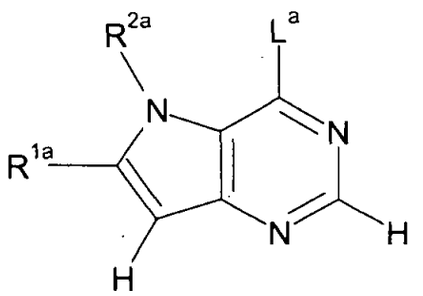
una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

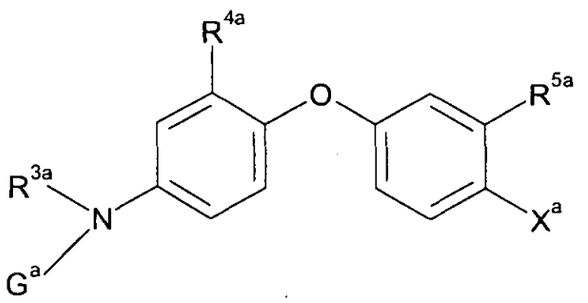
El compuesto (Ia) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIa)

en donde L^a es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIa)

en donde G^a es un átomo de hidrógeno o un átomo de

metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

G^a es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIIa) o una de sus sales se usan con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIa) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^a, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo de C_{1-4} inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados

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tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de

N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ia) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva

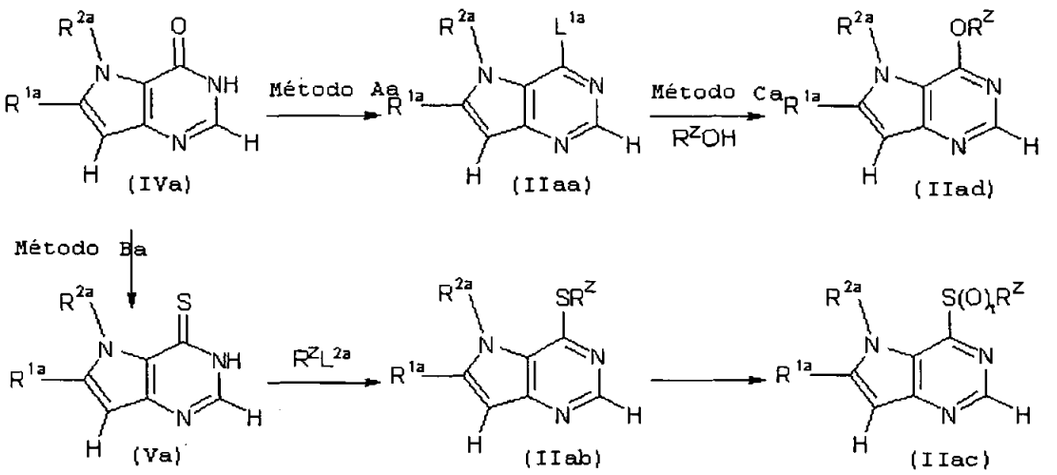
está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

El compuesto (Ia), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ia) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIa) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIa) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIaa), (IIab), (IIac) y (IIad) están comprendidos en el compuesto (IIa).



en donde L^{1a} y L^{2a} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Aa, el compuesto (IIaa) se puede producir haciendo reaccionar el compuesto (IVa) con un agente halogenante. Como método Ba, el compuesto (IVa) se hace reaccionar con un agente tionante para dar el compuesto (Va), que luego se hace reaccionar con un compuesto representado por R^zL^{2a} en presencia de una base para dar el compuesto (IIab), que luego se somete a una reacción de oxidación para dar el compuesto (IIac). Como método Ca, el compuesto (IIaa) se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIad).

Como agente halogenante en el Método Aa, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro

de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVa) en el compuesto (Va) en el Método Ba, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; y otros. La

reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2a} en la etapa de producción a partir del compuesto (Va) en el compuesto (IIab) en el Método Ba, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o

un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

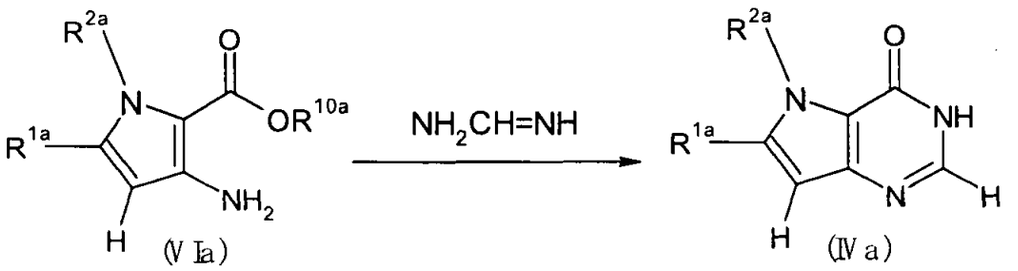
Como agente oxidante en la etapa de producción a partir del compuesto (IIab) en el compuesto (IIac) en el Método Ba, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIac) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIab), y cuando se produce el compuesto (IIac) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIab). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos

carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIaa) en el compuesto (IIad) en el Método Ca, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-

dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVa) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:

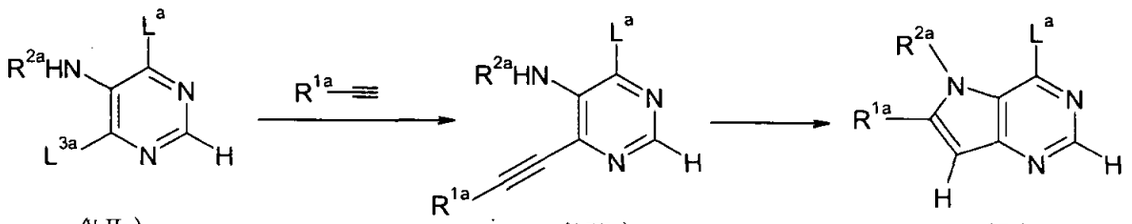


en donde R^{10a} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIa) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVa). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico,

tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IIa) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:



en donde L^{3a} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIa) en el compuesto (VIIIa) en este método, se puede llevar a cabo una reacción de conocimiento general en forma de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIa) se puede producir haciendo reaccionar el compuesto (VIIa) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:

R^{1a}—≡

en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o

un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIIa) en el compuesto (IIa) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0.01-1 equivalentes de yoduro de cobre para dar el compuesto (IIa). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-

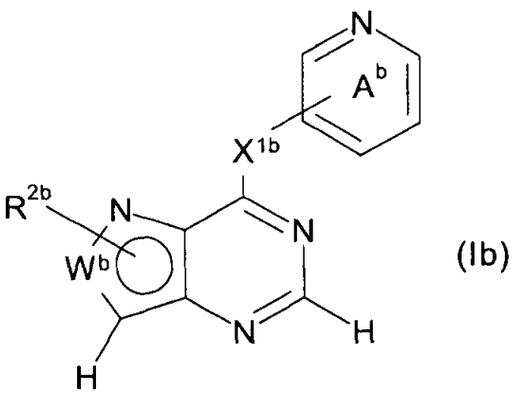
dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIa), se puede producir un compuesto de partida (IIa) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se

introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIa).

[Método de producción B]

El compuesto (Ib) de la presente invención se puede obtener, por ejemplo, por medio del método indicado por los siguientes esquemas de reacción o un método análogo y similares.



(Ib)

en donde cada símbolo es como se definió con anterioridad.

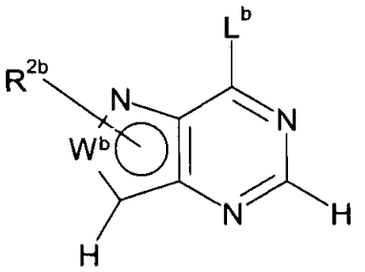
Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto (Ib) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de

una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

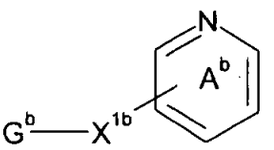
El compuesto (Ib) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIb)

en donde L^b es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIb)

en donde G^b es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

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Cuando X^{1b} es $-NR^{3b}-Y^{1b}-$, -O- o -S-, G^b es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

Cuando X^{1b} es $-CHR^{3b}-$, G^b puede ser un metal tales como litio, magnesio halogenado, cobre, cinc y similares.

El compuesto (IIIb) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIb) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^b, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados

tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de

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N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

El compuesto (Ib) en donde X^{1b} es -SO- o $-SO_2-$ se puede producir al someter el compuesto (Ib) en donde X^{1b} es -S-, a una reacción de oxidación. Como agente oxidante en la etapa de producción, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (Ib) en donde X^{1b} es -SO-, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto de partida, y cuando se produce el compuesto (Ib) en donde X^{1b} es $-SO_2-$, se emplea en aproximadamente 2-3 equivalentes referido al compuesto de partida. El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-

dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ib) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación

del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

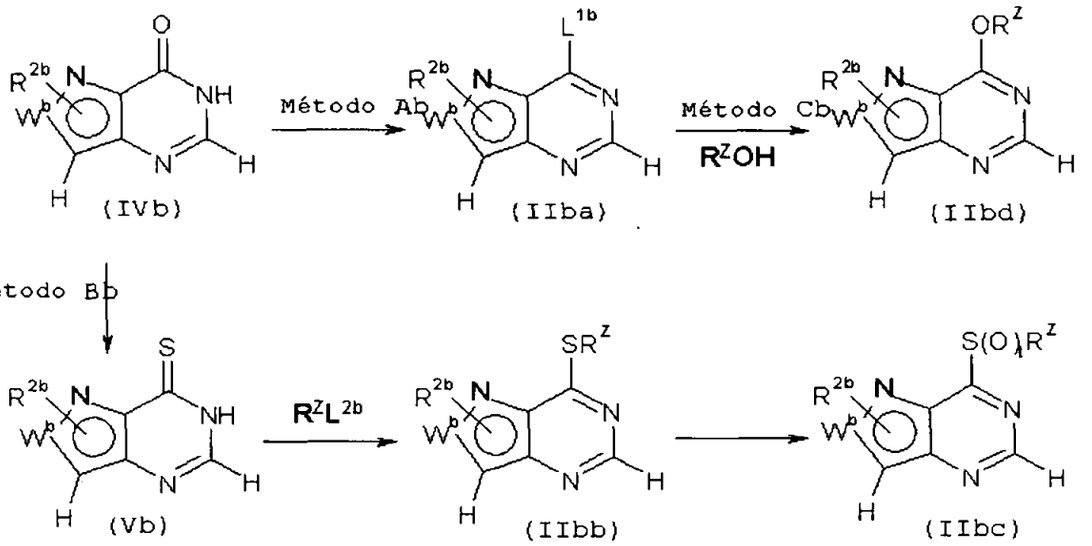
El compuesto (Ib), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ib) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIb) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIb) de este método de

producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIba), (IIbb), (IIbc), (IIbd) y (IIbe) están comprendidos en el compuesto (IIb).



en donde L^{1b} y L^{2b} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ab, el compuesto (IIba) se puede producir haciendo reaccionar el compuesto (IVb) con un agente halogenante. Como método Bb, el compuesto (IVb) se hace reaccionar con un agente tionante para dar el compuesto (Vb), que luego se hace reaccionar con un compuesto representado por R^zL^{2b} en presencia de una base para dar el compuesto (IIbb), que luego se somete a una reacción de oxidación para dar el compuesto (IIbc). Como método Cb, el compuesto (IIba) se hace reaccionar con un compuesto representado por R^zOH en

presencia de una base para dar el compuesto (IIbd).

Como agente halogenante en el Método Ab, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVb) en el compuesto (Vb) en el Método Bb, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden

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usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2b} en la etapa de producción a partir del compuesto (Vb) en el compuesto (IIbb) en el Método Bb, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol,

etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

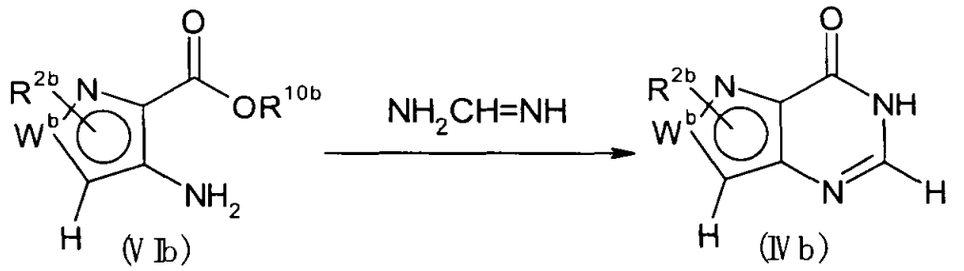
Como agente oxidante en la etapa de producción a partir del compuesto (IIbb) en el compuesto (IIbc) en el Método Bb, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIbc) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIbb), y cuando se produce el compuesto (IIbc) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIbb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo,

tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIba) en el compuesto (IIbd) en el Método Cb, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano,

cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVb) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:



en donde R^{10b} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIb) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVb). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol,

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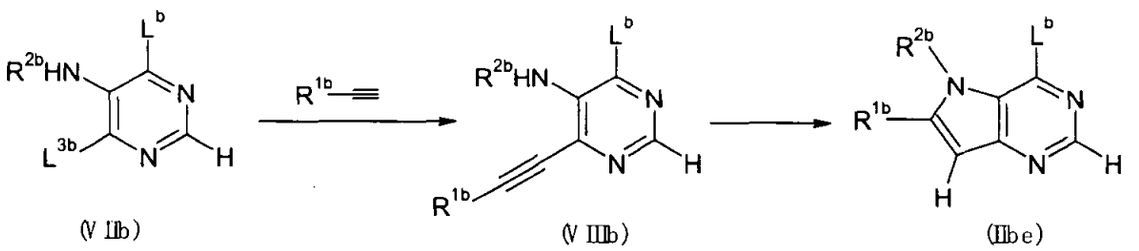
etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Cuando W^b es $C(R^{1b})$, el compuesto (IIbe) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:

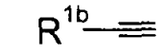


(VIIb) (VIIIb) (IIbe)

en donde L^{3b} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIb) en el compuesto (VIIIb) en este método, se puede llevar a cabo una reacción de conocimiento general en forma

de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIb) se puede producir haciendo reaccionar el compuesto (VIIb) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:



en presencia de una base, aproximadamente 0.01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter

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dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIIb) en el compuesto (IIbe) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIbe). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno,

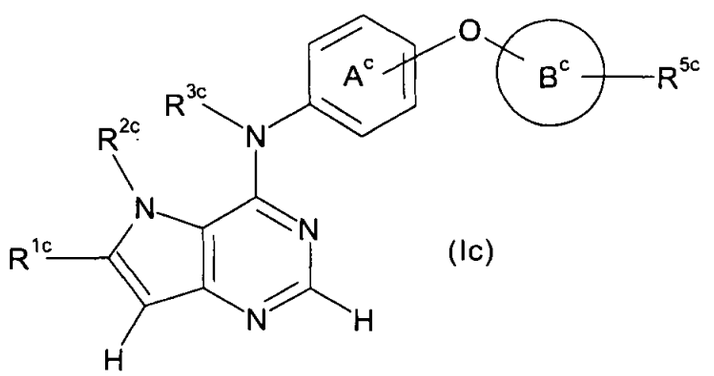
tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIb), se puede producir un compuesto de partida (IIb) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del

grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIb).

[Método de producción C]

El compuesto (Ic) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(Ic)

en donde cada símbolo es como se definió con anterioridad.

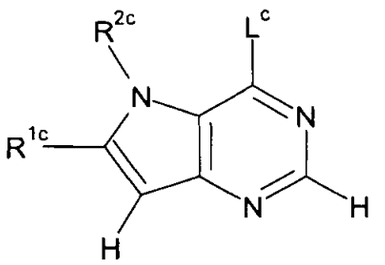
Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto

(Ic) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

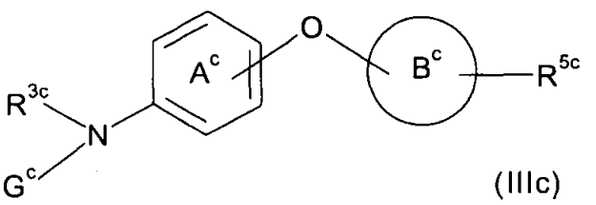
El compuesto (Ic) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIc)

en donde L^c es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIc)

en donde G^c es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

G^c es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIIc) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIc) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^c, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

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Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina,

clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ic) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y

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aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

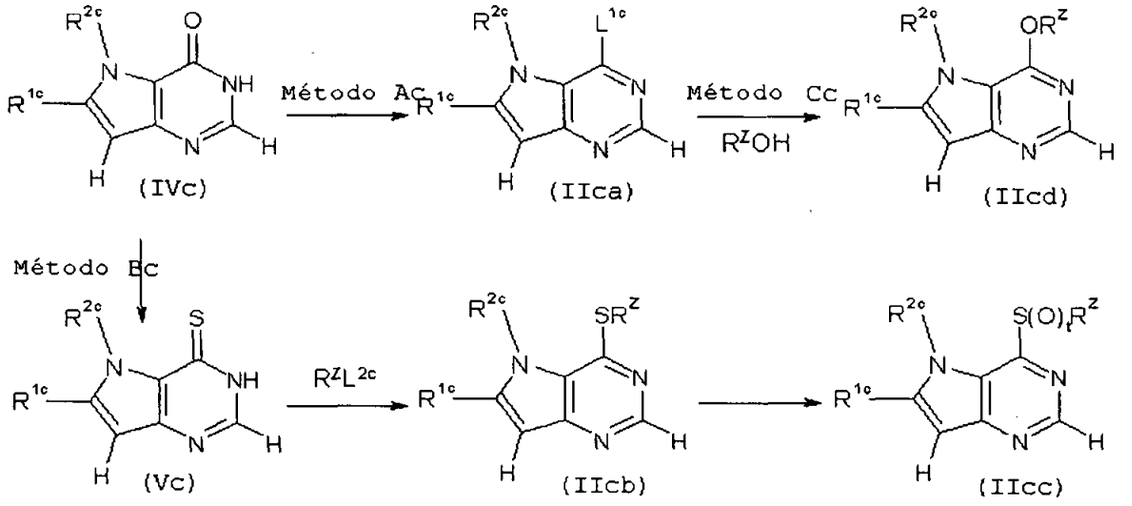
El compuesto (Ic), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ic) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIc) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIc) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los

compuestos (IIca), (IIcb), (IIcc) y (IIcd) están comprendidos en el compuesto (IIc).



en donde L^{1c} y L^{2c} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ac, el compuesto (IIca) se puede producir haciendo reaccionar el compuesto (IVc) con un agente halogenante. Como método Bc, el compuesto (IVc) se hace reaccionar con un agente tionante para dar el compuesto (Vc), que luego se hace reaccionar con un compuesto representado por R^zL^{2c} en presencia de una base para dar el compuesto (IIcb), que luego se somete a una reacción de oxidación para dar el compuesto (IIcc). Como método Cc, el compuesto (IIca) se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIcd).

Como agente halogenante en el Método Ac, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de

oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVc) en el compuesto (Vc) en el Método Bc, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como

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benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2c} en la etapa de producción a partir del compuesto (Vc) en el compuesto (IIcb) en el Método Bc, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-

dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente oxidante en la etapa de producción a partir del compuesto (IIcb) en el compuesto (IIcc) en el Método Bc, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIcc) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIcb), y cuando se produce el compuesto (IIcc) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIcb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol,

isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIca) en el compuesto (IIcd) en el Método Cc, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter

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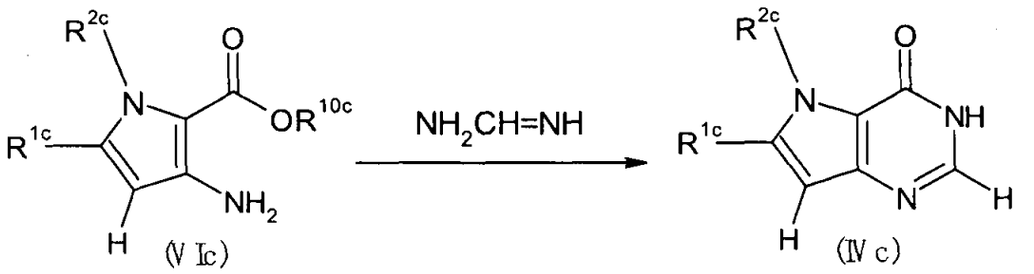
dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVc) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:



(VIc) (IVc)

en donde R^{10c} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIc) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVc). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno

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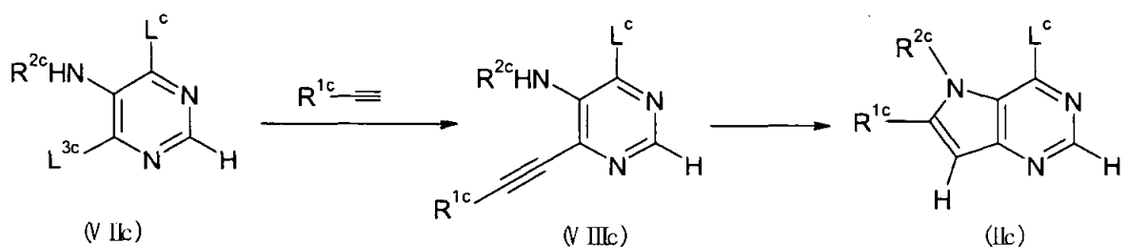
y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IIc) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:



en donde L^{3c} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIc) en el compuesto (VIIIc) en este método, se puede llevar a cabo una reacción de conocimiento general en forma de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIc) se puede producir haciendo reaccionar el compuesto (VIIc) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:

R^{1c}—≡

en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o

un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

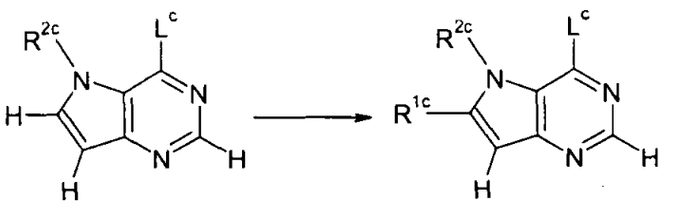
Para la etapa de producción a partir del compuesto (VIIIc) en el compuesto (IIc) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIc). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-

dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIc), se puede producir un compuesto de partida (IIc) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se

introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIc).

El compuesto de partida (IIc) de este método de producción también se puede producir, por ejemplo, por medio de un método usando el compuesto (IIc'), tal como se indica por medio del siguiente esquema de reacción:



(IIc') (IIc)

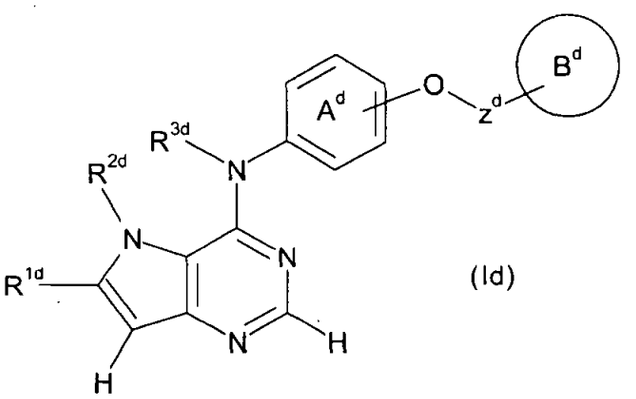
en donde cada símbolo es como se definió con anterioridad.

En este método, se convierte en general el compuesto (IIc') en el anión al retirar un protón del compuesto (IIc') usando una base que luego se hace reaccionar con un catión que tiene R^{1c} para dar el compuesto (IIc). Como base se pueden usar, por ejemplo, n-butil-litio, s-butil-litio, t-butil-litio, t-butóxido de litio, diisopropilamida de litio y similares. Como reactivo para generar el catión se pueden usar, por ejemplo, cloruro de p-toluensulfonilo, bromuro de bencensulfonilo, cianuro de p-toluensulfonilo, trifluorometansulfonato de S-(trifluorometil)dibenzotiofenio,

N,N-dimetilformamida y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares, un solvente mixto de ellos y similares. La reacción antes mencionada se puede llevar a cabo bajo enfriamiento, con preferencia aproximadamente no más de -20°C, y el tiempo de reacción es, generalmente, de aproximadamente 15 min-50 h, con preferencia aproximadamente 30 min-4 h.

[Método de producción D]

El compuesto (Id) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(Id)

en donde cada símbolo es como se definió con anterioridad.

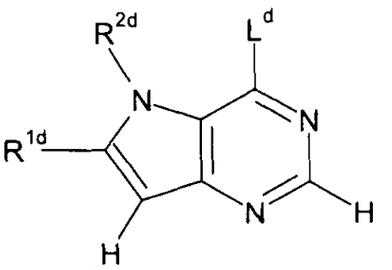
Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar,

por ejemplo, aquellas similares a las sales del compuesto (Id) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

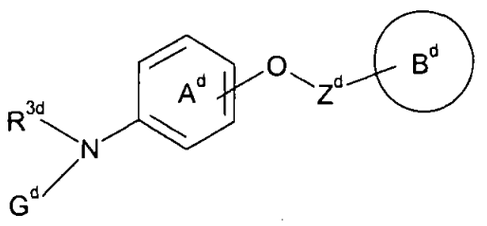
El compuesto (Id) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IId)

en donde L^d es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIId)

en donde G^d es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

G^d es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIId) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IId) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^d, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo,

etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Id) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo

carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

El compuesto (Id), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Id) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIId) de este método de producción, se usa uno comercialmente disponible o se puede

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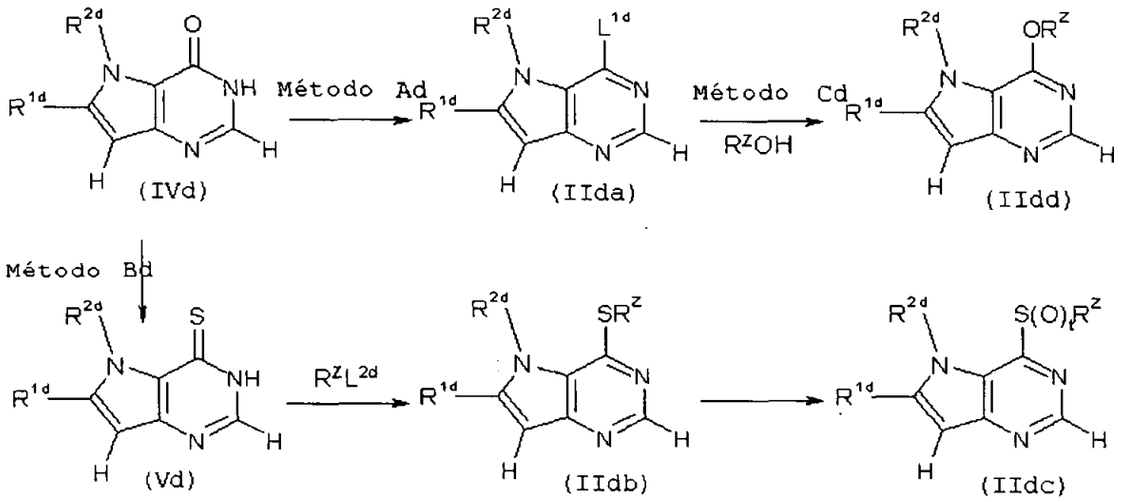
producir por un medio en sí conocido.

El compuesto de partida (IId) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIda), (IIdb), (IIdc) y (IIdd) están comprendidos en el compuesto (IId).



en donde L^{1d} y L^{2d} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ad, el compuesto (IIda) se puede producir haciendo reaccionar el compuesto (IVd) con un agente halogenante. Como método Bd, el compuesto (IVd) se hace reaccionar con un agente tionante para dar el compuesto (Vd), que luego se hace reaccionar con un compuesto representado por R^zL^{2d} en presencia de una base para dar el compuesto (IIdb), que luego se somete a una reacción de oxidación para dar el compuesto (IIdc). Como método Cd, el compuesto (IIda)

se hace reaccionar con un compuesto representado por R^2OH en presencia de una base para dar el compuesto (IIdd).

Como agente halogenante en el Método Ad, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVd) en el compuesto (Vd) en el Método Bd, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de

fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2d} en la etapa de producción a partir del compuesto (Vd) en el compuesto (IIdb) en el Método Bd, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno,

tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

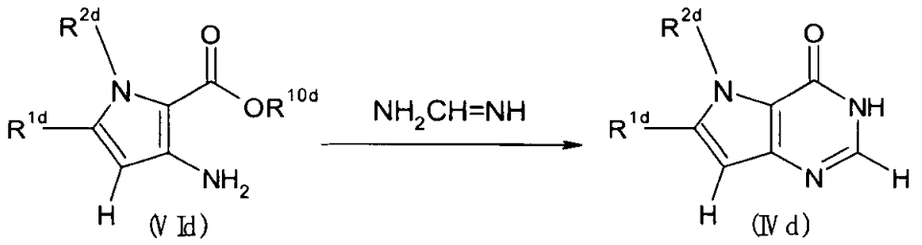
Como agente oxidante en la etapa de producción a partir del compuesto (IIdb) en el compuesto (IIdc) en el Método Bd, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIdc) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIdb), y cuando se produce el compuesto (IIdc) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIdb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos

halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zOH en la etapa de producción a partir del compuesto (IIda) en el compuesto (IIdd) en el Método Cd, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por

ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVd) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:

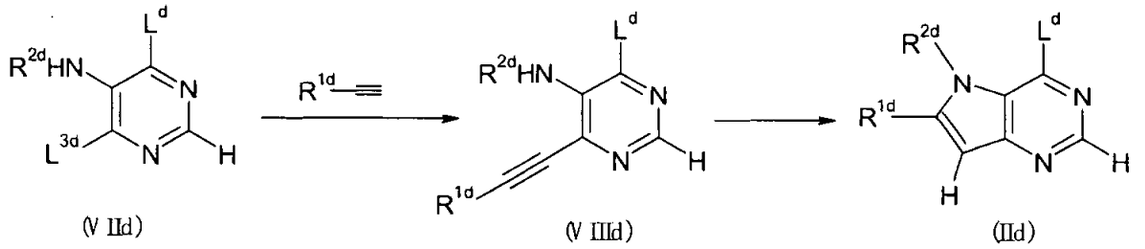


en donde R^{10d} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VId) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVd). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol,

etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IId) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:

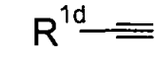


(VIId) (VIIId) (IId)

en donde L^{3d} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIId) en el compuesto (VIIId) en este método, se puede llevar a cabo una reacción de conocimiento general en forma

de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIId) se puede producir haciendo reaccionar el compuesto (VIId) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:



en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIId) en el compuesto (IId) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IId). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno,

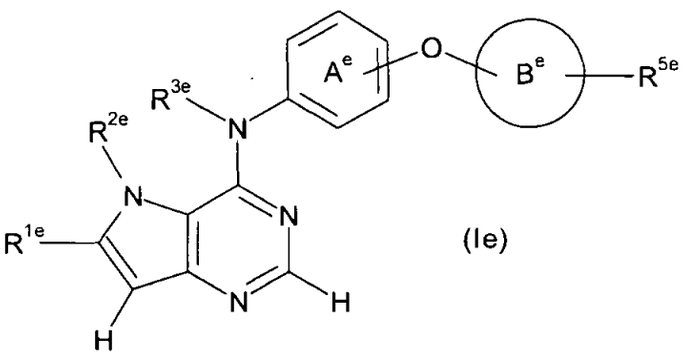
tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IId), Según el tipo de sustituyente del compuesto de partida un compuesto de partida (IId) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina,

alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IId).

[Método de producción E]

El compuesto (Ie) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(Ie)

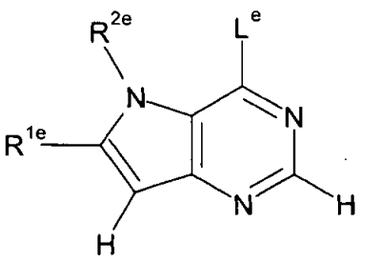
en donde cada símbolo es como se definió con anterioridad.

Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto (Ie) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

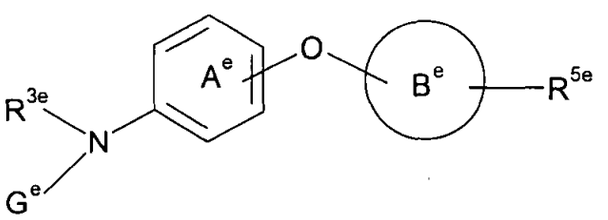
El compuesto (Ie) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIe)

en donde L^e es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIe)

en donde G^e es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

G^e es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIIe) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIe) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^e, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se

pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato

de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ie) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un

sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

El compuesto (Ie), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ie) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIe) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIe) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIea), (IIeb), (IIec) y (IIed) están comprendidos

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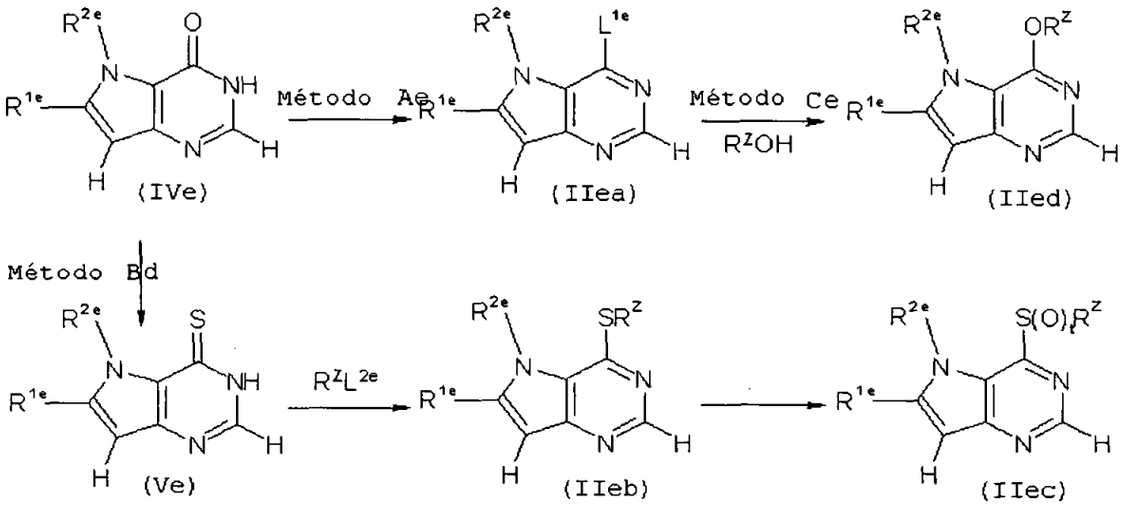
en el compuesto (IIe).



en donde L^{1e} y L^{2e} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ae, el compuesto (IIea) se puede producir haciendo reaccionar el compuesto (IVe) con un agente halogenante. Como método Be, el compuesto (IVe) se hace reaccionar con un agente tionante para dar el compuesto (Ve), que luego se hace reaccionar con un compuesto representado por R^zL^{2e} en presencia de una base para dar el compuesto (IIeb), que luego se somete a una reacción de oxidación para dar el compuesto (IIec). Como método Ce, el compuesto (IIea) se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIed).

Como agente halogenante en el Método Ae, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de

fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVe) en el compuesto (Ve) en el Método Be, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2e} en la etapa de producción a partir del compuesto (Ve) en el compuesto (IIeb) en el Método Be, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-

pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

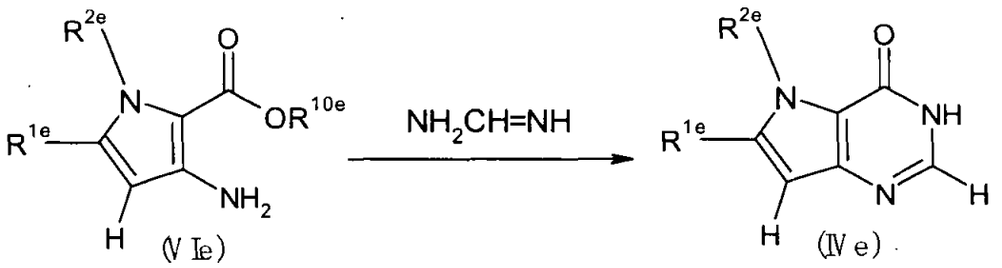
Como agente oxidante en la etapa de producción a partir del compuesto (IIeb) en el compuesto (IIec) en el Método Be, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIec) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIeb), y cuando se produce el compuesto (IIec) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIeb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIea) en el compuesto (IIed) en el Método Ce, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona,

acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVe) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:

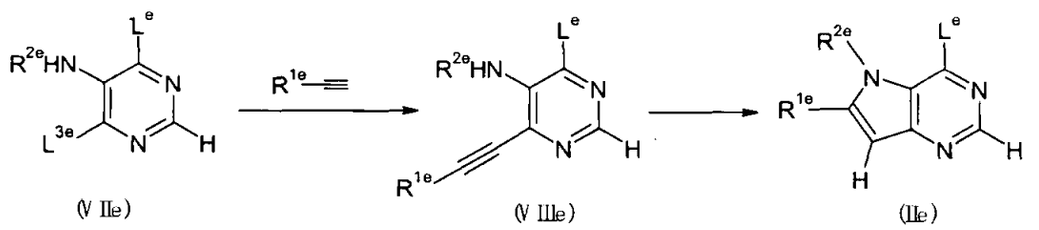


en donde R^{10e} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIe) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVe). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno

y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IIe) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:



en donde L^{3e} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIe) en el compuesto (VIIIe) en este método, se puede llevar a cabo una reacción de conocimiento general en forma de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIe) se puede producir haciendo reaccionar el compuesto (VIIe) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:

R^{1e}—≡

en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o

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un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIIe) en el compuesto (IIe) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIe). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-

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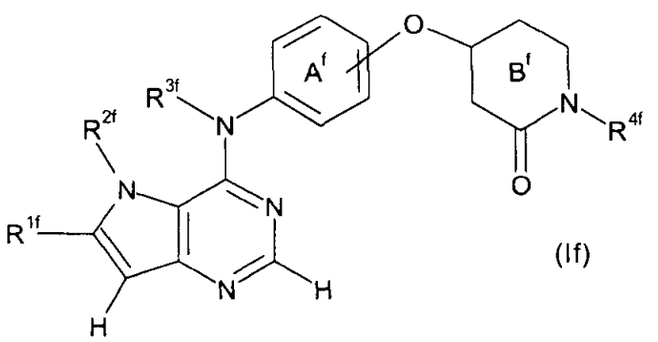
dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIe), se puede producir un compuesto de partida (IIe) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se

introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIe).

[Método de producción F]

El compuesto (If) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(If)

en donde cada símbolo es como se definió con anterioridad.

Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto (If) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional,

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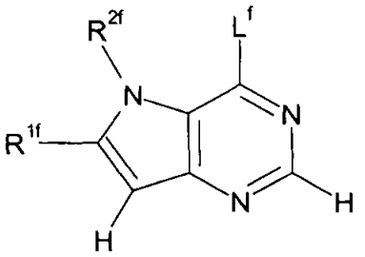
y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

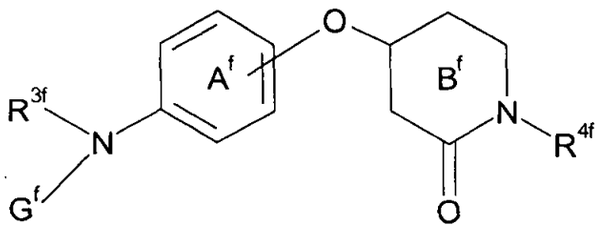
El compuesto (If) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIf)

en donde L^f es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIf)

en donde G^f es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

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G^f es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIIf) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIf) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^f, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares;

alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo

calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (If) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo

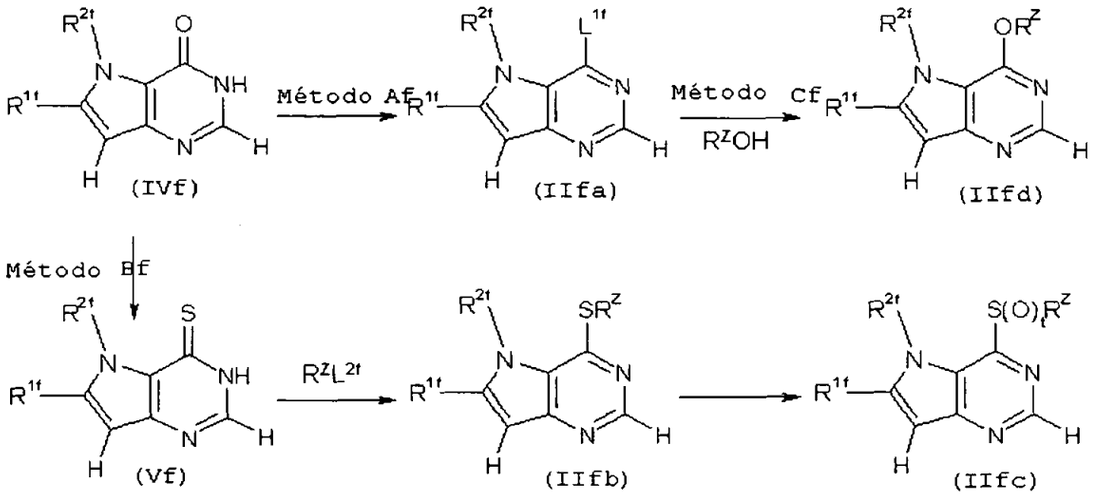
por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

El compuesto (If), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (If) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIf) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIf) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIfa), (IIfb), (IIfc) y (IIfd) están comprendidos en el compuesto (IIf).



en donde L^{1f} y L^{2f} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Af, el compuesto (IIfa) se puede producir haciendo reaccionar el compuesto (IVf) con un agente halogenante. Como método Bf, el compuesto (IVf) se hace reaccionar con un agente tionante para dar el compuesto (Vf), que luego se hace reaccionar con un compuesto representado por R^zL^{2f} en presencia de una base para dar el compuesto (IIfb), que luego se somete a una reacción de oxidación para dar el compuesto (IIfc). Como método Cf, el compuesto (IIfa) se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIfd).

Como agente halogenante en el Método Af, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de

fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVf) en el compuesto (Vf) en el Método Bf, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^zL^{2f} en la etapa de producción a partir del compuesto (Vf) en el compuesto (IIfb) en el Método Bf, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-

pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

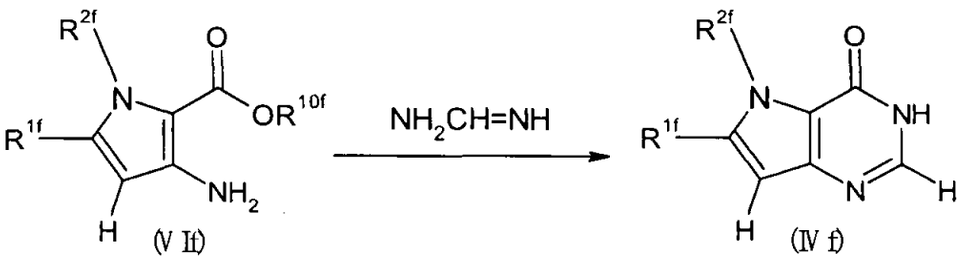
Como agente oxidante en la etapa de producción a partir del compuesto (IIfb) en el compuesto (IIfc) en el Método Bf, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIfc) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIfb), y cuando se produce el compuesto (IIfc) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIfb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIfa) en el compuesto (IIfd) en el Método Cf, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona,

acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVf) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:

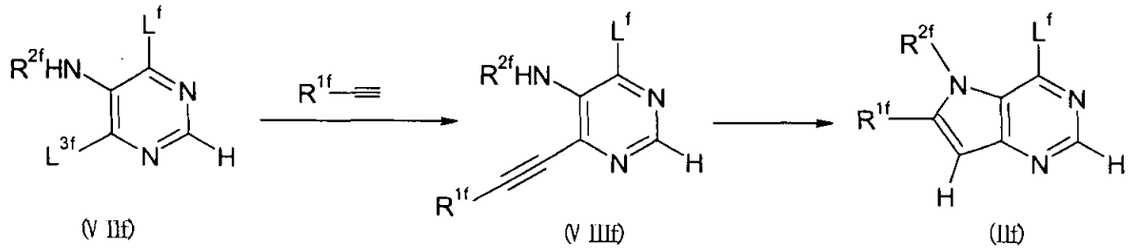


en donde R^{10f} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIf) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVf). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico,

tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IIf) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:



(V IIf) (V IIIf) (IIf)

en donde L^{3f} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIf) en el compuesto (VIIIf) en este método, se puede llevar a cabo una reacción de conocimiento general en forma de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIf) se puede producir haciendo reaccionar el compuesto (VIIf) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:

R^{1f}—≡

en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o

un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIIf) en el compuesto (IIf) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIf). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-

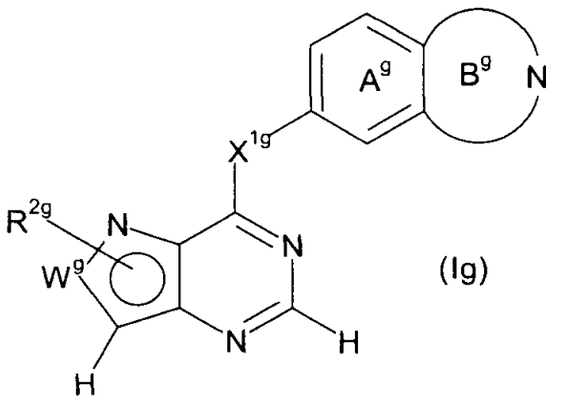
dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIf), se puede producir un compuesto de partida (IIf) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se

introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIf).

[Método de producción G]

El compuesto (Ig) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(Ig)

en donde cada símbolo es como se definió con anterioridad.

Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto (Ig) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de

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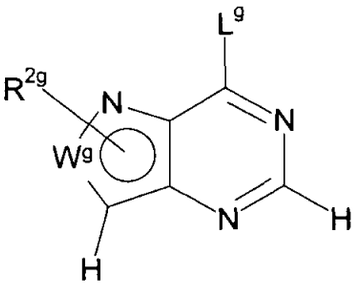
una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

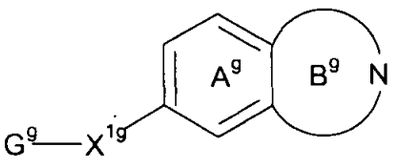
El compuesto (Ig) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIg)

en donde L^g es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIg)

en donde G^g es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

Cuando X^{1g} es $-NR^{3g}-Y^{1g}-$, -O- o -S-, G^g es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

Cuando X^{1g} es $-CHR^{3g}-$, G^g puede ser un metal tales como litio, magnesio halogenado, cobre, cinc y similares.

El compuesto (IIIg) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIg) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^g, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se

pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina, clorhidrato de pirazina, clorhidrato de triazina, clorhidrato

de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

El compuesto (Ig) en donde X^{1g} es -SO- o $-SO_2-$ se puede producir al someter el compuesto (Ig) en donde X^{1g} es -S-, a una reacción de oxidación. Como agente oxidante en la etapa de producción, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (Ig) en donde X^{1g} es -SO-, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto de partida, y cuando se produce el compuesto (Ig) en donde X^{1g} es $-SO_2-$, se emplea en aproximadamente 2-3 equivalentes referido al compuesto de partida. El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales

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como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ig) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación

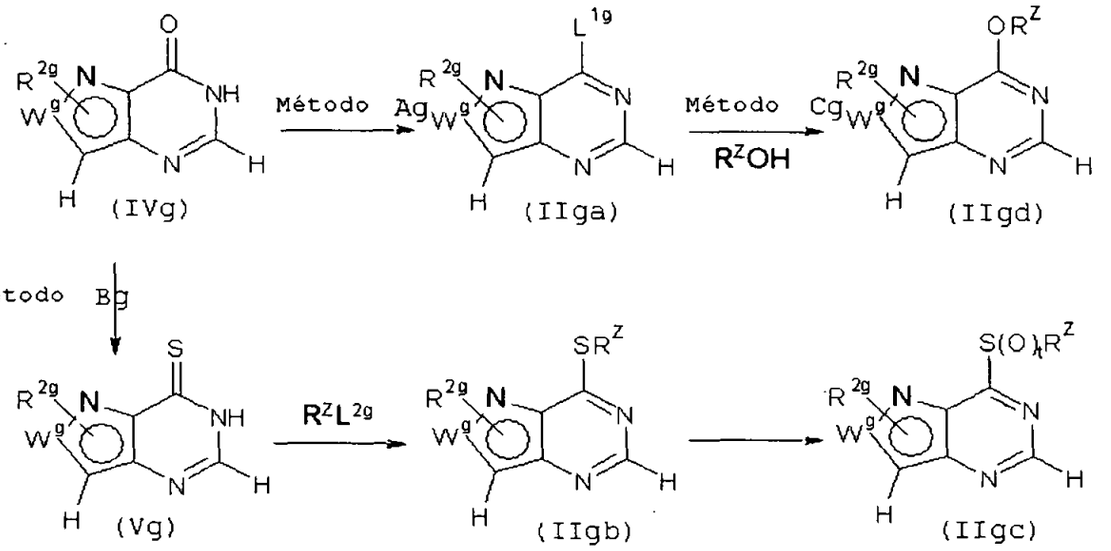
del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

El compuesto (Ig), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ig) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIg) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIg) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los compuestos (IIga), (IIgb), (IIgc), (IIgd) y (IIge) están comprendidos en el compuesto (IIg).



en donde L^{1g} y L^{2g} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ag, el compuesto (IIga) se puede producir haciendo reaccionar el compuesto (IVg) con un agente halogenante. Como método Bg, el compuesto (IVg) se hace reaccionar con un agente tionante para dar el compuesto (Vg), que luego se hace reaccionar con un compuesto representado por R^zL^{2g} en presencia de una base para dar el compuesto (IIgb), que luego se somete a una reacción de oxidación para dar el compuesto (IIgc). Como método Cg, el compuesto (IIga)

se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIgd).

Como agente halogenante en el Método Ag, se pueden usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

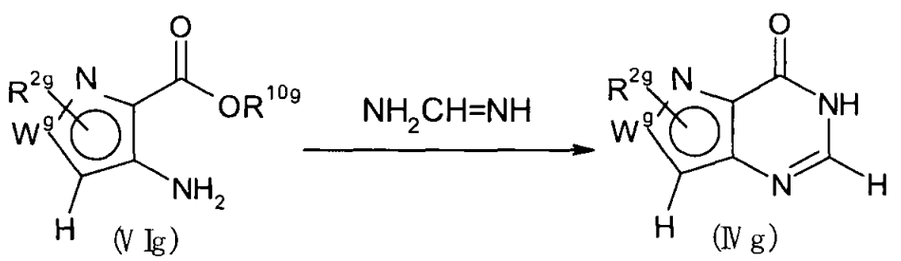
Como agente tionante usado en la etapa de producción a partir del compuesto (IVg) en el compuesto (Vg) en el Método Bg, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de

halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIga) en el compuesto (IIgd) en el Método Cg, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por

ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVg) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:

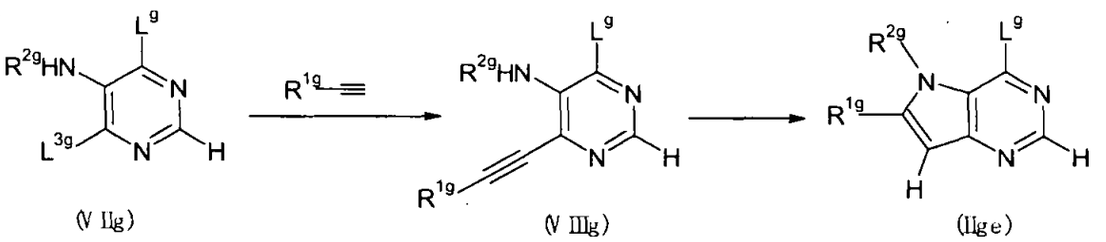


en donde R^{10g} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIg) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVg). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol,

etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Cuando W^g es $C(R^{1g})$, el compuesto (IIge) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:

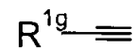


(VIIg) (VIIIg) (IIge)

en donde L^{3g} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIg) en el compuesto (VIIIg) en este método, se puede llevar a cabo una reacción de conocimiento general en forma

de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIg) se puede producir haciendo reaccionar el compuesto (VIIg) con aproximadamente 1-3 equivalentes de un compuesto representado por la fórmula:



en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter

dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Para la etapa de producción a partir del compuesto (VIIIg) en el compuesto (IIge) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIge). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno,

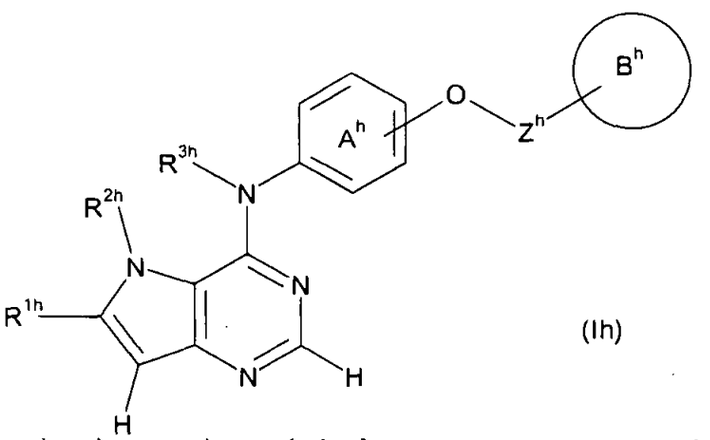
tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIg), un compuesto de partida (IIg) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del

grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIg).

[Método de producción H]

El compuesto (Ih) de la presente invención se puede obtener, por ejemplo, por medio del método indicado en el siguiente esquema de reacción o un método análogo y similares.



(Ih)

en donde cada símbolo es como se definió con anterioridad.

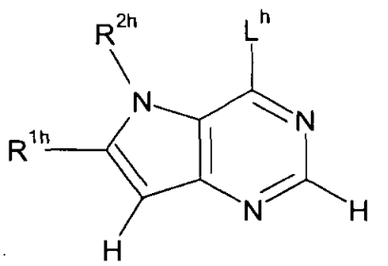
Cada compuesto en los siguientes esquemas de reacción incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales del compuesto

(Ih) y similares.

El compuesto obtenido en cada etapa se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional, y se puede purificar fácilmente a través de un medio de separación como recristalización, destilación, cromatografía y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo de los compuestos es como se definió con anterioridad.

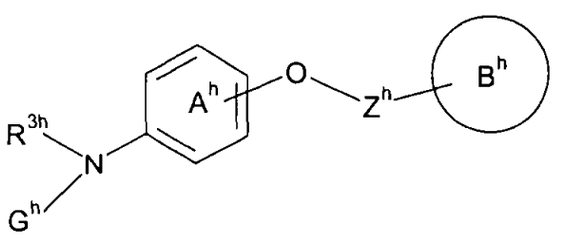
El compuesto (Ih) de la presente invención se puede producir, por ejemplo, haciendo reaccionar un compuesto representado por la fórmula:



(IIh)

en donde L^h es un grupo saliente, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales y un compuesto representado por la fórmula:



(IIIh)

en donde G^h es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad,

o una de sus sales.

G^h es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino tales como litio, sodio, potasio, cesio y similares, o un metal alcalinotérreo tales como magnesio, calcio y similares.

El compuesto (IIIh) o una de sus sales se usa con preferencia en una cantidad de 1-5 equivalentes, con preferencia 1-2 equivalentes, referido al compuesto (IIh) y la reacción se lleva a cabo preferentemente en un solvente. Además, se puede utilizar una base o una sal de amonio en una cantidad de aproximadamente 1-10 equivalentes, con preferencia 1-2 equivalentes.

En la fórmula antes mencionada, como grupo saliente para L^h, se pueden usar un átomo de halógeno tales como cloro, bromo, yodo y similares, un grupo representado por la fórmula: $-S(O)_kR^z$ en donde k es un número entero de 0, 1 ó 2, y R^z es un grupo alquilo (C_{1-4}) inferior tales como metilo, etilo, propilo y similares, un grupo arilo de C_{6-10} tales como fenilo, tolilo y similares, o un grupo representado por la fórmula: $-OR^z$ en donde R^z es como se definió con anterioridad, y similares.

Como solvente en la reacción antes mencionada, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares.

Como base en la reacción antes citada, se pueden usar una base inorgánica, una base orgánica y similares. Específicamente se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares.

Como sal de amonio en la reacción antes citada, se pueden usar clorhidrato de piridina, bromhidrato de piridina, p-toluensulfonato de piridinio, clorhidrato de quinolina, clorhidrato de isoquinolina, clorhidrato de pirimidina,

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clorhidrato de pirazina, clorhidrato de triazina, clorhidrato de trimetilamina, clorhidrato de trietilamina, clorhidrato de N-etildiisopropilamina y similares.

La reacción antes citada se puede llevar a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento (aproximadamente 40-200°C, con preferencia aproximadamente 40-160°C), y el tiempo de reacción es, en general, de aproximadamente 1-30 h, con preferencia de aproximadamente 1-20 h, con mayor preferencia de aproximadamente 1-10 h.

Un compuesto dentro del alcance de la presente invención también se puede producir por medios de aplicación en sí conocidos en el compuesto obtenido (Ih) de la presente invención para introducción de sustituyentes y conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en el grupo carboxi por hidrólisis del éster, conversión en el grupo carbamoilo por amidación del grupo carboxi, conversión en el grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y

aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción del objeto, pudiéndose producir también el compuesto dentro del alcance de la presente invención.

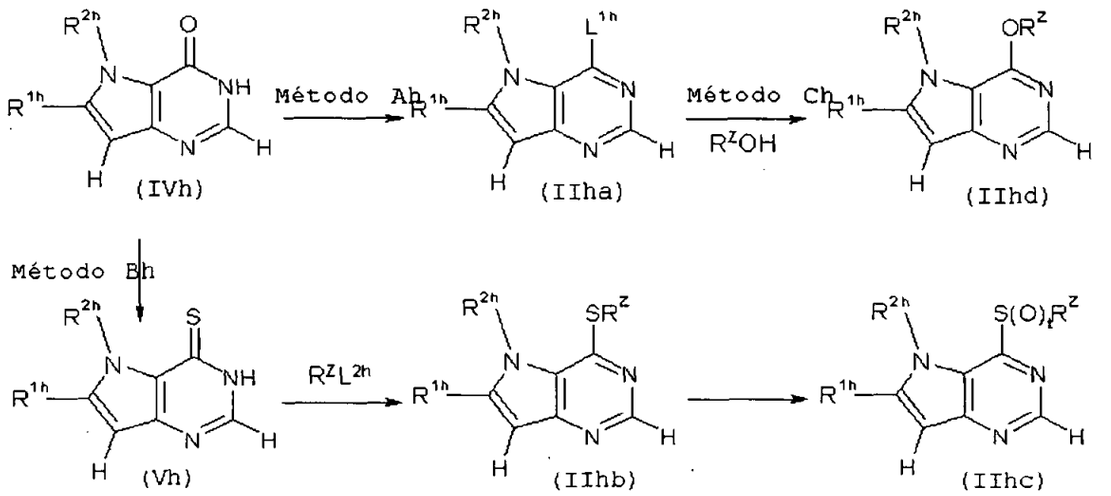
El compuesto (Ih), que es un producto de la reacción, se puede preparar como un compuesto individual o como una mezcla.

El compuesto (Ih) de la presente invención así obtenido se puede someter a un medio en sí conocido, tales como extracción de solvente, concentración, neutralización, filtración, cristalización, recristalización, cromatografía en columna, cromatografía líquida de alto rendimiento y similares, mientras que el compuesto del objeto se puede aislar y purificar con alta pureza de una mezcla de reacción.

Como compuesto de partida (IIIh) de este método de producción, se usa uno comercialmente disponible o se puede producir por un medio en sí conocido.

El compuesto de partida (IIh) de este método de producción se puede preparar, por ejemplo, mediante un método indicado en el siguiente esquema de reacción. Aquí, los

compuestos (IIha), (IIhb), (IIhc) y (IIhd) están comprendidos en el compuesto (IIh).



en donde L^{1h} y L^{2h} son átomos de halógeno, R^z es como se definió con anterioridad, y t es un número entero de 1 ó 2.

Como método Ah, el compuesto (IIha) se puede producir haciendo reaccionar el compuesto (IVh) con un agente halogenante. Como método Bh, el compuesto (IVh) se hace reaccionar con un agente tionante para dar el compuesto (Vh), que luego se hace reaccionar con un compuesto representado por R^zL^{2h} en presencia de una base para dar el compuesto (IIhb), que luego se somete a una reacción de oxidación para dar el compuesto (IIhc). Como método Ch, el compuesto (IIha) se hace reaccionar con un compuesto representado por R^zOH en presencia de una base para dar el compuesto (IIhd).

Como agente halogenante en el Método Ah, se pueden

usar, por ejemplo, aproximadamente 1-100 equivalentes de oxicloruro de fósforo, pentacloruro de fósforo, tricloruro de fósforo, cloruro de tionilo, cloruro de sulfurilo, tribromuro de fósforo y similares. En este caso, la reacción se puede llevar a cabo en presencia de una base tales como dietilanilina, dimetilanilina, piridina y similares. Mientras la reacción se puede llevar a cabo sin solvente, como solvente de reacción se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetonitrilo, acetato de etilo y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente tionante usado en la etapa de producción a partir del compuesto (IVh) en el compuesto (Vh) en el Método Bh, se pueden usar, por ejemplo, aproximadamente 1-5 equivalentes de un reactivo de Lawesson, pentasulfuro de fósforo y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-

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dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; y otros. La reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como $R^{z}L^{2h}$ en la etapa de producción a partir del compuesto (Vh) en el compuesto (IIhb) en el Método Bh, por ejemplo, se pueden usar aproximadamente 1-5 equivalentes de yoduro de metilo, cloruro de bencilo, bromuro de bencilo y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares;

acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como agente oxidante en la etapa de producción a partir del compuesto (IIhb) en el compuesto (IIhc) en el Método Bh, se pueden usar, por ejemplo, ácido m-cloroperbenzoico, peróxido de hidrógeno, ácido peracético, hidroperóxido de t-butilo, peroxisulfato de potasio, permanganato de potasio, perborato de sodio, peryodato de sodio, hipoclorito de sodio, halógeno y similares. Cuando se produce el compuesto (IIhc) en donde t=1, el agente oxidante se emplea en aproximadamente 1-1,5 equivalentes referido al compuesto (IIhb), y cuando se produce el compuesto (IIhc) en donde t=2, se emplea en aproximadamente 2-3 equivalentes referido al compuesto (IIhb). El solvente de reacción no está particularmente limitado, siempre que no reaccione con el agente oxidante y, por ejemplo, se pueden usar hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno

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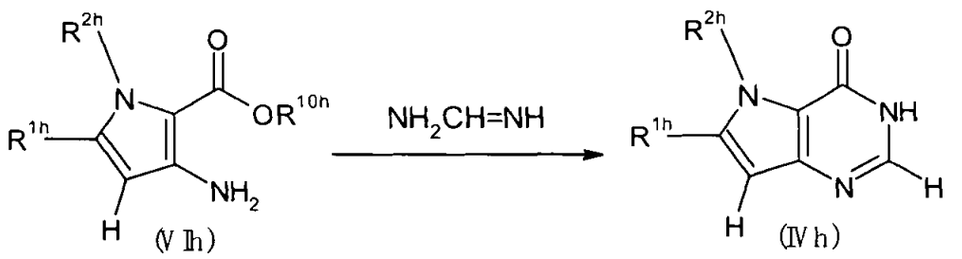
y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; ácidos carboxílicos tales como ácido acético, ácido trifluoroacético y similares; acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Como R^2OH en la etapa de producción a partir del compuesto (IIha) en el compuesto (IIhd) en el Método Ch, se pueden usar, por ejemplo, aproximadamente 1-10 equivalentes de metanol, etanol, fenol y similares, y como base, se pueden usar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, piridina, N,N-dimetilaminopiridina, metóxido de sodio, etóxido de sodio, t-butóxido de potasio, hidruro de sodio, amida de sodio, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno,

tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

Por otra parte, el compuesto (IVh) se puede producir, por ejemplo, por medio de un método indicado por la siguiente fórmula:



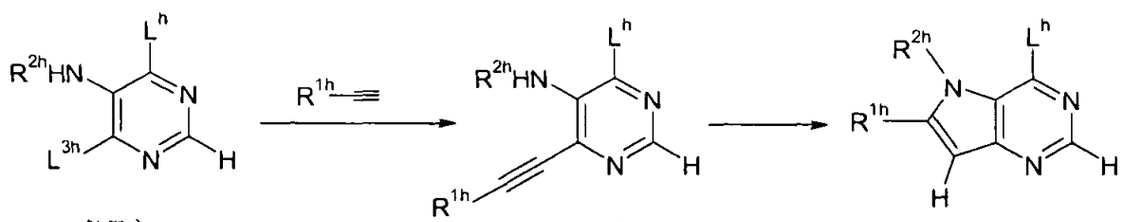
(VIh) (IVh)

en donde R^{10h} es un grupo alquilo de C_{1-4}, y los otros símbolos son como se definieron con anterioridad.

Es decir, el compuesto (VIh) se hace reaccionar con aproximadamente 1-4 equivalentes de formamidina o una de sus sales para dar el compuesto (IVh). Como solvente de reacción se pueden usar, por ejemplo, alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares;

hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo bajo enfriamiento, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción varía, en general, de aproximadamente 1-20 h, con preferencia aproximadamente 1-10 h.

El compuesto (IIh) también se puede preparar, por ejemplo, por medio de un método indicado por la siguiente fórmula:



(VIIh) (VIIIh) (IIh)

en donde L^{3h} es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

Para la etapa de producción a partir del compuesto (VIIh) en el compuesto (VIIIh) en este método, se puede llevar a cabo una reacción de conocimiento general en forma de una reacción de Sonogashira o una reacción análoga y, en general, el compuesto (VIIIh) se puede producir haciendo reaccionar el compuesto (VIIh) con aproximadamente 1-3

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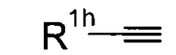
equivalentes de un compuesto representado por la fórmula:



en presencia de una base, aproximadamente 0,01-1 equivalentes de un catalizador de paladio y yoduro de cobre. Como base se pueden usar, por ejemplo, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU), carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio y similares. Como catalizador de paladio se pueden usar, por ejemplo, diclorobis(trifenilfosfina)paladio (II), paladio sobre carbón, diacetato de paladio (II), bis(benzonitrilo)dicloropaladio (II) y similares. Esta reacción se puede llevar a cabo en co-presencia de un compuesto de fosfina terciaria tales como trifenilfosfina, tributilfosfina y similares como ligando. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-

pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. Esta reacción se lleva a cabo a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

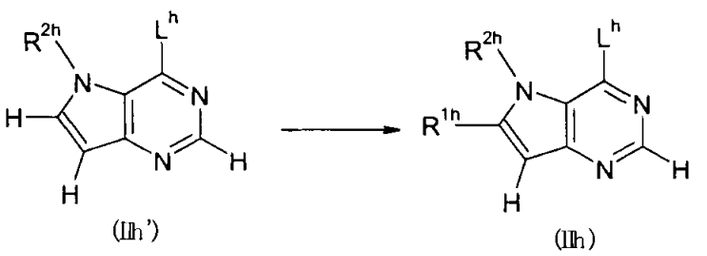
Para la etapa de producción a partir del compuesto (VIIIh) en el compuesto (IIh) en este método, se lleva a cabo en general una reacción de ciclación en presencia de aproximadamente 1-3 equivalentes de base o aproximadamente 0,01-1 equivalentes de yoduro de cobre para dar el compuesto (IIh). Como base se pueden usar, por ejemplo, t-butóxido de potasio, t-butóxido de sodio, t-butóxido de cesio, etóxido de sodio, hidruro de potasio, hidruro de sodio, hidróxido de cesio, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato ácido de sodio, carbonato ácido de potasio, trietilamina, N-etildiisopropilamina, diisopropilamina, piridina, N,N-dimetilaminopiridina, diazabicicloundeceno (DBU) y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; alcoholes tales como metanol, etanol, isopropanol, t-butanol y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano

y similares; acetona, acetonitrilo, acetato de etilo, N,N-dimetilformamida, N,N-dimetilacetamida, 1-metil-2-pirrolidona, dimetilsulfóxido, hexametilfosforamida, agua o un solvente mixto de ellos y similares. La reacción se lleva a cabo a baja temperatura, a temperatura ambiente o bajo calentamiento, y el tiempo de reacción es, generalmente, de aproximadamente 1-50 h, con preferencia aproximadamente 1-20 h.

Según el tipo de sustituyente del compuesto de partida (IIh), un compuesto de partida (IIh) con un sustituyente diferente por conversión del sustituyente, como material de partida, a partir de un compuesto producido por medio del método de producción antes mencionado. Para la conversión del sustituyente, se puede emplear un método general conocido. Por ejemplo, conversión en el grupo carbamoilo por hidrólisis y amidación del éster, conversión en grupo hidroximetilo por reducción del grupo carboxi, conversión en el compuesto alcohólico por reducción o alquilación del grupo carbonilo, aminación reductiva del grupo carbonilo, oximación del grupo carbonilo, acilación del grupo amino, alquilación del grupo amino, sustitución y aminación del halógeno activo por amina, alquilación del grupo hidroxi, sustitución y aminación del grupo hidroxi y similares. Cuando un sustituyente reactivo que provoca una reacción no objetiva está presente durante la introducción de

sustituyentes y la conversión de los grupos funcionales, se introduce antes un grupo protector de ser necesario en el sustituyente reactivo por un medio en sí conocido, y el grupo protector se elimina por un medio en sí conocido después de la reacción objeto, pudiendo producir también el compuesto de partida (IIh).

El compuesto de partida (IIh) de este método de producción también se puede producir, por ejemplo, por medio de un método usando el compuesto (IIh'), tal como se indica por medio del siguiente esquema de reacción:



(IIh') (IIh)

en donde cada símbolo es como se definió con anterioridad.

En este método, se convierte en general el compuesto (IIh') en el anión al retirar un protón del compuesto (IIh') usando una base que luego se hace reaccionar con un catión que tiene R^{1h} para dar el compuesto (IIh). Como base se pueden usar, por ejemplo, n-butil-litio, s-butil-litio, t-butil-litio, t-butóxido de litio, diisopropilamida de litio y similares. Como reactivo para generar el catión se pueden usar, por ejemplo, cloruro de p-toluensulfonilo, bromuro de bencensulfonilo, cianuro de p-toluensulfonilo,

trifluorometansulfonato de S-(trifluorometil)dibenzotiofenio, N,N-dimetilformamida y similares. Como solvente de reacción, se pueden usar, por ejemplo, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano y similares; éteres tales como éter dietílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares, un solvente mixto de ellos y similares. La reacción antes mencionada se puede llevar a cabo bajo enfriamiento, con preferencia aproximadamente no más de -20°C, y el tiempo de reacción es, generalmente, de aproximadamente 15 min-50 h, con preferencia aproximadamente 30 min-4 h.

Los compuestos (Ia)-(Ih) así obtenidos se pueden aislar y purificar a través un medio de separación en sí conocido, tal como concentración, concentración a presión reducida, extracción del solvente, cristalización, recristalización, transferencia de fase, cromatografía y similares.

Si los compuestos (Ia)-(Ih) se obtienen en forma libre, se pueden convertir en una sal deseada por medio de un método en sí conocido o una modificación del mismo; por el contrario, si los compuestos (Ia)-(Ih) se obtienen como una sal, se pueden convertir en una forma libre o en otra sal deseada por medio de un método en sí conocido o una modificación del mismo.

Cuando los compuestos (Ia)-(Ih) tienen isómeros

tales como isómero óptico, estereoisómero, isómero de posición, isómero de rotación y similares, y cualquier isómero y mezclas están comprendidos en el compuesto (Ia)-(Ih). Por ejemplo, cuando los compuestos (Ia)-(Ih) tienen un isómero óptico, un isómero óptico separado del racemato también está comprendido en el compuesto (Ia)-(Ih). Estos isómeros se pueden obtener como productos independientes por medio de una síntesis o una separación (concentración, extracción del solvente, cromatografía en columna, recristalización y similares) en sí conocidos.

Los compuestos (Ia)-(Ih) pueden ser un cristal, y tanto un cristal individual como mezclas de cristales están comprendidos en el compuesto (Ia)-(Ih). Los cristales se pueden producir por cristalización de acuerdo con métodos de cristalización en sí conocidos.

Los compuestos (Ia)-(Ih) pueden ser un solvato (por ejemplo, hidrato, etc.) o un no solvato, y ambos están comprendidos en el compuesto (Ia)-(Ih).

Un compuesto marcado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S, ^{125}I y similares) también está incluido en el compuesto (Ia)-(Ih).

Un profármaco de los compuestos (Ia)-(Ih) o sus sales (de ahora en más mencionado como compuesto (Ia)-(Ih)) significa un compuesto que se convierte en los compuestos (Ia)-(Ih) con una reacción debida a una enzima, un ácido

gástrico, etc. en la condición fisiológica en el organismo viviente, es decir, un compuesto que se convierte en los compuestos (Ia)-(Ih) con oxidación, reducción, hidrólisis, etc. debido a una enzima; un compuesto que se convierte en los compuestos (Ia)-(Ih) por hidrólisis, etc. debido a ácido gástrico, etc. Un profármaco para los compuestos (Ia)-(Ih) puede ser un compuesto obtenido al someter un grupo amino en los compuestos (Ia)-(Ih) a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido al someter un grupo amino en los compuestos (Ia)-(Ih) a una eicosanoilación, alanilación, pentilaminocarbonilación, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilación, tetrahidrofuranoilación, pirrolidilmetilación, pivaloiloximetilación o ter-butilación); un compuesto obtenido al someter un grupo hidroxi en los compuestos (Ia)-(Ih) a una acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido al someter un grupo hidroxi en los compuestos (Ia)-(Ih) a una acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumarilación, alanilación o dimetilaminometilcarbonilación); un compuesto obtenido al someter un grupo carboxilo en los compuestos (Ia)-(Ih) a una esterificación o amidación (por ejemplo, un compuesto obtenido al someter un grupo carboxilo en los compuestos (Ia)-(Ih) a una etilesterificación, fenilesterificación, carboximetilesterificación,

dimetilaminometilesterificación,
pivaloiloximetilesterificación,
etoxicarboniloxietilesterificación, ftalidilesterificación,
(5-metil-2-oxo-1,3-dioxolen-4-il)metilesterificación,
ciclohexiloxicarboniletilesterificación o metilamidación) y similares. Cualquiera de estos compuestos se puede producir a partir de los compuestos (Ia)-(Ih) por medio de un método en sí conocido.

Un profármaco para los compuestos (Ia)-(Ih) también puede ser uno que se convierte en los compuestos (Ia)-(Ih) en una condición fisiológica, por ejemplo las descritas en IYAKUHIN no KAIHATSU (Development de Pharmaceuticals), Vol. 7, Design of Molecules, p,163-198, Publicado por HIROKAWA SHOTEN (1990).

Los compuestos (Ia)-(Ih) de la presente invención, o una de sus sales o uno de sus profármacos (en adelante referido como el compuesto de la presente invención) poseen actividad inhibidora de tirosina cinasa y se pueden usar para la profilaxis o tratamiento de enfermedades dependientes de tirosina cinasa en mamíferos. Las enfermedades dependientes de tirosina cinasa incluyen enfermedades caracterizadas al aumentar la proliferación celular debido a la actividad anormal de la enzima tirosina cinasa.

Particularmente, el compuesto de la presente invención inhibe específicamente HER2 cinasa y/o EGFR cinasa

y en consecuencia también es útil como agente terapéutico para suprimir el crecimiento de cáncer que expresa HER2 y/o EGFR cinasa. Además, el compuesto de la presente invención es útil como agente de prevención para prevenir cáncer dependiente de hormonas y la transición de cáncer dependiente de hormonas a cáncer independiente de hormonas.

Además, el compuesto de la presente invención es útil como agente farmacéutico dado que muestra baja toxicidad (por ejemplo, toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, cardiotoxicidad, interacción de fármaco, carcinogenicidad y similares), elevada solubilidad en agua, y es superior en estabilidad, farmacocinética (absorción, distribución, metabolismo, excreción y similares) y expresión de eficacia.

En consecuencia, el compuesto de la presente invención se puede usar como agente seguro para la profilaxis o tratamiento de enfermedades debido a la proliferación de células anormales tales como diversos tumores malignos (particularmente, cáncer de mama (por ejemplo, carcinoma ductal invasivo, cáncer ductal *in situ*, cáncer inflamatorio de mama, etc.), cáncer de próstata (por ejemplo, cáncer de próstata dependiente de hormonas, cáncer de próstata no dependiente de hormonas, etc.), cáncer de páncreas (por ejemplo, cáncer de conducto pancreático, etc.), cáncer gástrico (por ejemplo, adenocarcinoma papilar, adenocarcinoma

de mucosa, carcinoma adenopavimentoso, etc.), cáncer de pulmón (por ejemplo, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, mesotelioma maligno, etc.), cáncer colorectal (por ejemplo, cáncer colorectal familiar, cáncer colorectal no de pólipos hereditario, tumor del estroma gastrointestinal, etc.), cáncer de colon (por ejemplo, tumor del estroma gastrointestinal, etc.), cáncer rectal (por ejemplo, tumor del estroma gastrointestinal, etc.), cáncer de esófago, cáncer de duodeno, cáncer de lengua, cáncer de faringe (por ejemplo, carcinoma nasofaríngeo, cáncer bucofaríngeo, cáncer hipofaríngeo, etc.), cáncer de glándulas salivales, tumor de encéfalo (por ejemplo, astrocitoma pineal, astrocitoma pilocítico, astrocitoma difuso, astrocitoma anaplásico, etc.), neurinoma, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, cáncer de hígado (por ejemplo, cáncer de hígado primario, cáncer de conducto biliar extrahepático, etc.), cáncer de riñón (por ejemplo, carcinoma de células renales, pelvis renal y uréter, cáncer de células de transición, etc.), cáncer del conducto biliar, cáncer del cuerpo del útero, carcinoma endometrial, cáncer de cuello uterino, cáncer de ovario (por ejemplo, tumor de células epiteliales ováricas, células germinales extragonadales, tumor de células germinales ováricas, tumor ovárico de bajo potencial maligno, etc.), cáncer de vejiga, cáncer de uretra,

cáncer de piel (por ejemplo, melanoma ocular, carcinoma de células de Merkel, etc.), hemangioma, linfoma maligno, melanoma maligno, cáncer de tiroides (por ejemplo, carcinoma de médula de tiroides, etc.), cáncer de paratiroides, cáncer de cavidad nasal, cáncer de de seno paranasal, tumores óseos (por ejemplo, osteosarcoma, tumor de Ewing, sarcoma uterino, sarcoma de tejidos blandos, etc.), fibroma vascular, retinoblastoma, cáncer de penes, cáncer sólido de la infancia, sarcoma de Kaposi, sarcoma de Kaposi derivado de sida, tumor maxilar, histiocitoma fibroso, leiomiosarcoma, rabdomiosarcoma, leucemia (por ejemplo, leucemia mieloide agudo, leucemia linfoblástico agudo, etc.) etc.), aterosclerosis, angiogénesis (por ejemplo, angiogénesis asociado con crecimiento de tumores malignos sólidos y sarcoma, angiogénesis asociado con metástasis tumoral, angiogénesis asociado con retinopatía diabética, etc.), y enfermedades virales (infección por VIH, etc.).

Las enfermedades dependientes de tirosina cinasa también incluyen enfermedades cardiovasculares asociadas con actividad anormal de la enzima tirosina cinasa. En consecuencia, el compuesto de la presente invención se puede usar como agente de profilaxis o tratamiento de enfermedades cardiovasculares tales como restenosis.

El compuesto de la presente invención es útil como agente antineoplásico para la profilaxis o tratamiento de

cáncer, especialmente cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas, cáncer de riñón y similares.

El compuesto de la presente invención muestra baja toxicidad y se puede usar como agente farmacéutico como tal, o como composición farmacéutica mezclado con un portador farmacéuticamente aceptable comúnmente conocido, etc. en mamíferos (por ejemplo, humanos, caballos, bovinos, perros, gatos, ratas, ratones, conejos, cerdos, monos y similares).

Además del compuesto de la presente invención, dicha composición farmacéutica puede contener otros ingredientes activos, por ejemplo, los siguientes agentes terapéuticos hormonales, agentes antineoplásicos (por ejemplo, agentes quimioterapéuticos, agentes inmunoterapéuticos, o agentes farmacéuticos que inhiben la acción de factores de crecimiento celular o de receptores de factor de crecimiento celular), y similares.

Como agente farmacéutico para mamíferos tales como humanos, el compuesto de la presente invención se puede administrar por vía oral, por ejemplo, en la forma de comprimidos, cápsulas (incluso cápsulas blandas y microcápsulas), polvos, gránulos y similares, o parenteralmente en la forma de inyecciones, supositorios, gránulos y similares. Los ejemplos de "vía de administración

parenteral" incluyen las vías intravenosa, intramuscular, subcutánea, intratisular, intranasal, intradérmica, instilación, intracerebral, intrarectal, intravaginal, intraperitoneal, intratumoral, yuxtaposición de tumor y administración directamente a la lesión.

La dosis del compuesto de la presente invención varía según la vía de administración, los síntomas, etc. Por ejemplo, cuando se administra por vía oral como agente antineoplásico a un paciente (peso corporal 40 a 80 kg) con cáncer de mama o cáncer de próstata, la dosis es, por ejemplo, de 0.5 a 100 mg/kg de peso corporal por día, de preferencia 1 a 50 mg/kg de peso corporal por día, y con mayor preferencia 1 a 25 mg/kg de peso corporal por día. Esta cantidad se puede administrar una vez o en 2 a 3 porciones divididas por día.

El compuesto de la presente invención se puede administrar con seguridad por vía oral o parenteral (por ejemplo, administraciones tópica, rectal, intravenosa, etc.) como agente único, o una composición farmacéutica que contiene un portador farmacológicamente aceptable de acuerdo con un método convencional (por ejemplo, un método descrito en Japanese Pharmacopoeia etc.), por ejemplo un comprimido (incluso comprimido recubierto por azúcar, comprimido recubierto de película), polvo, gránulo, cápsula, líquido, emulsión, suspensión, inyección, supositorio, preparación de

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liberación sostenida, parches y similares.

Y (1) la administración de una cantidad efectiva de un compuesto de la presente invención y (2) una combinación de 1 a 3 seleccionada del grupo que consiste en (i) administrar una cantidad efectiva de otros agentes anticancerosos, (ii) administrar una cantidad efectiva de agentes terapéuticos hormonales y (iii) la terapia no farmacológicas pueden prevenir y/o tratar el cáncer en forma más efectiva. Como terapéutica no farmacológica, por ejemplo, cirugía, radioterapia, terapia génica, termoterapia, crioterapia, cauterización con láser y similares son ejemplos y se pueden combinar dos o más de ellos.

Por ejemplo, el compuesto de la presente invención se puede administrar al mismo sujeto simultáneamente con agentes terapéuticos hormonales, agentes antineoplásicos (por ejemplo, agentes quimioterapéuticos, agentes inmunoterapéuticos, o agentes farmacéuticos que inhiben la acción de factores de crecimiento celular o receptores de factor de crecimiento celular) (en adelante, se refieren como fármaco concomitante).

Si bien el compuesto de la presente invención exhibe excelente acción anticancerosa, aun cuando se usa como agente único, su efecto se puede aumentar al usarlo en combinación con uno o más de los concomitante(s) fármaco(s) antes mencionados (coadministración de agentes múltiples).

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Como ejemplos de los "agentes terapéuticos hormonales" se pueden mencionar fosfestrol, dietilestilbestrol, clorotrianiseno, acetato de medroxiprogesterona, acetato de megestrol, acetato de clormadinona, acetato de ciproterona, danazol, dienogest, asoprisnilo, alilestrenol, gestrinona, nomegestrol, tadenano, mepartricina, raloxifeno, ormeloxifeno, levormeloxifeno, antiestrógenos (por ejemplo, citrato de tamoxifeno, citrato de toremifeno, y similares), regulador hacia debajo de ER (por ejemplo, fulvestrant, y similares), gonadotropina de menopausia humana, hormona foliculoestimulante, preparaciones en píldoras, mepitiostano, testrolactona, aminoglutetimida, agonistas de LH-RH (por ejemplo, acetato de goserelina, buserelina, leuprorelina, y similares), droloxifeno, epitioestanol, sulfonato de etinilestradiol, inhibidores de aromatasa (por ejemplo, clorhidrato de fadrozol, anastrozol, retrozol, exemestano, vorozol, formestano, y similares), antiandrógenos (por ejemplo, flutamida, bicartamida, nilutamida, y similares), inhibidores de 5α-reductasa (por ejemplo, finasterida, dutasterida, epristerida, y similares), fármacos de hormona adrenocorticotrófica (por ejemplo, dexametasona, prednisolona, betametasona, triamcinolona, y similares), inhibidores de síntesis de andrógenos (por ejemplo, abiraterona, y similares), retinoides y fármacos que retardan el metabolismo de retinoides (por ejemplo, liarozol,

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y similares), etc., y se prefieren los agonistas de LH-RH (por ejemplo, acetato de goserelina, buserelina, leuprorelina).

Como ejemplos de los "agentes quimioterapéuticos" se pueden mencionar agentes alquilantes, antimetabolitos, antibióticos anticancerosos, agentes antineoplásicos derivados de vegetales, y similares.

Como ejemplos de "agentes alquilantes" se pueden mencionar mostaza nitrogenada, clorhidrato de N-óxido de mostaza nitrogenada, clorambutilo, ciclofosfamida, ifosfamida, tiotepa, carbocuona, tosilato de improsulfano, busulfano, clorhidrato de nimustina, mitobronitol, melfalano, dacarbazina, ranimustina, fosfato de estramustina sódica, trietilenemelamina, carmustina, lomustina, estreptozocina, pipobromano, etoglúcido, carboplatino, cisplatino, miboplatino, nedaplatino, oxaliplatino, altretamina, ambamustina, clorhidrato de dibrospidio, fotemustina, prednimustina, pumitepa, ribomustina, temozolomida, treosulfano, trofosfamida, estimalámero de zinostatina, adozelesina, cistemustina, bizelesina, y similares.

Como ejemplos de "antimetabolitos" se pueden mencionar mercaptopurina, ribosideo de 6-mercaptopurina, tioinosina, metotrexato, enocitabina, citarabina, octofosfato de citarabina, clorhidrato de ancitabina, fármacos 5-FU (por ejemplo, fluorouracilo, tegafur, UFT, doxifluridina,

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carmofur, galocitabina, emitefur, y similares), aminopterina, leucovorina cálcica, tabloide, butocina, folinato cálcico, levofolinato cálcico, cladribina, emitefur, fludarabina, gemcitabina, hidroxicarbamida, pentostatina, piritrexima, idoxuridina, mitoguazona, tiazofrina, ambamustina, y similares.

Como ejemplos de "antibióticos anticáncer", se pueden mencionar actinomicina-D, actinomicina-C, mitomicina-C, cromomicina-A3, clorhidrato de bleomicina, sulfato de bleomicina, sulfato de peplomicina, clorhidrato de daunorrubicina, clorhidrato de doxorrubicina, clorhidrato de aclarrubicina, clorhidrato de pirarrubicina, clorhidrato de epirrubicina, neocarzinostatina, mitramicina, sarcomicina, carzinofilina, mitotano, clorhidrato de zorrubicina, clorhidrato de mitoxantrona, clorhidrato idarrubicina, y similares.

Como ejemplos de "agentes anticáncer derivados de vegetales", se pueden mencionar etopósida, fosfato de etopósida, sulfato de vinblastina, sulfato de vincristina, sulfato de vindesina, tenipósida, paclitaxel (Taxol (marca comercial)), docetaxel, vinorelbina, y similares.

Como ejemplos de los "agentes inmunoterapéuticos (BRM)", se pueden mencionar picibanilo, crestina, sizofirano, lentinano, ubenimex, interferones, interleucinas, factor estimulante de colonias de macrófagos, factor estimulante de

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colonias de granulocitos, eritropoyetina, linfotoxina, vacuna BCG, *Corinebacterium parvum*, levamisol, polisacárido K, procodazol, y similares.

Como "factor de crecimiento" de dicho "agentes farmacéuticos inhibidores de la acción de factores de crecimiento celular o receptores de factor de crecimiento celular", se puede mencionar cualquier sustancia que favorece la proliferación celular, que normalmente son péptidos con peso molecular de más de 20,000, capaces de exhibir su actividad con bajas concentraciones al unirse a un receptor, incluso (1) EGF (factor de crecimiento epidérmico) o sustancias que poseen sustancialmente la misma actividad [por ejemplo, EGF, herregulina, y similares], (2) insulina o sustancias que poseen sustancialmente la misma actividad [por ejemplo, insulina, IGF (factor de crecimiento símil insulina)-1, IGF-2, y similares], (3) FGF (factor de crecimiento de fibroblastos) o sustancias que poseen sustancialmente la misma actividad [por ejemplo, FGF ácido, FGF básico, KGF (factor de crecimiento de queratinocitos), FGF-10, y similares], (4) otros factores de crecimiento celular [por ejemplo, CSF (factor estimulante de colonias), EPO (eritropoyetina), IL-2 (interleuquina-2), NGF (factor de crecimiento nervioso), PDGF (factor de crecimiento derivado de plaquetas), TGFβ (factor de crecimiento de transformación β), HGF (factor de crecimiento de hepatocitos), VEGF (factor

de crecimiento de endotelio vascular), y similares], y similares.

Como ejemplos de los "receptores de factor de crecimiento", se puede mencionar cualquier receptor capaz de fijarse a los antes mencionados factores de crecimiento, incluso receptor de EGF, receptor de herregulina (HER2), receptor de insulina, receptor de IGF, receptor de FGF-1 o receptor de FGF-2, y similares.

Como ejemplos de los "agentes farmacéuticos inhibidores de la acción de factor de crecimiento celular", se pueden mencionar anticuerpo HER2 (trastuzumab (Herceptin (marca comercial))), mesilato de imatinib, anticuerpo ZD1839 o EGFR (cetuximab (Erbitux (marca comercial)) etc.), anticuerpo contra VEGF (por ejemplo, bevacizumab (Avastin (marca comercial))), anticuerpo VEGFR, inhibidor de VEGFR, inhibidor de EGFR (gefitinib (Iressa (marca comercial)), erlotinib (Tarceva (marca comercial)) etc.) y similares.

Además de los antes mencionados fármacos, se puede usar L-asparaginasa, aceglatona, clorhidrato de procarbazina, sal compleja de protoporfirina-cobalto, hematoporfirina mercúrico-sódica, inhibidores de topoisomerasa I (por ejemplo, irinotecano, topotecano, y similares), inhibidores de topoisomerasa II (por ejemplo, sobuzoxano, y similares), inductores de diferenciación (por ejemplo, retinoide, vitamina D, y similares), inhibidores de angiogénesis (por

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ejemplo, talidomida, SU11248, y similares), α-bloqueadores (por ejemplo, clorhidrato de tamsulosina, naftopidilo, urapidilo, alfuzosina, terazosina, prazosina, silodosina, y similares), inhibidor de serina/treonina cinasa, antagonista de receptor de endotelina (por ejemplo, atrasentano, y similares), inhibidor de proteasomas (por ejemplo, bortezomib, y similares), inhibidor de Hsp 90 (por ejemplo, 17-AAG, y similares), espironolactona, minoxidilo, 11α-hidroxiprogesterona, agente supresor de la inhibición/metástasis de resorción ósea (por ejemplo, ácido zoledrónico, ácido alendrónico, ácido pamidrónico, ácido etidrónico, ácido ibandrónico, ácido clodrónico) y similares.

De los antes mencionados como fármaco concomitante, se prefieren agonista de LH-RH (por ejemplo, acetato de goserelina, buserelina, leuprorelina, y similares), anticuerpo de HER2 (trastuzumab (Herceptin (marca comercial))), anticuerpo de EGFR (cetuximab (Erbitux) (marca comercial) etc.), inhibidor de EGFR (erlotinib (Tarceva) (marca comercial), gefitinib (Iressa (marca comercial)) etc.), agente inhibidor de VEGFR o agente quimioterapéutico (paclitaxel (Taxol (marca comercial) etc.).

Particularmente, son preferibles trastuzumab (Herceptin (marca comercial)), cetuximab (Erbitux (marca comercial)), erlotinib (Tarceva) (marca comercial)), gefitinib (Iressa (marca comercial)), paclitaxel (Taxol(marca

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comercial)) y similares.

En combinación con el compuesto de la presente invención y el fármaco concomitante, el momento de la administración del compuesto de la presente invención y el fármaco concomitante no está restringido, y el compuesto de la presente invención y fármaco concomitante se puede administrar al sujeto de administración simultáneamente, o se puede administrar en diferentes momentos. La dosis del fármaco concomitante se puede determinar de acuerdo con la cantidad de administración de uso clínico, y se puede seleccionar en forma adecuada según el sujeto de administración, la vía de administración, la enfermedad, la combinación y similares.

El modo de administración del compuesto de la presente invención y el fármaco concomitante no está particularmente restringido, y es suficiente combinar el compuesto de la presente invención y el fármaco concomitante en la administración. Los ejemplos de modos de dicha administración incluyen los siguientes métodos:

(1) El compuesto de la presente invención y el fármaco concomitante se produce simultáneamente para dar una única preparación administrada. (2) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran simultáneamente por la misma vía de

administración. (3) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran por la misma vía de administración, pero en distintos momentos. (4) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran simultáneamente por distintas vías de administración. (5) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran por distintas vías de administración, en distintos momentos (por ejemplo, el compuesto de la presente invención y el fármaco concomitante se administran en ese orden, o en orden inverso).

Ejemplos

La presente invención se explica en detalle por medio de los siguientes Ejemplos, Ejemplos de formulación y Ejemplos experimentales, pero no limitan la presente invención.

Ejemplos

La presente invención se explica a continuación en detalle haciendo referencia a Ejemplos, Ejemplos de Preparación y Ejemplos experimentales, que no se construyen como limitativos.

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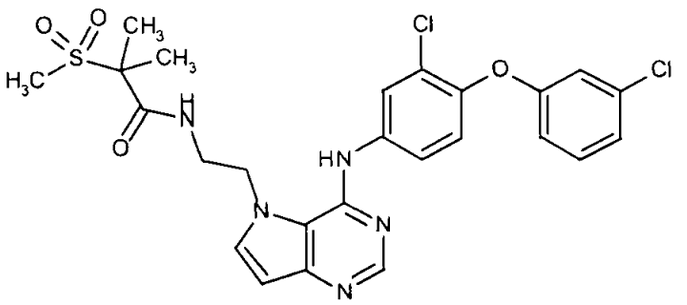
Ejemplo A-1



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

A una solución de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-clorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (487 mg), ácido 2-metil-2-(metilsulfonil)propanoico (249 mg) y 1-hidroxibenzotriazol (225 mg) en N,N-dimetilformamida (5.0 ml) se añadieron trietilamina (0.69 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (316 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→90:10) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (419 mg) en

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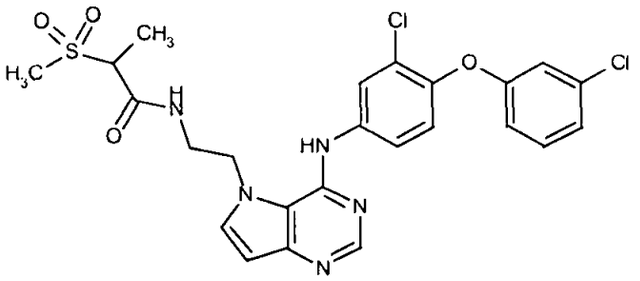
forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.60-3.80 (2H, m), 4.40-4.60 (2H, m), 6.46 (1H, d, J = 2.8 Hz), 6.85-7.00 (2H, m), 7.00-7.15 (2H, m), 7.15-7.30 (2H, m), 7.30-7.40 (1H, m), 7.85-7.95 (1H, m), 8.00-8.05 (1H, m), 8.36 (1H, br s), 8.54 (1H, s).

Ejemplo A-2



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)propanamida

A una solución de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-clorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 2-cloropropanoico (67 mg) y 1-hidroxibenzotriazol (90 mg) en N,N-dimetilformamida (4.0 ml) se añadieron trietilamina (0.29 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (126 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 17 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio

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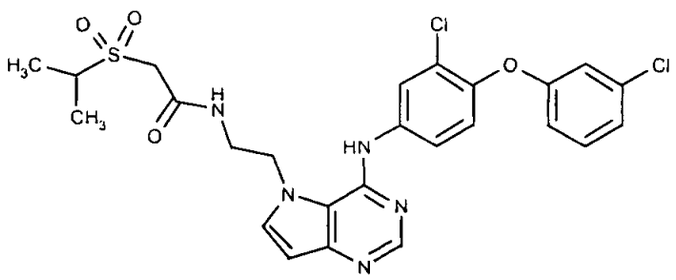
anhidro. Después de concentrar a presión reducida, el residuo se disolvió en N,N-dimetilformamida (2 ml), se añadieron ácido metansulfínico de sodio (420 mg) y piridina (0.40 ml), y la mezcla se agitó a 70°C durante 2 días. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (97 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.71 (3H, d, J = 7.2 Hz), 2.98 (3H, s), 3.65-3.75 (2H, m), 3.81 (1H, q, J = 7.2 Hz), 4.45-4.55 (2H, m), 6.61 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.90-6.95 (1H, m), 7.00-7.10 (2H, m), 7.20-7.30 (1H, m), 7.30-7.40 (1H, m), 7.75-7.85 (1H, m), 7.97 (1H, d, J = 2.4 Hz), 8.28 (1H, s), 8.51 (1H, s).

Ejemplo A-3



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(isopropilsulfonil)acetamida

(i) Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(isopropiltio)acetamida

A una solución de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-clorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (300 mg), ácido cloroacético (87 mg) y 1-hidroxibenzotriazol (135 mg) en N,N-dimetilformamida (5.0 ml) se añadieron trietilamina (0.43 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (189 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se disolvió en N,N-dimetilformamida (2 ml)/tetrahidrofurano (4 ml), se añadió propan-2-tiolato de sodio (605 mg), y la mezcla se agitó a temperatura ambiente durante 6 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel

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de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (201 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.24 (6H, d, J = 6.9 Hz), 2.80-2.90 (1H, m), 3.33 (2H, s), 3.60-3.70 (2H, m), 4.45-4.55 (2H, m), 6.62 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 8.7 Hz), 7.20-7.30 (2H, m), 7.40-7.50 (1H, m), 7.73 (1H, dd, J = 2.4, 8.7 Hz), 8.05 (1H, d, J = 2.4 Hz), 8.51 (1H, s).

(ii) Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(isopropilsulfonil)acetamida

A una solución de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(isopropiltio)acetamida en metanol (6 ml)/agua (1.5 ml) se añadió compuesto OXONE® monopersulfatado (339 mg), y la mezcla se agitó a temperatura ambiente durante 21 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con diclorometano. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se recristalizó en diclorometano/metanol/éter diisopropílico para dar el compuesto del título (173 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.23 (6H, d, J = 6.9 Hz), 3.40-

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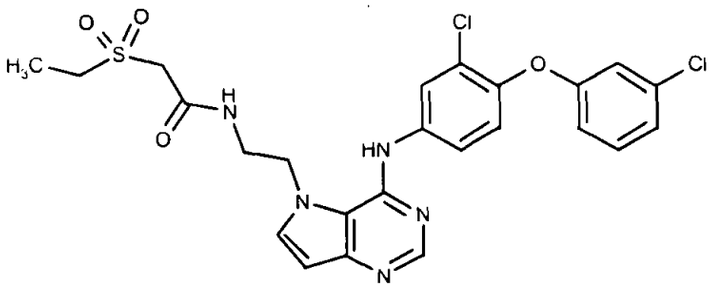
3.65 (3H, m), 4.03 (2H, s), 4.50-4.70 (2H, m), 6.58 (1H, s), 6.90-6.95 (1H, m), 6.99 (1H, s), 7.15-7.25 (1H, m), 7.30 (1H, d, J = 8.7 Hz), 7.40-7.50 (1H, m), 7.65-7.75 (1H, m), 7.79 (1H, s), 7.92 (1H, s), 8.53 (1H, s), 8.70-8.80 (1H, m), 9.28 (1H, br s).

Ejemplo A-4



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida

(i) Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etiltio)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-clorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido etiltioacético (99 mg), 1-hidroxibenzotriazol (123 mg), trietilamina (0.57 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (173 mg) y N,N-dimetilformamida (4.0 ml) y de la misma manera que en el Ejemplo A-1, se obtuvo el compuesto del título (186 mg) en forma de un polvo blanco.

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^{1}H-RMN ($CDCl_3$) δ: 1.24 (3H, t, J = 7.5 Hz), 2.52 (2H, q, J = 7.5 Hz), 3.32 (2H, s), 3.60-3.70 (2H, m), 4.45-4.55 (2H, m), 6.62 (1H, d, J = 3.0 Hz), 6.88 (1H, d, J = 8.1 Hz), 6.95-7.00 (1H, m), 7.00-7.10 (2H, m), 7.15-7.25 (1H, m), 7.40-7.50 (1H, m), 7.70-7.80 (1H, m), 8.05-8.10 (1H, m), 8.50 (1H, s), 8.51 (1H, s).

(ii) Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida

Al usar N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etiltio)acetamida (180 mg), compuesto OXONE® monopersulfatado (322 mg) y metanol (6 ml)/agua (1.2 ml) y de la misma manera que en el Ejemplo A-3(ii), se obtuvo el compuesto del título (149 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.21 (3H, t, J = 7.2 Hz), 3.22 (2H, q, J = 7.2 Hz), 3.45-3.55 (2H, m), 4.03 (2H, s), 4.55-4.65 (2H, m), 6.55-6.60 (1H, m), 6.90-6.95 (1H, m), 6.99 (1H, s), 7.15-7.20 (1H, m), 7.29 (1H, d, J = 8.7 Hz), 7.41 (1H, t, J = 8.2 Hz), 7.65-7.75 (1H, m), 7.75-7.80 (1H, m), 7.93 (1H, s), 8.52 (1H, s), 8.72 (1H, br s), 9.22 (1H, br s).

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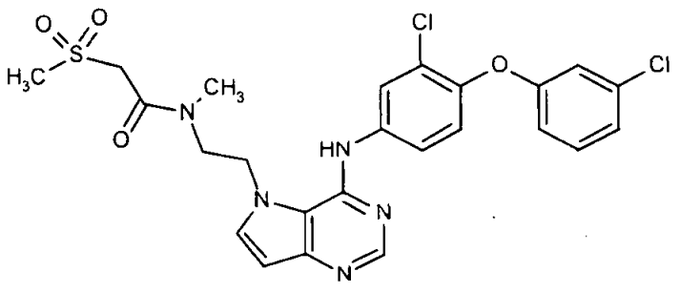
Ejemplo A-5



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N-metil-2-(metilsulfonil)acetamida

(i) Producción de [2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]metilcarbamato de ter-butilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]metilcarbamato de ter-butilo (2.56 g), 3-cloro-4-(3-clorofenoxi)anilina (2.51 g) y alcohol isopropílico (25 ml) se agitó a 80°C durante 18 h. Tras enfriar hasta temperatura ambiente, la mezcla se agitó durante 5 h. El precipitado se recogió por filtración, y se lavó con éter diisopropílico para dar el compuesto del título (3.72 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.52 (9H, s), 3.01 (3H, s), 3.50-3.60 (2H, m), 4.40-4.50 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 9.0 Hz), 7.15-7.25 (2H, m), 7.90 (1H, d, J = 9.0 Hz), 8.01 (1H, br s), 8.52 (1H, s), 8.83 (1H, s).

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(ii) Producción de diclorhidrato de N-[3-cloro-4-(3-clorofenoxi)fenil]-5-[2-(metilamino)etil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]metilcarbamato de ter-butilo (3.72 g) y ácido clorhídrico al 10% (p/p)/metanol (30 ml) se agitó a 65°C durante 24 h. La mezcla de reacción se concentró a presión reducida, y el precipitado se recogió por filtración, y se lavó con éter dietílico para dar el compuesto del título (2.70 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 2.50-2.60 (3H, m), 3.30-3.50 (2H, m), 5.00-5.20 (2H, m), 6.75 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.02 (1H, s), 7.21 (1H, d, J = 7.8 Hz), 7.32 (1H, d, J = 8.7 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.93 (1H, s), 8.07 (1H, d, J = 3.0 Hz), 8.73 (1H, s), 9.10-9.30 (2H, m), 10.17 (1H, br s).

(iii) Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N-metil-2-(metilsulfonil)acetamida

Al usar diclorhidrato de N-[3-cloro-4-(3-clorofenoxi)fenil]-5-[2-(metilamino)etil]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido metilsulfonilacético (83 mg), 1-hidroxibenzotriazol (87 mg), trietilamina (0.28 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida

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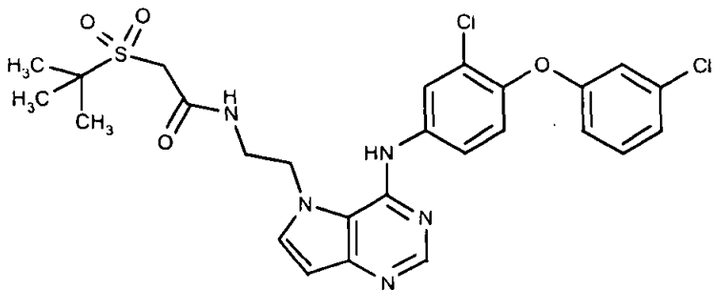
(123 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo A-1, se obtuvo el compuesto del título (164 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.17 (3H, s), 3.33 (3H, s), 3.70-3.85 (2H, m), 4.17 (2H, s), 4.45-4.55 (2H, m), 6.63 (1H, d, J = 3.0 Hz), 6.85-6.95 (2H, m), 7.00-7.10 (2H, m),7.20-7.30 (2H, m), 7.82 (1H, dd, J = 2.7 Hz, 9.0 Hz), 7.92 (1H, d, J = 2.7 Hz), 8.44 (1H, s), 8.52 (1H, s).

Ejemplo A-6



Producción de 2-(ter-butilsulfonil)-N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]acetamida

(i) Producción de 2-(ter-butiltio)-N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]acetamida

A una solución de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-clorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido cloroacético (58 mg) y 1-hidroxibenzotriazol (90 mg) en N,N-dimetilformamida (4.0 ml) se añadieron trietilamina (0.29 ml) y clorhidrato de 1-etil-

729

3-(3-dimetilaminopropil)carbodiimida (126 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se disolvió en N,N-dimetilformamida (2 ml)/tetrahidrofurano (4 ml), se añadió 2-metilpropano-2-tiolato de sodio (511 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (159 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.30 (9H, s), 3.33 (2H, s), 3.60-3.70 (2H, m), 4.40-4.50 (2H, m), 6.61 (1H, d, J = 3.3 Hz), 6.85-6.90 (1H, m), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.07 (1H, d, J = 9.0 Hz), 7.15-7.25 (2H, m), 7.45-7.55 (1H, m), 7.73 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.06 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.56 (1H, s).

(ii) Producción de 2-(ter-butilsulfonil)-N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-

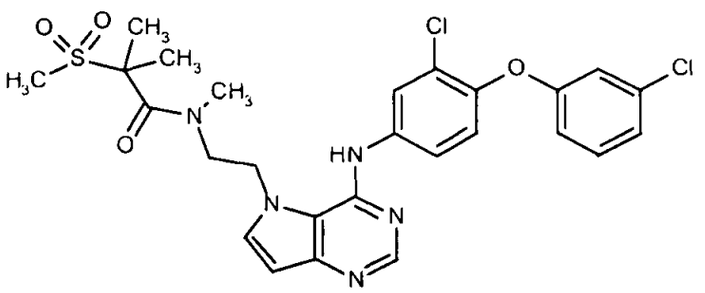
730

d]pirimidin-5-il)etil]acetamida

Al usar 2-(ter-butiltio)-N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]acetamida (159 mg), compuesto OXONE® monopersulfatado (269 mg) y metanol (5 ml)/agua (1.5 ml) y de la misma manera que en el Ejemplo A-3(ii), se obtuvo el compuesto del título (99 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (95%$CDCl_3$+5%DMSO-d_6) δ: 1.43 (9H, s), 3.50-3.70 (2H, m), 4.00 (2H, s), 4.60-4.70 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (2H, m), 7.05-7.15 (2H, m), 7.31 (1H, t, J = 8.1 Hz), 7.60-7.70 (2H, m), 7.92 (1H, s), 8.49 (1H, s), 8.80-8.90 (1H, m), 9.30-9.50 (1H, m).

Ejemplo A-7



Producción de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N,2-dimetil-2-(metilsulfonil)propanamida

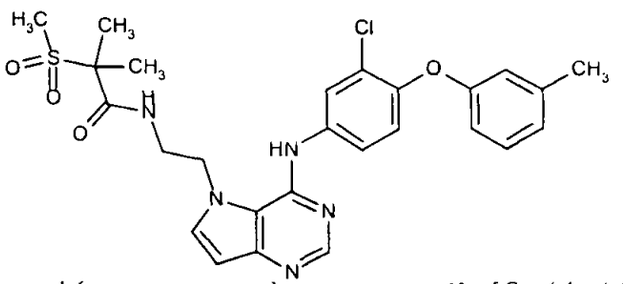
A una solución de diclorhidrato de N-[3-cloro-4-(3-clorofenoxi)fenil]-5-[2-(metilamino)etil]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg) y ácido 2-metil-2-(metilsulfonil)propanoico (100 mg) en N,N-dimetilformamida

731

(5.0 ml) se añadieron trietilamina (0.28 ml) y dietilcianofosfonato (0.097 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 25 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→90:10) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (94 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.85 (6H, s), 2.97 (3H, s), 3.47 (3H, s), 3.70-3.80 (2H, m), 4.40-4.50 (2H, m), 6.63 (1H, d, J = 3.6 Hz), 6.85-6.95 (2H, m), 7.00-7.05 (1H, m), 7.06 (1H, d, J = 8.7 Hz), 7.20-7.30 (2H, m), 7.90-8.00 (1H, m), 8.01 (1H, d, J = 2.4 Hz), 8.52 (1H, s), 8.69 (1H, br s).

Ejemplo A-8



Producción de N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

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(i) Producción de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-metilfenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (594 mg), 3-cloro-4-(3-metilfenoxi)anilina (467 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante 6 h. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, y el residuo obtenido se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. A una solución del residuo en metanol (10 ml) se añadió ácido clorhídrico concentrado (3 ml), y la mezcla se agitó a temperatura ambiente durante la noche y también a 60°C durante 3 h. La mezcla de reacción se concentró a presión reducida. Se añadieron alcohol isopropílico y tolueno al residuo, y la mezcla se concentró a presión reducida. Se añadió metanol al residuo, y la mezcla se concentró a presión reducida. Se añadieron alcohol isopropílico y éter diisopropílico al residuo, y el sólido precipitado se recogió por filtración para dar el compuesto del título (805 mg) en forma de un polvo de color amarillo

733.

pálido.

^{1}H-RMN (DMSO-d_6) δ: 2.31(3H, s), 3.23-3.37 (2H, m), 5.04 (2H, t, J= 6.2 Hz), 6.72-6.80 (2H, m), 6.83 (1H, m), 6.98 (1H, d, J= 7.5 Hz), 7.18 (1H, d, J= 8.9 Hz), 7.29 (1H, t, J= 7.8 Hz), 7.59 (1H, dd, J= 8.8, 2.5 Hz), 7.87 (1H, d, J= 2.5 Hz), 8.07 (1H, d, J= 3.2 Hz), 8.35 (3H, br s), 8.73 (1H, s), 10.15 (1H, br s).

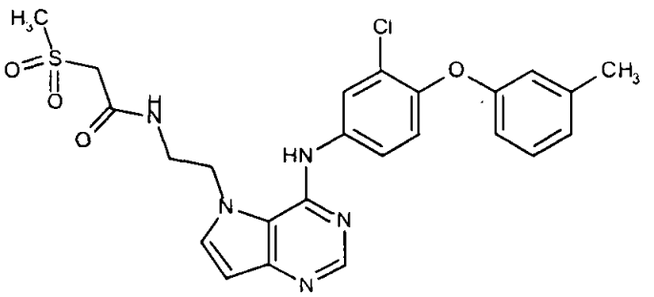
(ii) Producción de N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-metilfenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (140 mg), ácido 2-metil-2-(metilsulfonil)propanoico (75 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se

cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (155 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.69 (6H, s), 2.33 (3H, s), 2.93 (3H, s), 3.61-3.74 (2H, m), 4.41-4.51 (2H, m), 6.61 (1H, d, J= 3.3 Hz), 6.75-6.84 (2H, m), 6.89 (1H, d, J= 7.7 Hz), 7.02 (1H, d, J= 8.8 Hz), 7.16-7.24 (2H, m), 7.34 (1H, t, J= 5.8 Hz), 7.80 (1H, dd, J= 8.8 Hz, 2.5 Hz), 7.97 (1H, d, J= 2.5 Hz), 8.31 (1H, br s), 8.51 (1H, s).

Ejemplo A-9



Producción de N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

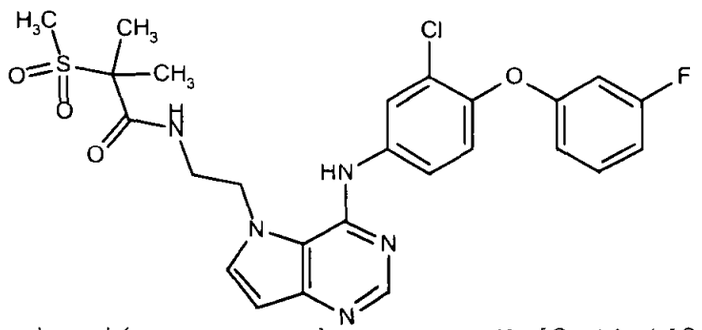
Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-metilfenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (140 mg), ácido metilsulfonilacético (62 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La

735.

capa orgánica se lavó sucesivamente con agua y salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (147 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.33 (3H, s), 3.13 (3H, s), 3.63-3.76 (2H, m), 3.70 (2H, s), 4.41-4.53 (2H, m), 6.58 (1H, d, J= 3.3 Hz), 6.75-6.84 (2H, m), 6.90 (1H, d, J= 7.4 Hz), 7.01 (1H, d, J= 8.7 Hz), 7.16-7.24 (2H, m), 7.55-7.64 (1H, m), 7.69 (1H, dd, J= 8.7, 2.7 Hz), 7.89 (1H, d, J= 2.7 Hz), 8.14 (1H, br s), 8.48 (1H, s).

Ejemplo A-10



Producción de N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

(i) Producción de diclorhidrato de 5-(2-aminoetil)-

N-[3-cloro-4-(3-fluorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (594 mg), 3-cloro-4-(3-fluorofenoxi)anilina (475 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante 6 h. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Se añadieron metanol (10 ml), tetrahidrofurano (1 ml) y ácido clorhídrico concentrado (3 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante la noche y luego se agitó a 60°C durante 3 h. La mezcla de reacción se concentró a presión reducida. Se añadieron alcohol isopropílico y tolueno al residuo, y la mezcla se concentró a presión reducida. Se añadió metanol al residuo, y la mezcla se concentró a presión reducida. Se añadieron alcohol isopropílico y éter diisopropílico al residuo y el sólido precipitado se recogió por filtración para dar el compuesto del título (809 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.22-3.39 (2H, m), 5.09 (2H, t, J= 6.3 Hz), 6.73-6.82 (2H, m), 6.83-6.92 (1H, m), 6.96-7.05 (1H, m), 7.31 (1H, d, J= 8.9 Hz), 7.39-7.51 (1H, m), 7.66 (1H, dd, J= 2.4 Hz, 8.9 Hz), 7.93 (1H, d, J =2.4 Hz), 8.10 (1H, d, J= 3.2 Hz), 8.42 (3H, br s), 8.74 (1H, s), 10.30 (1H, br s).

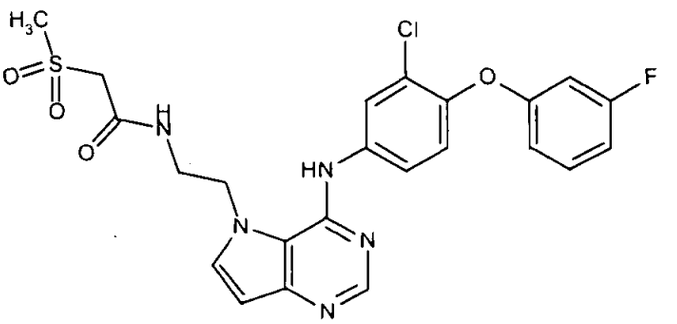
(ii) Producción de N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-fluorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (141 mg), ácido 2-metil-2-(metilsulfonil)propanoico (75 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar

el compuesto del título (161 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.63-3.74 (2H, m), 4.42-4.53 (2H, m), 6.63 (1H, d, J= 3.3 Hz), 6.64-6.71 (1H, m), 6.74-6.82 (2H, m), 7.09 (1H, d, J= 8.9 Hz), 7.19-7.32 (2H, m), 7.37 (1H, t, J= 5.8 Hz), 7.88 (1H, dd, J= 2.7 Hz, 8.9 Hz), 8.02 (1H, d, J= 2.7 Hz), 8.36 (1H, br s), 8.53 (1H, s).

Ejemplo A-11



Producción de N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-fluorofenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (141 mg), ácido metilsulfonilacético (62 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó sucesivamente con agua y

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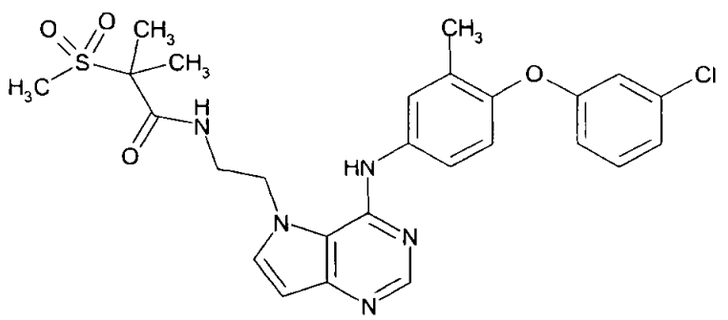
salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (146 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 3.14 (3H, s), 3.64-3.76 (2H, m), 3.98 (2H, s), 4.43-4.54 (2H, m), 6.59 (1H, d, J= 3.3 Hz), 6.63-6.70 (1H, m), 6.73-6.82 (2H, m), 7.08 (1H, d, J= 8.9 Hz), 7.18-7.31 (2H, m), 7.57-7.65 (1H, m), 7.75 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.93 (1H, d, J= 2.5 Hz), 8.19 (1H, br s), 8.49 (1H, s).

Ejemplo A-12



Producción de N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

(i) Producción de [2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-

740

il)etil]carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.0 g) y 3-metil-4-[3-clorofenoxi]anilina (1.18 g) en alcohol isopropílico (10 ml) se agitó a 80°C durante 12 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 8:2→acetato de etilo) para dar el compuesto del título (1.7 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (9H, s), 2.20 (3H, s), 3.48 (2H, m), 4.45 (2H, m), 5.16 (1H, m), 6.57 (1H, d, J= 3 Hz), 6.80-7.00 (4H, m), 7.10-7.30 (2H, m), 7.68 (2H, m), 8.40 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-[4-(3-clorofenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.6 g), ácido clorhídrico 2 N (23 ml) y tetrahidrofurano (46 ml) se agitó a 60°C durante 20 h. El solvente se evaporó a presión reducida, se añadió

etanol, y la mezcla luego se concentró. Los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter isopropílico para dar el compuesto del título (1.35 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 2.19 (3H, s), 3.30 (2H, m), 5.04 (2H, m), 6.72 (1H, d, J= 3 Hz), 6.80-7.00 (2H, m), 7.08 (1H, d, J= 9 Hz), 7.16 (1H, dd, J= 2 Hz, 8 Hz), 7.30-7.50 (2H, m), 7.54 (1H, m), 8.06 (1H, m), 8.40 (3H, br s), 8.68 (1H, s), 10.00 (1H, br s).

(iii) Producción de N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[4-(3-clorofenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (167 mg), ácido 2-metil-2-(metilsulfonil)propanoico (89 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por

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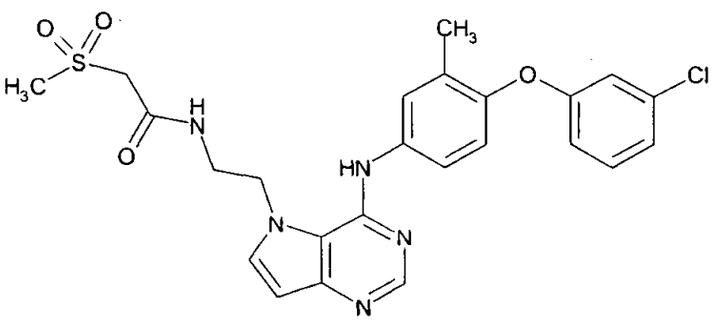
cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar el compuesto del título (179 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.42 (6H, s), 2.14 (3H, s), 2.96 (3H, s), 3.47 (2H, q, J= 6 Hz), 4.56 (2H, t, J= 6 Hz), 6.45 (1H, d, J= 3 Hz), 6.80-6.90 (2H, m), 7.02 (1H, d, J= 9 Hz), 7.11 (1H, dd, J= 1 Hz, 8 Hz), 7.37 (1H, t, J= 8 Hz), 7.52 (1H, d, J= 3 Hz), 7.58 (2H, m), 8.20 (1H, t, J= 6 Hz), 8.28 (1H, s), 8.49 (1H, br s).

Ejemplo A-13



Producción de N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[4-(3-clorofenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (167 mg), ácido metilsulfonilacético (74 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura

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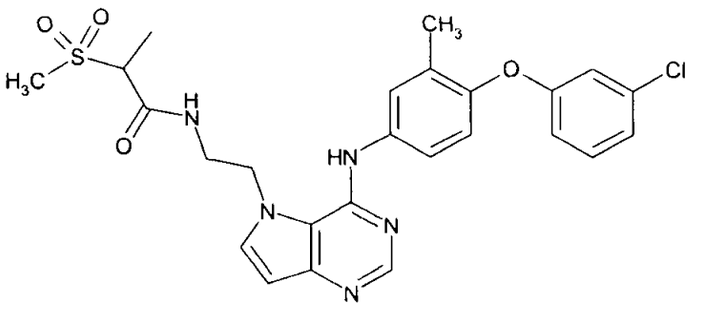
ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar el compuesto del título (177 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 2.13 (3H, s), 3.09 (3H, s), 3.45 (2H, q, J= 6 Hz), 4.05 (2H, s), 4.55 (2H, t, J= 6 Hz), 6.46 (1H, d, J= 3 Hz), 6.80-6.95 (2H, m), 7.00 (1H, d, J= 9 Hz), 7.11 (1H, m), 7.37 (1H, t, J= 8 Hz), 7.56 (3H, m), 8.28 (1H, s), 8.52 (1H, br s), 8.66 (1H, m).

Ejemplo A-14



Producción de N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)propanamida

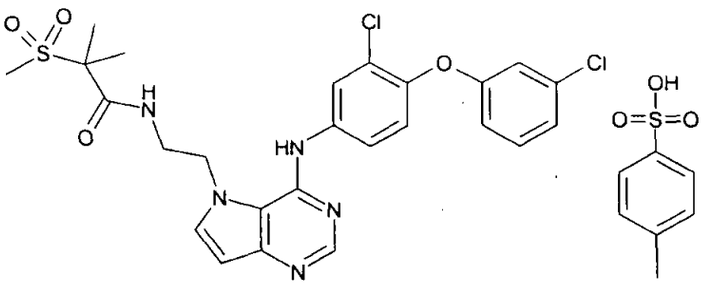
Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[4-(3-clorofenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-

4-amina (192 mg), ácido 2-cloropropanoico (0.057 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (126 mg), 1-hidroxibenzotriazol (90 mg), trietilamina (0.29 ml) y N,N-dimetilformamida (4 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 90:10), y la fracción que contenía 2-cloro-N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]propanamida se concentró a presión reducida. El residuo se disolvió en N,N-dimetilformamida (4 ml) y piridina (0.4 ml), se añadió ácido metansulfínico de sodio (420 mg) y la mezcla se agitó a 70°C durante 2 días. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar el compuesto del título (116 mg) en forma de cristales

incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (3H, d, J= 7 Hz), 2.13 (3H, s), 2.95 (3H, s), 3.50 (2H, m), 3.82 (1H, m), 4.53 (2H, m), 6.46 (1H, d, J= 3 Hz), 6.80-6.90 (2H, m), 7.01 (1H, d, J= 9 Hz), 7.10 (1H, d, J= 8 Hz), 7.37 (1H, t, J= 8 Hz), 7.57 (3H, m), 8.28 (1H, s), 8.49 (1H, br s), 8.59 (1H, t, J= 6 Hz).

Ejemplo A-15



Producción de p-toluensulfonato de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Se añadieron acetato de etilo (200 ml) y etanol (70 ml) a N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida (9.0 g), la mezcla se disolvió por calentamiento a 65°C, y se añadió ácido p-toluensulfónico monohidratado (3.04 g). La mezcla se dejó reposar a temperatura ambiente bajo protección de la luz durante 23 h y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con una pequeña cantidad de acetato de etilo y éter diisopropílico para dar el compuesto del título

(11.5 g) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.40 (6H, s), 2.28 (3H, s), 2.93 (3H, s), 3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.10 (2H, d, J = 7.8 Hz), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 9.0 Hz), 7.40-7.50 (3H, m), 7.60-7.70 (1H, m), 7.89 (1H, d, J = 3.0 Hz), 7.91 (1H, d, J = 1.8 Hz), 8.15-8.25 (1H, m), 8.74 (1H, s), 9.80 (1H, br s).

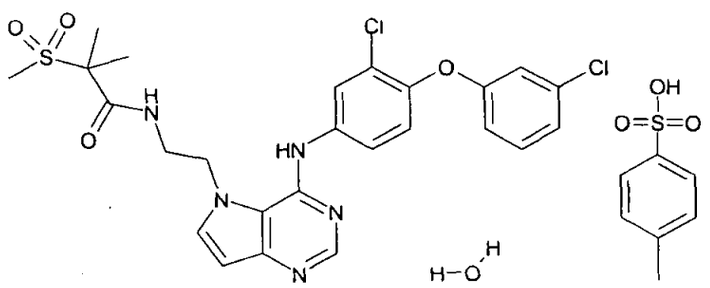
Análisis elemental para $C_{32}H_{33}Cl_2N_5O_7S_2$

Calculado: C,52.32; H,4.53; N,9.53.

Experimental: C,52.35; H,4.54; N,9.49.

P. f. 217-218°C.

Ejemplo A-16



Producción de p-toluensulfonato de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida monohidratado

Se añadió acetona (20 ml) a N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida (500 mg), y la

mezcla se disolvió por calentamiento a 40°C, y se agregó ácido p-toluensulfónico monohidratado (168 mg). La mezcla se dejó reposar a temperatura ambiente bajo protección de la luz durante 4 días, y se concentró a presión reducida. Se añadieron acetato de etilo (12 ml) y etanol (4 ml) al residuo, y la mezcla se disolvió por calentamiento a 60°C. La mezcla se dejó reposar a temperatura ambiente durante 17 h bajo protección de la luz, y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter diisopropílico para dar el compuesto del título (543 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.40 (6H, s), 2.29 (3H, s), 2.93 (3H, s), 3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.10 (2H, d, J = 7.8 Hz), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 9.0 Hz), 7.40-7.50 (3H, m), 7.67 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.88 (1H, d, J = 3.0 Hz), 7.92 (1H, d, J = 2.4 Hz), 8.15-8.25 (1H, m), 8.73 (1H, s), 9.76 (1H, br s).

Análisis elemental para $C_{32}H_{33}Cl_2N_5O_7S_2 \cdot 1.0H_2O$

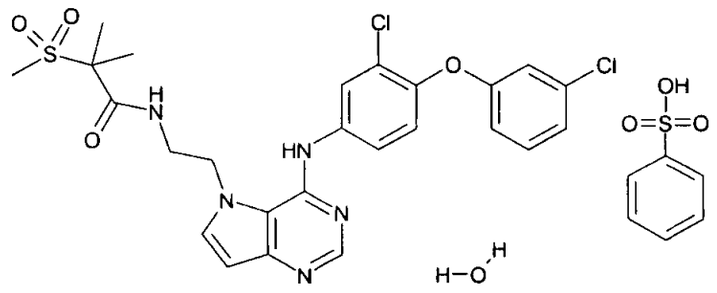
Calculado: C,51.06; H,4.69; N,9.30.

Experimental: C,50.49; H,4.52; N,9.23.

P. f. 216-217°C.

748.

Ejemplo A-17



Producción de bencensulfonato de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida monohidratado

A N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida (400 mg) se añadieron acetato de etilo (12 ml) y etanol (4 ml), y la mezcla se disolvió por calentamiento a 60°C, y se agregó ácido bencensulfónico monohidratado (132 mg). La mezcla se dejó reposar a temperatura ambiente durante 17 h bajo protección de la luz y se concentró a presión reducida, y se añadió acetato de etilo (10 ml) al residuo. La mezcla se dejó reposar a temperatura ambiente durante 17 h bajo protección de la luz, y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter diisopropílico para dar el compuesto del título (447 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.41 (6H, s), 2.93 (3H, s),

749

3.50-3.60 (2H, m), 4.65-4.75 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.95-7.00 (1H, m), 7.00-7.05 (1H, m), 7.20-7.25 (1H, m), 7.25-7.35 (3H, m), 7.35 (1H, d, J = 8.4 Hz), 7.45 (1H, t, J = 8.4 Hz), 7.55-7.65 (2H, m), 7.67 (1H, dd, J = 2.4, 8.7 Hz), 7.88 (1H, d, J = 3.0 Hz), 7.93 (1H, d, J = 2.4 Hz), 8.20-8.25 (1H, m), 8.73 (1H, s), 9.74 (1H, br s).

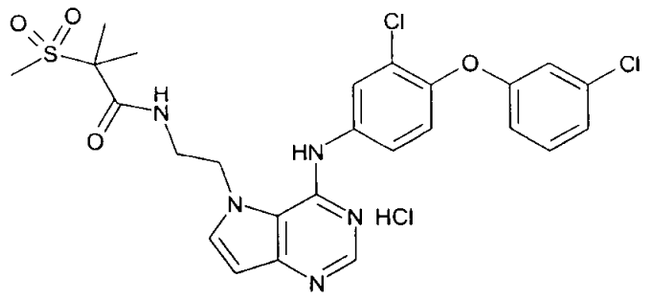
Análisis elemental para $C_{31}H_{31}Cl_2N_5O_7S_2 \cdot 1.0H_2O$

Calculado: C,50.41; H,4.50; N,9.48.

Experimental: C,50.53; H,4.43; N,9.48.

P. f. 142-144°C.

Ejemplo A-18



Producción de clorhidrato de N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Se añadió acetona (20 ml) a N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida (400 mg), y la mezcla se disolvió por calentamiento a 40°C. Se agregó una solución de cloruro de hidrógeno 4 N/acetato de etilo (0.196 ml). La mezcla se dejó reposar a temperatura ambiente durante

750.

4 días bajo protección de la luz, y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter diisopropílico para dar el compuesto del título (401 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.40 (6H, s), 2.93 (3H, s), 3.50-3.65 (2H, m), 4.4,70-4.80 (2H, m), 6.65 (1H, d, J = 3.0 Hz), 6.90-7.00 (1H, m), 7.00-7.05 (1H, m), 7.20-7.25 (1H, m), 7.35 (1H, d, J = 8.7 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.68 (1H, dd, J = 2.4 Hz, 8.7 Hz), 7.89 (1H, d, J = 3.0 Hz), 7.94 (1H, d, J = 2.4 Hz), 8.20-8.30 (1H, m), 8.73 (1H, s), 9.89 (1H, br s).

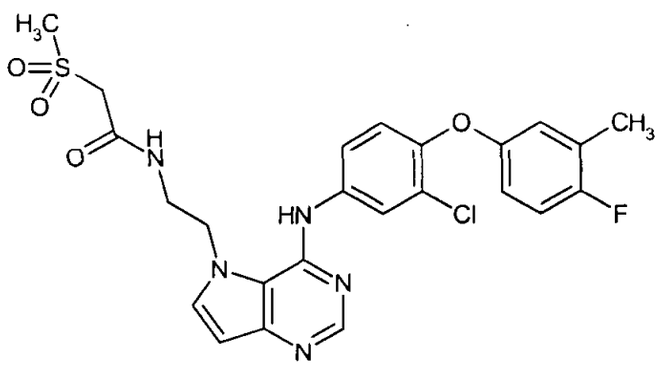
Análisis elemental para $C_{25}H_{26}Cl_3N_5O_4S$

Calculado: C, 50.13; H,4.38; N,11.69.

Experimental: C, 49.70; H,4.41; N,11.48.

P. f. 194-195°C.

Ejemplo A-19



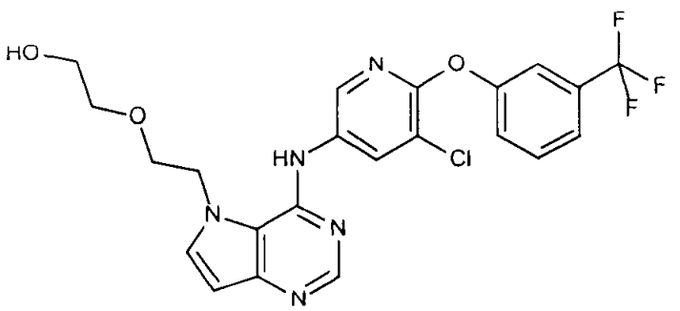
Producción de N-(2-(4-((3-cloro-4-(4-fluoro-3-metilfenoxi)fenil)amino)-5H-pirrolo[3,2-d]pirimidin-5-il)etil)-2-(metilsulfonil)acetamida

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.00 g), 3-cloro-4-(4-fluoro-3-metilfenoxi)anilina (1.51 g) y alcohol isopropílico (10 ml) se agitó a 80°C durante 12 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción bajo enfriamiento con hielo y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0) para dar un producto crudo (1.52 g). El producto crudo obtenido (150 mg) se disolvió en tetrahidrofurano (22.2 ml). Se añadió una solución de cloruro de hidrógeno 4 N/acetato de etilo (11.5 ml), y la mezcla se agitó a 70°C durante 20 h. El solvente se evaporó a presión reducida, se añadió etanol, y la mezcla luego se concentró. Se añadió éter diisopropílico, y el polvo precipitado se recogió por filtración. Una mezcla del polvo obtenido, ácido metilsulfonilacético (74 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (7.0 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión

reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 90:10) y se cristalizó en éter diisopropílico para dar el compuesto del título (116 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 2.22 (3H, s), 3.10 (3H, s), 3.46 (2H, q, J = 6.0 Hz), 4.04 (2H, s), 4.55 (2H, t, J = 6.0 Hz), 6.49-7.17 (5H, m), 7.61-7.93 (3H, m), 8.33 (1H, s), 8.65-8.66 (2H, m).

Ejemplo B-1



Producción de 2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 3-cloro-5-nitro-2-[3-(trifluorometil)fenoxi]piridina

Bajo una atmósfera de argón, se añadió a una solución de 3-(trifluorometil)fenol (0.42 g) en tetrahidrofurano (8.0 ml) hidruro de sodio (dispersión al 60% en aceite mineral, 0.11 g) bajo enfriamiento con hielo. Tras agitar bajo enfriamiento con hielo durante 1 h, se añadió

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2.3-dicloro-5-nitropiridina (0.50 g). Tras agitar a temperatura ambiente durante 2.5 h, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 9:1→3:1) para dar el compuesto del título (746 mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 7.35-7.43 (1H, m), 7.45-7.51 (1H, m), 7.55-7.65 (1H, m), 8.61 (1H, d, J= 2.7 Hz), 8.88 (1H, d, J= 2.7 Hz).

(ii) Producción de 5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-amina

Una mezcla de 3-cloro-5-nitro-2-[3-(trifluorometil)fenoxi]piridina (746 mg), hierro reducido (0.65 g), cloruro de calcio (0.13 g) y 15% de etanol con contenido de agua (23 ml) se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1) para

dar el compuesto del título (290 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 3.65 (2H, br s), 7.20 (1H, d, J= 2.9 Hz), 7.22-7.26 (1H, m), 7.27-7.32 (1H, m), 7.37-7.40 (1H, m), 7.44-7.50 (1H, m), 7.59 (1H, d, J= 2.9 Hz).

(iii) Producción de 2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Una solución de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (100 mg) y 5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-amina (100 mg) en alcohol isopropílico (2.0 ml) se agitó a 80°C durante 16 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 1:1→acetato de etilo) para dar benzoato de 2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etilo (130 mg) en forma de un amorfo incoloro. A una solución de benzoato de 2-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etilo (130 mg) en alcohol

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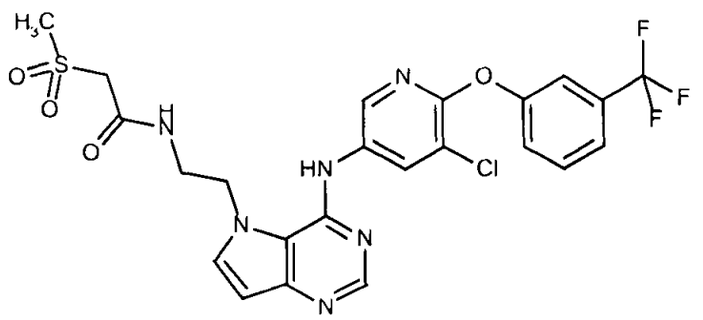
isopropílico-tetrahidrofurano (3 ml-2 ml) se añadió solución acuosa 1 N de hidróxido de sodio (0.5 ml) a temperatura ambiente y la mezcla se agitó durante 3 h. La mezcla de reacción se diluyó con acetato de etilo, y la capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 9:1) para dar el compuesto del título (72 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.69-3.80 (4H, m), 4.00-4.04 (2H, m), 4.54-4.59 (2H, m), 6.65 (1H, d, J= 3.3 Hz), 7.23 (1H, d, J= 3.3 Hz), 7.31-7.36 (1H, m), 7.40-7.55 (3H, m), 8.24 (1H, d, J= 2.7 Hz), 8.47 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.83 (1H, s).

Ejemplo B-2



Producción de N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de {2-[4-({5-cloro-6-[3-

(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (189 mg) y 5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-amina (184 mg) en alcohol isopropílico (4.0 ml) se agitó a 80°C durante 20 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:1→acetato de etilo) para dar el compuesto del título (257 mg) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.49 (9H, s), 3.43-4.54 (2H, m), 4.40-4.51 (2H, m), 5.05-5.15 (1H, m), 6.60 (1H, d, J= 3.0 Hz), 7.19 (1H, d, J= 3.0 Hz), 7.33-7.39 (1H, m), 7.41-7.53 (3H, m), 8.39 (1H, d, J= 2.4 Hz), 8.47 (1H, s), 8.64 (1H, d, J= 2.4 Hz), 8.79 (1H, s).

(ii) Producción de triclorhidrato de 5-(2-aminoetil)-N-{5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}-5H-pirrolo[3,2-d]pirimidin-4-amina

A una solución de {2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (257 mg) en

tetrahidrofurano (10 ml) se añadió ácido clorhídrico 2 N (5.0 ml) a temperatura ambiente, y la mezcla se agitó a 60°C durante 20 h. Después de concentrar a presión reducida, se añadió etanol al residuo, y la mezcla se volvió a concentrar. Se recogió el sólido precipitado por filtración y el sólido se lavó con éter diisopropílico para dar el compuesto del título (220 mg) en forma de un sólido de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.23-3.37 (2H, m), 4.95-5.08 (2H, m), 6.74 (1H, d, J= 2.7 Hz), 7.56 (1H, d, J= 8.4 Hz), 7.64-7.74 (3H, m), 8.06 (1H, br s), 8.23-8.45 (5H, m), 8.71 (1H, s), 10.15 (1H, br s).

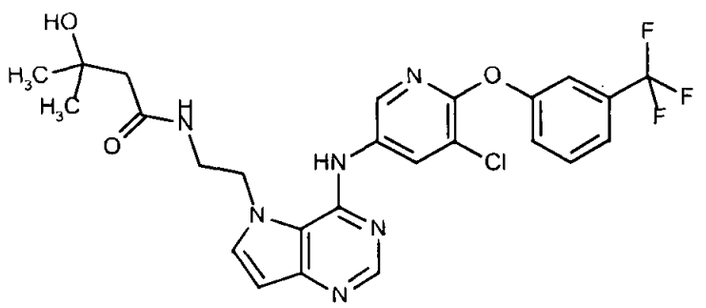
(iii) Producción de N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Una mezcla de triclorhidrato de 5-(2-aminoetil)-N-{5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (95 mg), ácido metilsulfonilacético (47 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (98 mg), 1-hidroxibenzotriazol (78 mg) y trietilamina (0.12 ml) en N,N-dimetilformamida (5.0 ml) se agitó a temperatura ambiente durante 14 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó

sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de silice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar el compuesto del título (86 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.10 (3H, s), 3.62-3.78 (2H, m), 3.98 (2H, s), 4.41-4.53 (2H, m), 6.63 (1H, d, J= 3.0 Hz), 7.21 (1H, d, J= 3.0 Hz), 7.29-7.55 (5H, m), 8.41-8.50 (4H, m).

Ejemplo B-3



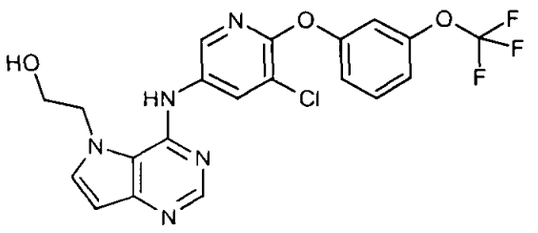
Producción de N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

Al usar triclorhidrato de 5-(2-aminoetil)-N-{5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (95 mg), ácido 3-hidroxi-3-metilbutanoico (46 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (98 mg), 1-hidroxibenzotriazol (78 mg), trietilamina (0.12 ml) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el

Ejemplo B-2(iii), se obtuvo el compuesto del título (73 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.33 (6H, s), 2.36-2.43 (1H, m), 2.48 (2H, s), 3.55-3.66 (2H, m), 4.41-4.50 (2H, m), 6.60 (1H, d, J= 3.0 Hz), 7.18-7.22 (2H, m), 7.34-7.39 (1H, m), 7.42-7.53 (3H, m), 8.44 (1H, d, J= 2.4 Hz), 8.47 (1H, s), 8.54 (1H, d, J= 2.4 Hz), 8.97 (1H, s).

Ejemplo B-4



Producción de 2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 3-cloro-5-nitro-2-[3-(trifluorometoxi)fenoxi]piridina

Bajo una atmósfera de argón, al usar 3-(trifluorometoxi)fenol (0.93 g), 2.3-dicloro-5-nitropiridina (1.0 g), hidruro de sodio (dispersión al 60% en aceite mineral, 0.23 g) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo B-1(i), se obtuvo el compuesto del título (1.57 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 7.06-7.22 (3H, m), 7.49 (1H, t, J

= 8.3 Hz), 8.59 (1H, d, J = 2.4 Hz), 8.88 (1H, d, J = 2.4 Hz).

(ii) Producción de 5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-amina

Al usar 3-cloro-5-nitro-2-[3-(trifluorometoxi)fenoxi]piridina (1.57 g), hierro reducido (1.31 g), cloruro de calcio (0.26 g) y 15% de etanol con contenido de agua (50 ml) y de la misma manera que en el Ejemplo B-1(ii), se obtuvo el compuesto del título (1.23 g) en forma de un aceite anaranjado.

^{1}H-RMN ($CDCl_3$) δ: 3.65 (2H, br s), 6.91-7.02 (3H, m), 7.18 (1H, d, J = 2.7 Hz), 7.35 (1H, t, J = 8.1 Hz), 7.59 (1H, d, J = 2.7 Hz).

(iii) Producción de 2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Una solución de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg) y 5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-amina (101 mg) en alcohol isopropílico (2.0 ml) se agitó a 80°C durante 2 días. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió solución acuosa 1 N de hidróxido de sodio (1.0 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 h, a ello se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y

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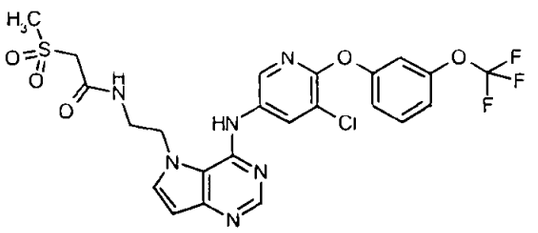
salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, acetato de etilo→acetato de etilo:metanol = 9:1) para dar el compuesto del título (112 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 4.11-4.19 (2H, m), 4.39-4.45 (2H, m), 4.83-4.99 (1H, m), 6.31 (1H, d, J = 3.3 Hz), 7.02-7.10 (4H, m), 7.36-7.42 (1H, m), 8.17 (1H, d, J = 2.7 Hz), 8.31 (1H, s), 8.34 (1H, d, J = 2.7 Hz), 9.44 (1H, s).

Ejemplo B-5



Producción de N-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de {2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (300 mg), 5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-amina (308 mg) y alcohol isopropílico (3.0 ml) y de la misma manera que en el Ejemplo

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B-2(i), se obtuvo el compuesto del título (372 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.49 (9H, s), 3.45-3.53 (2H, m), 4.43-4.49 (2H, m), 5.10 (1H, t, J = 5.4 Hz), 6.60 (1H, d, J = 3.0 Hz), 7.02-7.12 (3H, m), 7.18 (1H, d, J = 3.0 Hz), 7.36-7.42 (1H, m), 8.38 (1H, d, J = 2.4 Hz), 8.47 (1H, s), 8.65 (1H, d, J = 2.4 Hz), 8.77 (1H, br s).

(ii) Producción de triclorhidrato de 5-(2-aminoetil)-N-{5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (350 mg), ácido clorhídrico 2 N (5.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo B-2(ii), se obtuvo el compuesto del título (294 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.20-3.34 (2H, m), 4.91-5.03 (2H, m), 6.66-6.76 (1H, m), 7.20-7.32 (3H, m), 7.59 (1H, t, J = 8.1 Hz), 8.01 (1H, br s), 8.12-8.37 (5H, m), 8.68 (1H, br s), 9.94-10.06 (1H, m).

(iii) Producción de N-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

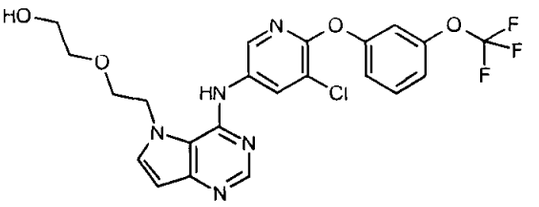
Al usar triclorhidrato de 5-(2-aminoetil)-N-{5-

763.

cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (90 mg), ácido metilsulfonilacético (43 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (90 mg), monohidrato de 1-hidroxibenzotriazol (72 mg), trietilamina (0.12 ml) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo B-2(iii), se obtuvo el compuesto del título (59 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.10 (3H, s), 3.64-3.75 (2H, m), 3.98 (2H, s), 4.43-4.53 (2H, m), 6.62 (1H, d, J = 3.0 Hz), 7.03-7.13 (3H, m), 7.15-7.23 (2H, m), 7.41 (1H, t, J = 8.4 Hz), 8.42 (1H, s), 8.44-8.47 (2H, m), 8.49 (1H, s).

Ejemplo B-6



Producción de 2-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

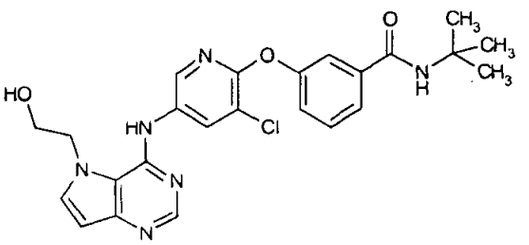
Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (100 mg), 5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-amina (80 mg), alcohol isopropílico (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo B-4(iii), se obtuvo el compuesto del título (71 mg) en forma de

764

cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.77 (1H, br s), 3.66-3.80 (4H, m), 4.01 (2H, t, J = 4.5 Hz), 4.56 (2H, t, J = 4.5 Hz), 6.64 (1H, d, J = 3.3 Hz), 7.01-7.09 (3H, m), 7.22 (1H, d, J = 3.3 Hz), 7.36-7.42 (1H, m), 8.25 (1H, d, J = 2.7 Hz), 8.47 (1H, d, J = 2.7 Hz), 8.49 (1H, s), 8.83 (1H, s).

Ejemplo B-7



Producción de N-(ter-butil)-3-[(3-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}piridin-2-il)oxi]benzamida

(i) Producción de 3-[(3-cloro-5-nitropiridin-2-il)oxi]benzoato de metilo

Al usar 3-hidroxibenzoato de metilo (0.83 g), 2.3-dicloro-5-nitropiridina (1.0 g), hidruro de sodio (dispersión al 60% en aceite mineral, 0.24 g) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo B-1(i), se obtuvo el compuesto del título (1.61 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 3.93 (3H, s), 7.37-7.41 (1H, m), 7.52-7.57 (1H, m), 7.84-7.86 (1H, m), 7.98-8.02 (1H, m), 8.58 (1H, d, J = 2.7 Hz), 8.86 (1H, d, J = 2.7 Hz).

(ii) Producción de ácido 3-[(3-cloro-5-

765.

nitropiridin-2-il)oxi]benzoico

A una solución de 3-[(3-cloro-5-nitropiridin-2-il)oxi]benzoato de metilo (1.61 g) en alcohol isopropílico (20 ml) y tetrahidrofurano (10 ml) se añadió solución acuosa 1 N de hidróxido de sodio (6.0 ml) a temperatura ambiente. Tras agitar a temperatura ambiente durante 24 h, se agregó ácido clorhídrico 1 N (6.0 ml) a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter diisopropílico para dar el compuesto del título (0.62 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 7.42-7.48 (2H, m), 7.57-7.63 (1H, m), 7.90-7.94 (1H, m), 8.06-8.08 (1H, m), 8.60-8.61 (1H, m), 8.88 (1H, d, J = 2.4 Hz).

(iii) Producción de N-(ter-butil)-3-[(3-cloro-5-nitropiridin-2-il)oxi]benzamida

A una solución de ácido 3-[(3-cloro-5-nitropiridin-2-il)oxi]benzoico (0.62 g) y N,N-dimetilformamida (0.1 ml) en tetrahidrofurano (12 ml) se añadió cloruro de tionilo (0.23 ml) a temperatura ambiente. Tras agitar a temperatura ambiente durante 2 h, la mezcla se concentró a presión reducida. Una solución del residuo en tetrahidrofurano (10

766.

ml) se añadió gota a gota a una solución de ter-butilamina (0.3 g) y trietilamina (0.89 ml) en tetrahidrofurano (5.0 ml) a 0°C. Tras agitar a temperatura ambiente durante 20 h, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 9:1→2:1) para dar el compuesto del título (0.61 g) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (9H, s), 5.93 (1H, br s), 7.28-7.32 (1H, m), 7.52 (1H, t, J = 8.0 Hz), 7.57 (1H, t, J = 2.1 Hz), 7.62-7.65 (1H, m), 8.59 (1H, d, J = 2.4 Hz), 8.87 (1H, d, J = 2.4 Hz).

(iv) Producción de 3-[(5-amino-3-cloropiridin-2-il)oxi]-N-(ter-butil)benzamida

Al usar N-(ter-butil)-3-[(3-cloro-5-nitropiridin-2-il)oxi]benzamida (570 mg), hierro reducido (0.46 g), cloruro de calcio (90 mg) y 15% de etanol con contenido de agua (17 ml) y de la misma manera que en el Ejemplo B-1(ii), se obtuvo el compuesto del título (373 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 3.63 (2H, br s), 5.91 (1H, br s), 7.15-7.19 (2H, m), 7.36-7.47 (3H, m), 7.56

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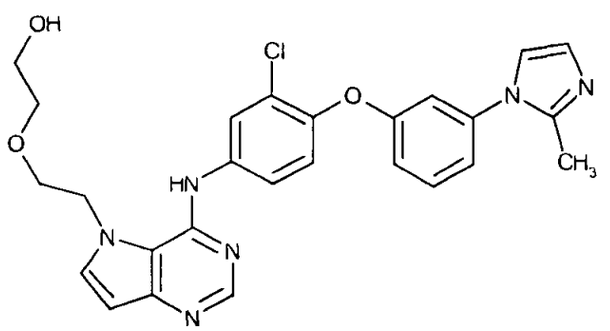
(1H, d, J = 2.7 Hz).

(v) Producción de N-(ter-butil)-3-[(3-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}piridin-2-il)oxi]benzamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (80 mg), 3-[(5-amino-3-cloropiridin-2-il)oxi]-N-(ter-butil)benzamida (85 mg), alcohol isopropílico (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo B-4(iii), se obtuvo el compuesto del título (78 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.49 (9H, s), 4.11 (2H, t, J = 4.5 Hz), 4.41 (2H, t, J = 4.5 Hz), 5.44-5.56 (1H, m), 5.98 (1H, s), 6.30 (1H, d, J = 3.0 Hz), 7.06 (1H, d, J = 3.0 Hz), 7.20-7.28 (1H, m), 7.37-7.43 (1H, m), 7.46-7.50 (2H, m), 8.09 (1H, d, J = 2.7 Hz), 8.28 (1H, s), 8.31 (1H, d, J = 2.7 Hz), 9.57 (1H, s).

Ejemplo C-1



Producción de 2-{2-[4-({3-cloro-4-[3-(2-metil-1H-imidazol-1-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

768.

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2-metil-1H-imidazol

A una solución de 3-(2-metil-1H-imidazol-1-il)fenol (1.10 g) y 3-cloro-4-fluoronitrobenceno (1.28 g) en N,N-dimetilformamida (10 ml) se añadió carbonato de potasio (1.31 g) y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió salmuera a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo dos veces, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (1.86 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.40 (3H, s), 7.00-7.25 (6H, m), 7.54 (1H, t, J = 8.2 Hz), 8.12 (1H, dd, J = 2.7, 9.0 Hz), 8.41 (1H, d, J = 2.4 Hz).

(ii) Producción de 3-cloro-4-[3-(2-metil-1H-imidazol-1-il)fenoxi]anilina

A una solución de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2-metil-1H-imidazol (1.86 g) en acetato de etilo (30 ml)/metanol (2 ml) se añadió platino-carbón activado al 5% (0.37 g) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3.5 h, el platino-carbón

activado se filtró, y el filtrado se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0) para dar el compuesto del título (1.26 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 2.34 (3H, s), 3.73 (2H, br s), 6.58 (1H, dd, J = 2.7, 8.7 Hz), 6.74 (1H, t, J = 2.1 Hz), 6.79 (1H, d, J = 2.4 Hz), 6.9-7.05 (5H, m), 7.37 (1H, t, J = 8.1 Hz).

(iii) Producción de 2-{2-[4-({3-cloro-4-[3-(2-metil-1H-imidazol-1-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (207 mg), 3-cloro-4-[3-(2-metil-1H-imidazol-1-il)fenoxi]anilina (180 mg), 1-metil-2-pirrolidona (4.0 ml) y clorhidrato de piridina (139 mg) se agitó a 120°C durante 17 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (2.6 ml) y tetrahidrofurano (5 ml) y la

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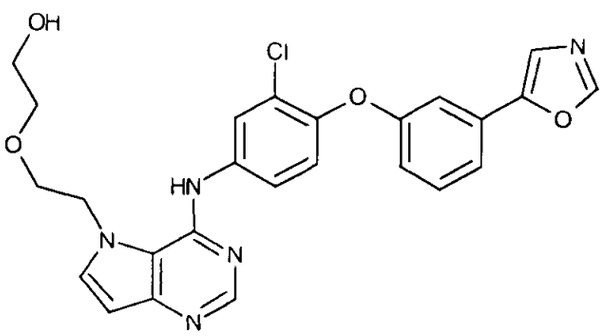
mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) y el sólido obtenido se recogió por filtración y se lavó con éter diisopropílico para dar el compuesto del título (158 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.35 (3H, s), 3.70-3.75 (2H, m), 3.75-3.85 (2H, m), 4.02 (2H, t, J = 4.4 Hz), 4.57 (2H, t, J = 4.4 Hz), 6.64 (1H, d, J = 3.0 Hz), 6.80-6.85 (1H, m), 6.95-7.05 (4H, m), 7.11 (2H, d, J = 9.0 Hz), 7.22 (1H, d, J = 3.6 Hz), 7.40 (1H, t, J = 8.4 Hz), 7.64 (1H, dd, J = 2.4, 9.0 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.53 (1H, s), 8.82 (1H, s).

Ejemplo C-2



Producción de 2-{2-[4-({3-cloro-4-[3-(1,3-oxazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 5-[3-(benciloxi)fenil]-1,3-oxazol

A una solución de 3-(benciloxi)benzaldehído (2.12 g) y p-toluensulfonilmetilisocianuro (1.95 g) en metanol (40 ml) se añadió carbonato de potasio (1.66 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 20 min y se calentó a reflujo durante 1 h. Después de concentrar a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→50:50) para dar el compuesto del título (2.04 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 5.12 (2H, s), 6.90-7.00 (1H, m), 7.25-7.50 (9H, m), 7.91 (1H, s).

(ii) Producción de 3-(1,3-oxazol-5-il)fenol

A una solución de 5-[3-(benciloxi)fenil]-1,3-oxazol (2.01 g) en metanol (10 ml)/tetrahidrofurano (10 ml) se añadió paladio-carbón activado al 10% (0.40 g) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 h. El paladio-carbón activado se filtró, y el filtrado se concentró a presión reducida. El precipitado se lavó con éter diisopropílico y hexano para dar el compuesto del título (1.25 g) en forma de cristales de color gris pálido.

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^{1}H-RMN (95%$CDCl_3$+5%DMSO-d_6) δ: 6.80-6.90 (1H, m), 7.10-7.20 (2H, m), 7.24 (1H, t, J = 8.0 Hz), 7.31 (1H, s), 7.94 (1H, s), 9.13 (1H, s).

(iii) Producción de 5-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-oxazol

A una solución de 3-(1,3-oxazol-5-il)fenol (1.20 g) y 3-cloro-4-fluoronitrobenceno (1.45 g) en N,N-dimetilformamida (10 ml) se añadió carbonato de potasio (1.54 g) y la mezcla se agitó a temperatura ambiente durante 18 h. A la mezcla de reacción se añadió salmuera bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se recristalizó en acetato de etilo/éter diisopropílico/hexano para dar el compuesto del título (2.00 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 6.96 (1H, t, J = 9.0 Hz), 7.00-7.10 (1H, m), 7.35-7.45 (2H, m), 7.45-7.60 (2H, m), 7.93 (1H, s), 8.08 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.40 (1H, d, J = 3.0 Hz).

(iv) Producción de 3-cloro-4-[3-(1,3-oxazol-5-il)fenoxi]anilina

Al usar 5-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-oxazol (1.95 g), platino-carbón activado al 5% (0.33 g) y acetato de etilo (30 ml)/metanol (5 ml) y de la misma manera

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que en el Ejemplo C-1(ii), se obtuvo el compuesto del título (1.80 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN (95%$CDCl_3$+5%DMSO-d_6) δ: 6.8-6.9 (2H, m), 6.95-7.05 (2H, m), 7.15-7.2 (2H, m), 7.3-7.4 (3H, m), 7.91 (1H, s), 8.09 (1H, s).

(v) Producción de 2-{2-[4-({3-cloro-4-[3-(1,3-oxazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (346 mg), 3-cloro-4-[3-(1,3-oxazol-5-il)fenoxi]anilina (344 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante 18 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción bajo enfriamiento con hielo y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Se añadieron solución acuosa 1 N de hidróxido de sodio (0.8 ml) y tetrahidrofurano (4.0 ml) al compuesto obtenido, y la mezcla se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y el extracto se secó sobre sulfato de magnesio anhidro. Después de concentrar a

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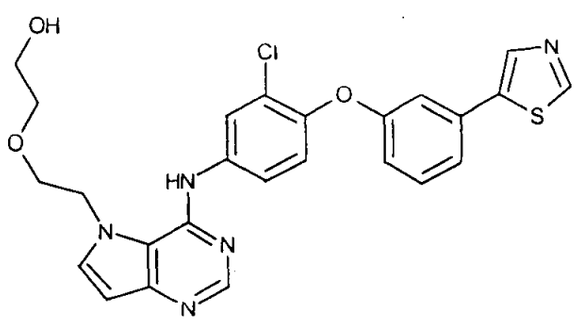
presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (26 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.70-3.75 (2H, m), 3.75-3.85 (2H, m), 4.03 (2H, t, J = 4.5 Hz), 4.58 (2H, t, J = 4.5 Hz), 6.64 (1H, d, J = 3.0 Hz), 6.90-6.95 (1H, m), 7.08 (1H, d, J = 9.0 Hz), 7.22 (1H, d, J = 3.3 Hz), 7.25-7.30 (1H, m), 7.30-7.40 (3H, m), 7.61 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.89 (2H, d, J = 2.1 Hz), 8.53 (1H, s), 8.78 (1H, s).

Ejemplo C-3



Producción de 2-{2-[4-({3-cloro-4-[3-(1,3-tiazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 5-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-tiazol

Al usar 3-(1,3-tiazol-5-il)fenol (343 mg), 3-cloro-4-fluoronitrobenceno (429 mg), carbonato de potasio (401 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo C-1(i), se obtuvo el compuesto del título (624 mg)

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en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 6.96 (1H, t, J = 9.3 Hz), 7.00-7.10 (1H, m), 7.30-7.35 (1H, m), 7.50-7.55 (2H, m), 8.07 (1H, d, J = 2.7 Hz), 8.10-8.15 (1H, m), 8.41 (1H, d, J = 2.4 Hz), 8.79 (1H, d, J = 0.6 Hz).

(ii) Producción de 2-{2-[4-({3-cloro-4-[3-(1,3-tiazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Una mezcla del compuesto obtenida usando 5-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-tiazol (624 mg), platino-carbón activado al 5% (312 mg) y acetato de etilo (10 ml) y de la misma manera que en el Ejemplo C-1(ii), benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (450 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante 20 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (2.2 ml) y tetrahidrofurano (5 ml) y la mezcla se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se añadieron bicarbonato de sodio acuoso y salmuera. La

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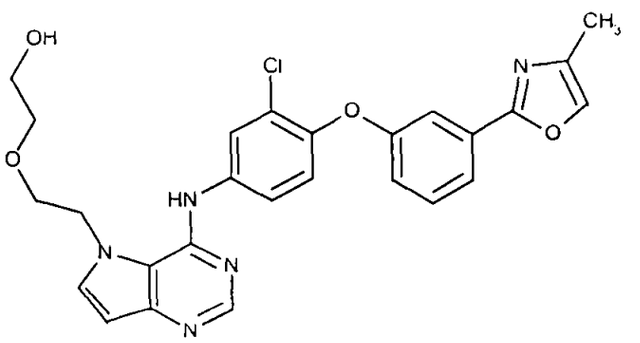
mezcla se extrajo con acetato de etilo y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) y luego se lavó con éter diisopropílico para dar el compuesto del título (63.5 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.70-3.85 (4H, m), 4.00-4.10 (2H, m), 4.50-4.60 (2H, m), 6.64 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 7.08 (1H, d, J = 8.7 Hz), 7.20-7.40 (4H, m), 7.61 (1H, dd, J = 2.4, 8.7 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.06 (1H, s), 8.53 (1H, s), 8.75 (1H, s), 8.78 (1H, s).

Ejemplo C-4



Producción de 2-{2-[4-({3-cloro-4-[3-(4-metil-1,3-oxazol-2-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 2-(3-metoxifenil)-4-metil-1,3-oxazol

Una suspensión de 3-metoxibenzamida (4.91 g) y cloroacetona (3.61 g) en tolueno (30 ml) se agitó a 110°C

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durante 2 días. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con bicarbonato de sodio acuoso y salmuera, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 10:90→30:70) para dar el compuesto del título (1.54 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.25 (3H, s), 3.88 (3H, s), 6.95-7.05 (1H, m), 7.35 (1H, t, J = 8.0 Hz), 7.40-7.45 (1H, m), 7.50-7.65 (2H, m).

(ii) Producción de 3-(4-metil-1,3-oxazol-2-il)fenol

Una solución (10 ml) de 2-(3-metoxifenil)-4-metil-1,3-oxazol (1.54 g) en ácido bromhídrico al 48% se calentó a reflujo durante 24 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con bicarbonato de sodio acuoso y salmuera, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 10:90→40:60) para dar el compuesto del título (1.14 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.24 (3H, s), 6.09 (1H, br s), 6.90-7.00 (1H, m), 7.30 (1H, t, J = 8.0 Hz), 7.40-7.45 (1H,

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m), 7.50-7.60 (2H, m).

(iii) Producción de 2-[3-(2-cloro-4-nitrofenoxi)fenil]-4-metil-1,3-oxazol

Al usar 3-(4-metil-1,3-oxazol-2-il)fenol (1.09 g), 3-cloro-4-fluoronitrobenceno (1.21 g), carbonato de potasio (1.29 g) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-1(i), se obtuvo el compuesto del título (1.86 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.38 (3H, s), 6.94 (1H, t, J = 9.2 Hz), 7.10-7.20 (1H, m), 7.40-7.45 (1H, m), 7.53 (1H, t, J = 8.0 Hz), 7.70-7.75 (1H, m), 7.85-7.95 (1H, m), 8.07 (1H, dd, J = 2.6, 9.2 Hz), 8.40 (1H, d, J = 2.6 Hz).

(iv) Producción de 3-cloro-4-[3-(4-metil-1,3-oxazol-2-il)fenoxi]anilina

Al usar 2-[3-(2-cloro-4-nitrofenoxi)fenil]-4-metil-1,3-oxazol (1.86 g), platino-carbón activado al 5% (0.31 g) y acetato de etilo (20 ml) y de la misma manera que en el Ejemplo C-1(ii), se obtuvo el compuesto del título (0.41 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 2.23 (3H, s), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 6.96 (1H, d, J = 6.9 Hz), 6.95-7.00 (1H, m), 7.36 (1H, t, J = 8.0 Hz), 7.35-7.40 (1H, m), 7.50-7.55 (1H, m), 7.70-7.75 (1H, m).

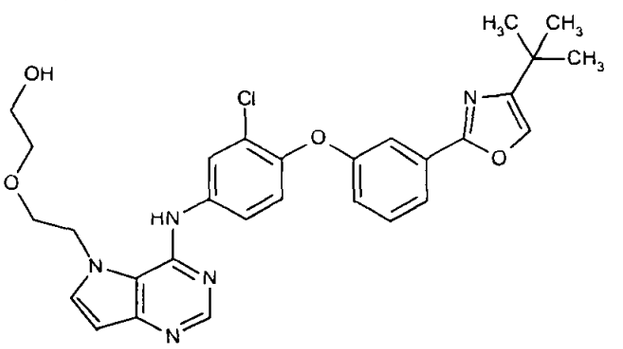
(v) Producción de 2-{2-[4-({3-cloro-4-[3-(4-metil-

1,3-oxazol-2-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (392 mg), 3-cloro-4-[3-(4-metil-1,3-oxazol-2-il)fenoxi]anilina (410 mg) y alcohol isopropílico (10 ml), la reacción se llevó a cabo de la misma manera que en el Ejemplo C-2(v). Luego, el compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-2(v) y se usó solución acuosa 1 N de hidróxido de sodio (4.7 ml) y tetrahidrofurano (10 ml) para dar el compuesto del título (371 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.21 (3H, s), 3.65-3.85 (4H, m), 4.02 (2H, t, J = 4.4 Hz), 4.57 (2H, t, J = 4.4 Hz), 6.62 (1H, d, J = 3.2 Hz), 7.05-7.15 (2H, m), 7.20 (1H, d, J = 3.0 Hz), 7.30-7.45 (2H, m), 7.50-7.55 (1H, m), 7.62 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.70-7.75 (1H, m), 7.90 (1H, d, J = 2.6 Hz), 8.52 (1H, s), 8.79 (1H, s).

Ejemplo C-5



Producción de 2-{2-[4-({4-[3-(4-ter-butil-1,3-oxazol-2-il)fenoxi]-3-clorofenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

780

(i) Producción de 4-ter-butil-2-(3-metoxifenil)-1,3-oxazol

Al usar 3-metoxibenzamida (1.51 g), 1-bromopinacolona (2.15 g) y tolueno (10 ml) y de la misma manera que en el Ejemplo C-4(i), se obtuvo el compuesto del título (2.01 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (9H, s), 3.88 (3H, s), 6.96 (1H, dd, J = 2.6 Hz, 8.4 Hz), 7.30-7.40 (2H, m), 7.55-7.65 (2H, m).

(ii) Producción de 3-(4-ter-butil-1,3-oxazol-2-il)fenol

Al usar 4-ter-butil-2-(3-metoxifenil)-1,3-oxazol (2.01 g) y ácido bromhídrico al 48% (10 ml) y de la misma manera que en el Ejemplo C-4(ii), se obtuvo el compuesto del título (0.62 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.31 (9H, s), 5.20-5.50 (1H, m), 6.90 (1H, dd, J = 1.8 Hz, 8.0 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.36 (1H, s), 7.45-7.55 (1H, m), 7.58 (1H, d, J = 7.2 Hz).

(iii) Producción de 4-ter-butil-2-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-oxazol

Al usar 3-(4-ter-butil-1,3-oxazol-2-il)fenol (1.48 g), 3-cloro-4-fluoronitrobenceno (1.26 g), carbonato de potasio (1.41 g) y N,N-dimetilformamida (12 ml) y de la misma

781

manera que en el Ejemplo C-1(i), se obtuvo el compuesto del título (2.13 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.31 (9H, s), 6.92 (1H, t, J = 9.3 Hz), 7.10-7.20 (1H, m), 7.37 (1H, s), 7.51 (1H, t, J = 8.1 Hz), 7.75-7.80 (1H, m), 7.94 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iv) Producción de 4-[3-(4-ter-butil-1,3-oxazol-2-il)fenoxi]-3-cloroanilina

Al usar 4-ter-butil-2-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-oxazol (1.12 g), platino-carbón activado al 5% (0.19 g) y acetato de etilo (20 ml)/metanol (4 ml) y de la misma manera que en el Ejemplo C-1(ii), se obtuvo el compuesto del título (985 mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.30 (9H, s), 3.68 (2H, br s), 6.58 (1H, dd, J = 2.6, 8.4 Hz), 6.80 (1H, d, J = 2.6 Hz), 6.85-6.95 (2H, m), 7.33 (2H, t, J = 8.4 Hz), 7.55-7.60 (1H, m), 7.70-7.75 (1H, m).

(v) Producción de 2-{2-[4-({4-[3-(4-ter-butil-1,3-oxazol-2-il)fenoxi]-3-clorofenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

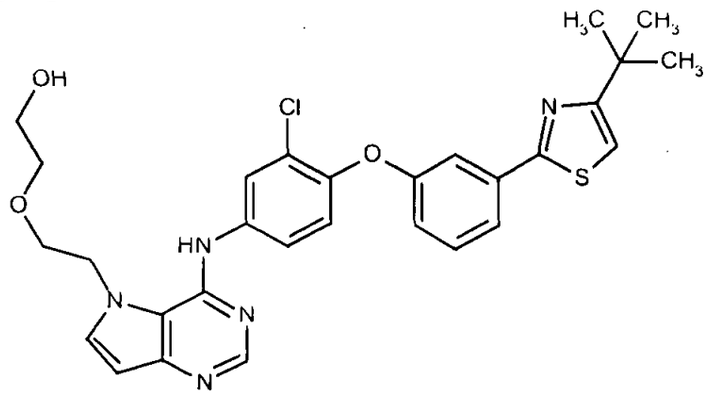
Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (444 mg), 4-[3-(4-ter-butil-1,3-oxazol-2-il)fenoxi]-3-cloroanilina (660 mg) y alcohol isopropílico (10 ml), la reacción se llevó a cabo de la misma

782

manera que en el Ejemplo C-2(v). Luego, el compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-2(v) y se usó solución acuosa 1 N de hidróxido de sodio (6.0 ml) y tetrahidrofurano (12 ml) para dar el compuesto del título (316 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.30 (9H, s), 3.70-3.80 (4H, m), 4.02 (2H, t, J = 4.2 Hz), 4.56 (2H, t, J = 4.2 Hz), 6.62 (1H, d, J = 3.3 Hz), 7.00 (1H, dd, J = 2.4 Hz, 8.4 Hz), 7.05 (1H, d, J = 8.7 Hz), 7.20 (1H, d, J = 3.3 Hz), 7.34 (1H, s), 7.37 (1H, t, J = 7.8 Hz), 7.59 (1H, dd, J = 2.4 Hz, 9.0 Hz), 7.60-7.65 (1H, m), 7.75 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.77 (1H, s).

Ejemplo C-6



Producción de 2-{2-[4-({4-[3-(4-ter-butil-1,3-tiazol-2-il)fenoxi]-3-clorofenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 3-metoxibencencarbotioamida

Una mezcla de 3-metoxibenzonitrilo (9.32 g), O,O-dietilditiofosfato (11.85 ml) y ácido clorhídrico 4 N (70 ml)

783

se agitó a temperatura ambiente durante 20 h. El precipitado se recogió por filtración, y se lavó con acetato de etilo y éter diisopropílico para dar el compuesto del título (8.51 g) en forma de un polvo verde pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.27 (2H, br s), 3.89 (3H, s), 7.10-7.20 (1H, m), 7.36 (1H, t, J = 7.8 Hz), 7.40-7.50 (1H, m), 7.50-7.60 (1H, m).

(ii) Producción de 4-ter-butil-2-(3-metoxifenil)-1,3-tiazol

Una solución de 3-metoxibencencarbotioamida (4.18 g) y 1-bromopinacolona (4.48 g) en etanol (50 ml) se agitó a temperatura ambiente durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con bicarbonato de sodio acuoso y salmuera, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 0:100→10:90) para dar el compuesto del título (4.91 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.39 (9H, s), 3.88 (3H, s), 6.88 (1H, s), 6.90-7.00 (1H, m), 7.32 (1H, t, J = 8.1 Hz), 7.50-7.60 (2H, m).

(iii) Producción de 3-(4-ter-butil-1,3-tiazol-2-il)fenol

784

Al usar 4-ter-butil-2-(3-metoxifenil)-1,3-tiazol (4.91 g) y ácido bromhídrico al 48% (30 ml) y de la misma manera que en el Ejemplo C-4(ii), se obtuvo el compuesto del título (3.59 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.40 (9H, s), 5.08 (1H, s), 6.80-6.85 (1H, m), 6.89 (1H, s), 7.28 (1H, t, J = 8.0 Hz), 7.45-7.55 (2H, m).

(iv) Producción de 4-ter-butil-2-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-tiazol

Al usar 3-(4-ter-butil-1,3-tiazol-2-il)fenol (3.13 g), 3-cloro-4-fluoronitrobenceno (2.48 g), carbonato de potasio (2.78 g) y N,N-dimetilformamida (24 ml) y de la misma manera que en el Ejemplo C-1(i), se obtuvo el compuesto del título (1.49 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.38 (9H, s), 6.93 (2H, t, J = 4.6 Hz), 7.05-7.15 (1H, m), 7.49 (1H, t, J = 8.0 Hz), 7.75-7.80 (1H, m), 7.80-7.90 (1H, m), 8.06 (1H, dd, J = 2.6, 8.8 Hz), 8.40 (1H, d, J = 2.6 Hz).

(v) Producción de 4-[3-(4-ter-butil-1,3-tiazol-2-il)fenoxi]-3-cloroanilina

Al usar 4-ter-butil-2-[3-(2-cloro-4-nitrofenoxi)fenil]-1,3-tiazol (1.49 g), platino-carbón activado al 5% (0.25 g) y acetato de etilo (10 ml) y de la misma manera que en el Ejemplo C-1(ii), se obtuvo el

785.

compuesto del título (1.37 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.38 (9H, s), 3.68 (2H, br s), 6.58 (1H, dd, J = 2.8, 8.6 Hz), 6.80-6.95 (4H, m), 7.30 (1H, t, J = 8.1 Hz), 7.55-7.65 (2H, m).

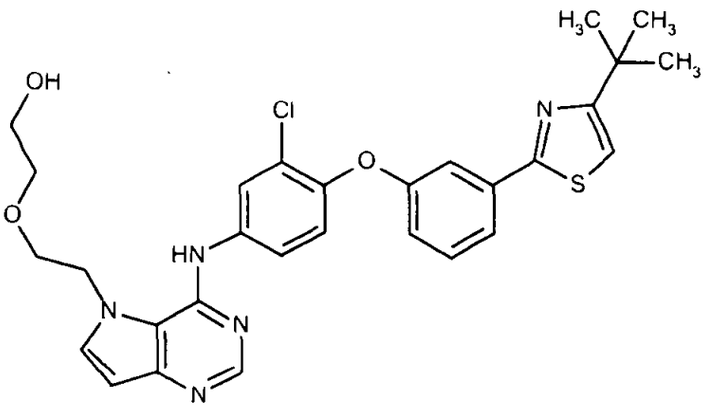
(vi) Producción de 2-{2-[4-({4-[3-(4-ter-butil-1,3-tiazol-2-il)fenoxi]-3-clorofenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (277 mg), 4-[3-(4-ter-butil-1,3-tiazol-2-il)fenoxi]-3-cloroanilina (359 mg) y alcohol isopropílico (5.0 ml), la reacción se llevó a cabo de la misma manera que en el Ejemplo C-2(v). Luego, el compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-2(v) y se usó solución acuosa 1 N de hidróxido de sodio (3.7 ml) y tetrahidrofurano (7.5 ml) para dar el compuesto del título (163 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.39 (9H, s), 3.70-3.80 (4H, m), 4.02 (2H, t, J = 4.5 Hz), 4.57 (2H, t, J = 4.5 Hz), 6.63 (1H, d, J = 3.3 Hz), 6.89 (1H, s), 6.92 (1H, d, J = 2.4 Hz), 7.05 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.34 (1H, t, J = 8.4 Hz), 7.58 (1H, dd, J = 2.4 Hz, 8.7 Hz), 7.65-7.70 (2H, m), 7.89 (1H, d, J = 2.4 Hz), 8.52 (1H, s), 8.75 (1H, s).

786.

Ejemplo C-7



Producción de 2-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol

(i) Producción de 2-(3-metoxifenil)-4-(trifluorometil)-1,3-tiazol

Al usar 3-metoxibencencarbotioamida (4.18 g), 3-bromo-1.1,1-trifluoroacetona (4.77 g) y etanol (50 ml) y de la misma manera que en el Ejemplo C-6(ii), se obtuvo el compuesto del título (4.29 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.90 (3H, s), 6.95-7.05 (1H, m), 7.37 (1H, d, J = 8.2 Hz), 7.50-7.60 (2H, m), 7.73 (1H, d, J = 1.0 Hz).

(ii) Producción de 3-[4-(trifluorometil)-1,3-tiazol-2-il]fenol

Al usar 2-(3-metoxifenil)-4-(trifluorometil)-1,3-tiazol (4.23 g) y ácido bromhídrico al 48% (30 ml) y de la misma manera que en el Ejemplo C-4(ii), se obtuvo el

787.

compuesto del título (4.61 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 5.10-5.50 (1H, m), 6.90-7.00 (1H, m), 7.33 (1H, t, J = 8.1 Hz), 7.50-7.60 (2H, m), 7.73 (1H, s).

(iii) Producción de 2-[3-(2-cloro-4-nitrofenoxi)fenil]-4-(trifluorometil)-1,3-tiazol

Al usar 3-[4-(trifluorometil)-1,3-tiazol-2-il]fenol (4.00 g), 3-cloro-4-fluoronitrobenceno (3.01 g), carbonato de potasio (3.38 g) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo C-1(i), se obtuvo el compuesto del título (4.82 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 6.96 (1H, t, J = 9.0 Hz), 7.15-7.25 (1H, m), 7.55 (1H, t, J = 8.1 Hz), 7.75-7.80 (2H, m), 7.85 (1H, t, J = 8.1 Hz), 8.09 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iv) Producción de 3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}anilina

Al usar 2-[3-(2-cloro-4-nitrofenoxi)fenil]-4-(trifluorometil)-1,3-tiazol (2.00 g), platino-carbón activado al 5% (0.33 g) y acetato de etilo (15 ml) y de la misma manera que en el Ejemplo C-1(ii), se obtuvo el compuesto del título (1.87 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 3.70 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.81 (1H, d, J = 2.7 Hz), 6.94 (2H, d, J =

8.7 Hz), 7.36 (1H, t, J = 8.1 Hz), 7.50-7.55 (1H, m), 7.63 (1H, d, J = 7.5 Hz), 7.73 (1H, s).

(v) Producción de 2-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (262 mg), 3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}anilina (338 mg) y alcohol isopropílico (5.0 ml), la reacción se llevó a cabo de la misma manera que en el Ejemplo C-2(v). Luego, el compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-2(v) y se usó solución acuosa 1 N de hidróxido de sodio (3.4 ml) y tetrahidrofurano (7 ml) para dar el compuesto del título (173 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 3.70-3.85 (4H, m), 4.02 (2H, t, J = 4.5 Hz), 4.57 (2H, t, J = 4.5 Hz), 6.63 (1H, d, J = 3.3 Hz), 7.00-7.10 (1H, m), 7.08 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.6-7.65 (2H, m), 7.67 (1H, d, J = 7.8 Hz), 7.74 (1H, s), 7.91 (1H, d, J = 2.7 Hz), 8.52 (1H, s), 8.79 (1H, s).

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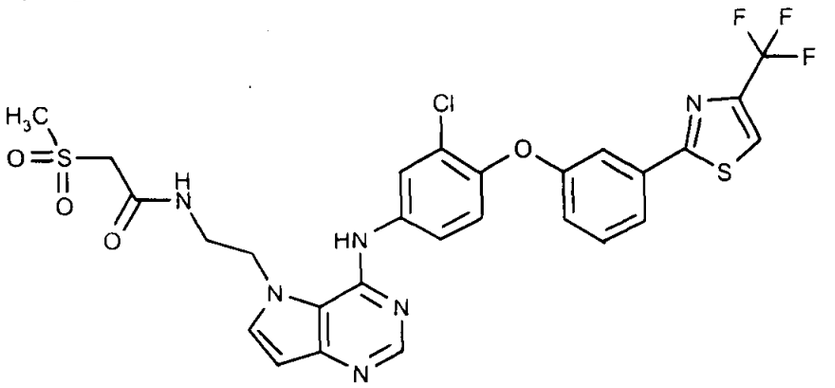
Ejemplo C-8



Producción de N-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de (2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.01 g), 3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}anilina (1.51 g) y alcohol isopropílico (10 ml) se agitó a 80°C durante 12 h. A la mezcla de reacción se añadió bicarbonato de sodio acuoso bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). El sólido obtenido se recogió por filtración, se lavó con éter

790.

diisopropílico y hexano para dar el compuesto del título (1.88 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 3.45-3.55 (2H, m), 4.45-4.55 (2H, m), 5.05-5.15 (1H, m), 6.61 (1H, d, J = 1.5 Hz), 7.00-7.10 (2H, m), 7.18 (1H, d, J = 2.1 Hz), 7.40 (1H, t, J = 8.5 Hz), 7.65 (1H, s), 7.68 (1H, d, J = 7.5 Hz), 7.74 (1H, s), 7.89 (1H, d, J = 9.0 Hz), 8.03 (1H, s), 8.51 (1H, s), 8.61 (1H, br s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de (2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo (1.70 g) y ácido clorhídrico al 10% (p/p)/metanol (12 ml) se agitó a 65°C durante 4 h. La mezcla de reacción se concentró a presión reducida, y el precipitado se recogió por filtración, y se lavó con éter dietílico para dar el compuesto del título (1.53 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.25-3.35 (2H, m), 5.00-5.10 (2H, m), 6.75 (1H, d, J = 3.3 Hz), 7.17 (1H, dd, J = 2.4, 8.1 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.5-7.7 (3H, m), 7.78 (1H, d, J = 7.8 Hz), 7.93 (1H, d, J = 2.4 Hz), 8.07 (1H, d, J = 3.0 Hz), 8.20-8.40 (3H, m), 8.61 (1H, s), 8.72 (1H, s), 10.10

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(1H, br s).

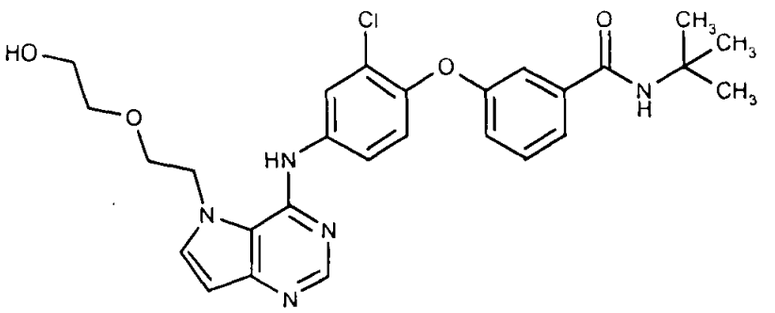
(iii) Producción de N-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

A una solución de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido metilsulfonilacético (69 mg) y 1-hidroxibenzotriazol (75 mg) en N,N-dimetilformamida (5.0 ml) se añadieron trietilamina (0.23 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (105 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 6 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (179 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.12 (3H, s), 3.65-3.75 (2H, m), 3.98 (2H, s), 4.45-4.55 (2H, m), 6.60-6.65 (1H, m), 7.08 (2H, d, J = 9.0 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.25-7.30 (2H, m), 7.42 (1H, t, J = 8.0 Hz), 7.65-7.75 (2H, m), 7.75 (1H, s),

7.95 (1H, s), 8.20 (1H, s), 8.51 (1H, s).

Ejemplo C-9



Producción de N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

(i) Producción de 3-hidroxibenzoato de difenilmetilo

A una solución de ácido 3-hidroxibenzoico (2.76 g) en acetona (40 ml) se añadió difenildiazometano (3.88 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 15:85→35:65). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (5.16 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 5.13 (1H, s), 7.03-7.08 (1H, m), 7.10 (1H, s), 7.25-7.46 (11H, m), 7.58-7.62 (1H, m), 7.70-7.76 (1H, m).

(ii) Producción de 3-(2-cloro-4-nitrofenoxi)benzoato de difenilmetilo

Una mezcla de 2-cloro-1-fluoro-4-nitrobenceno (2.81 g), 3-hidroxibenzoato de difenilmetilo (5.16 g), carbonato de potasio (3.32 g) y N,N-dimetilformamida (50 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió agua y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, éter diisopropílico se añadió al residuo obtenido, y el sólido precipitado se recogió por filtración para dar el compuesto del título (6.93 g) en forma de un polvo incoloro.

^{1}H-RMN ($CDCl_3$) δ: 6.90 (1H, d, J= 9.3 Hz), 7.12 (1H, s), 7.27-7.46 (11H, m), 7.55 (1H, t, J= 8.0 Hz), 7.82 (1H, m), 8.02-8.11 (2H, m), 8.40 (1H, d, J= 2.7 Hz).

(iii) Producción de 3-(4-amino-2-clorofenoxi)benzoato de difenilmetilo

A 3-(2-cloro-4-nitrofenoxi)benzoato de difenilmetilo (4.60 g) se añadieron acetato de etilo (80 ml) y platino-carbón activado al 5% (50 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 h. El catalizador se filtró, el filtrado se concentró y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano =

20:80→40:60), y cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 15:85→35:65). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (3.58 g) en forma de un sólido incoloro.

^{1}H-RMN ($CDCl_3$) δ: 3.69 (2H, br s), 6.57 (1H, dd, J= 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.91 (1H, d, J= 8.6 Hz), 7.04-7.10 (2H, m), 7.26-7.44 (11H, m), 7.62-7.65 (1H, m), 7.78-7.83 (1H, m).

(iv) Producción de clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (1.04 g), 3-(4-amino-2-clorofenoxi)benzoato de difenilmetilo (1.29 g) y alcohol isopropílico (20 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron ácido trifluoroacético (10 ml) y anisol

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(10 ml) y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida. Se añadió una solución de cloruro de hidrógeno 4 N/acetato de etilo al residuo, y la mezcla se concentró a presión reducida. Se añadieron acetato de etilo y acetonitrilo al residuo y el sólido precipitado se recogió por filtración para dar el compuesto del título (1.24 g) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 3.76-3.83 (2H, m), 3.91 (2H, t, J= 4.7 Hz), 4.27-4.33 (2H, m), 4.89 (2H, m), 6.60-6.64 (1H, m), 7.22 (1H, d, J= 8.8 Hz), 7.26-7.75 (10H, m), 7.91 (1H, d, J= 2.5 Hz), 8.01 (1H, d, J= 3.0 Hz), 8.64 (1H, s), 9.91 (1H, m).

(v) Producción de N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

Una mezcla de clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), ter-butilamina (0.038 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato

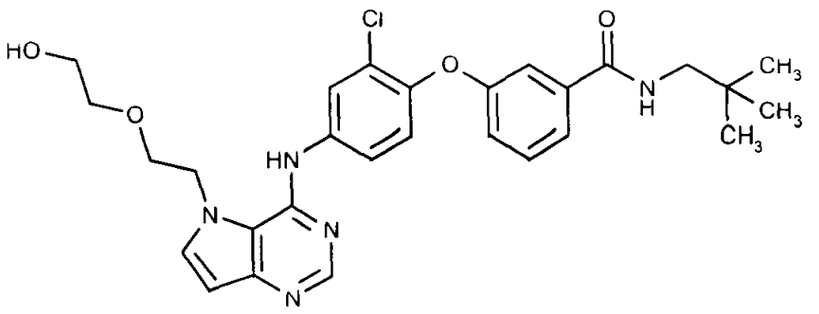
796.

de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter dietílico para dar el compuesto del título (106 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 2.36 (1H, br s), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.53-4.60 (2H, m), 5.96 (1H, br s), 6.61 (1H, d, J= 3.0 Hz), 7.03 (1H, d, J= 8.8 Hz), 7.05-7.12 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.27-7.37 (3H, m), 7.57 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.91 (1H, d, J= 2.5 Hz), 8.51 (1H, s), 8.79 (1H, br s).

797.

Ejemplo C-10



Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2,2-dimetilpropil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), neopentilamina (0.042 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (116 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 0.97 (9H, s), 2.30 (1H, br s), 3.25 (2H, d, J= 6.3 Hz), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.53-4.60 (2H, m), 6.14-6.26 (1H, m), 6.61 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 8.8 Hz), 7.06-7.12 (1H, m), 7.21 (1H, d, J= 3.3 Hz), 7.32-7.44 (3H, m), 7.57 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.90 (1H, d, J= 2.5 Hz), 8.51 (1H, s), 8.79 (1H, br s).

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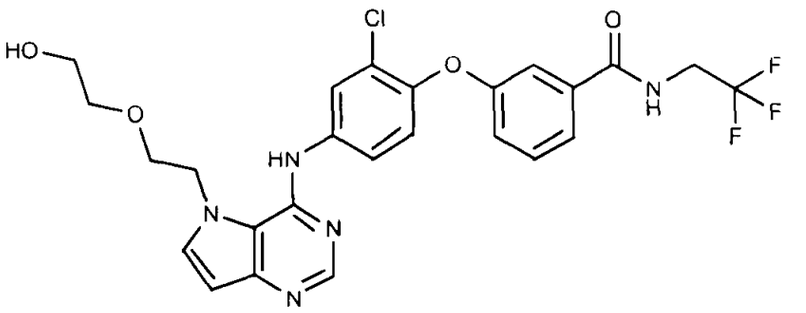
Ejemplo C-11



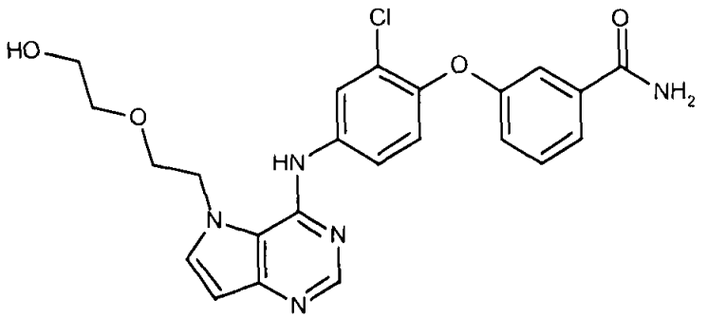
Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2,2,2-trifluoroetil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), 2,2,2-trifluoroetilamina (0.029 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (125 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 2.11 (1H, br s), 3.70-3.82 (4H, m), 3.99-4.17 (4H, m), 4.54-4.62 (2H, m), 6.61 (1H, d, J= 3.0 Hz), 6.67-6.78 (1H, m), 7.03 (1H, d, J= 8.8 Hz), 7.14-7.20 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.33 (1H, m), 7.40 (1H, t, J= 8.0 Hz), 7.46-7.51 (1H, m), 7.55 (1H, dd, J= 8.8, 2.6 Hz), 7.88 (1H, d, J= 2.6 Hz), 8.46 (1H, s), 8.78 (1H, br s).

799

Ejemplo C-12



Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

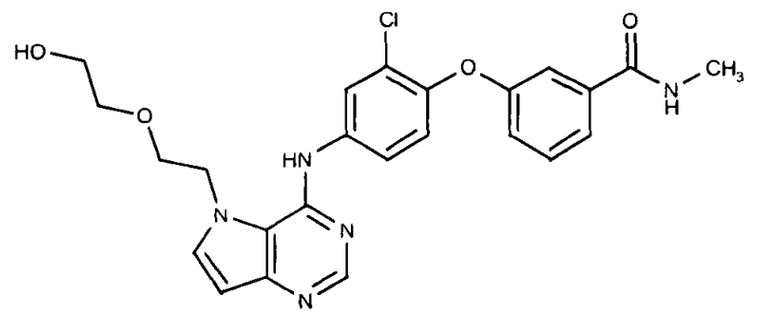
A una solución de clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg) en N,N-dimetilformamida (3 ml) se añadieron trietilamina (0.050 ml) y 1,1'-carbonilbis(1H-imidazol) (58 mg) y la mezcla se agitó a temperatura ambiente durante 0.5 h. Se añadió amoníaco 7 N/metanol (0.086 ml) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de

780.

sodio (0.6 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en etanol-acetato de etilo para dar el compuesto del título (95 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 3.49 (4H, m), 3.84 (2H, t, J= 4.4 Hz), 4.65 (2H, t, J= 4.4 Hz), 4.72 (1H, t, J= 4.4 Hz), 6.52 (1H, d, J= 2.7 Hz), 7.08-7.15 (1H, m), 7.21 (1H, d, J= 8.7 Hz), 7.36-7.50 (3H, m), 7.58-7.72 (3H, m), 7.98-8.08 (2H, m), 8.35 (1H, s), 8.97 (1H, br s).

Ejemplo C-13



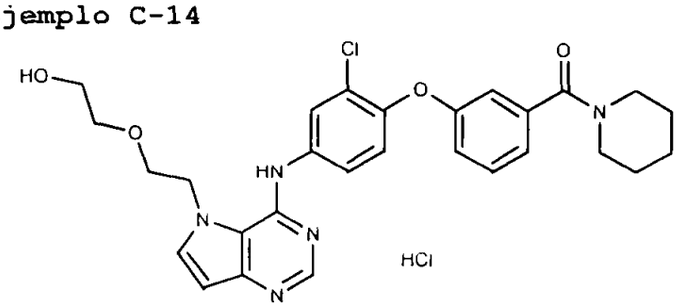
Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-metilbenzamida

781

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), N,N-dimetilformamida (3 ml), trietilamina (0.050 ml), 1,1'-carbonilbis(1H-imidazol) (58 mg), metilamina 2 M/tetrahidrofurano (0.30 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-12, se obtuvo el compuesto del título (114 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 2.76 (3H, d, J= 4.5 Hz), 3.50 (4H, m), 3.84 (2H, t, J= 4.4 Hz), 4.65 (2H, t, J= 4.4 Hz), 4.72 (1H, t, J= 4.5 Hz), 6.52 (1H, d, J= 3.0 Hz), 7.07-7.15 (1H, m), 7.20 (1H, d, J= 8.7 Hz), 7.34 (1H, m), 7.46 (1H, t, J= 7.8 Hz), 7.52-7.60 (1H, m), 7.61-7.73 (2H, m), 8.01 (1H, d, J= 2.7 Hz), 8.35 (1H, s), 8.44-8.53 (1H, m), 8.97 (1H, br s).

Ejemplo C-14



Producción de clorhidrato de 2-{2-[4-({3-cloro-4-[3-(piperidin-1-ilcarbonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

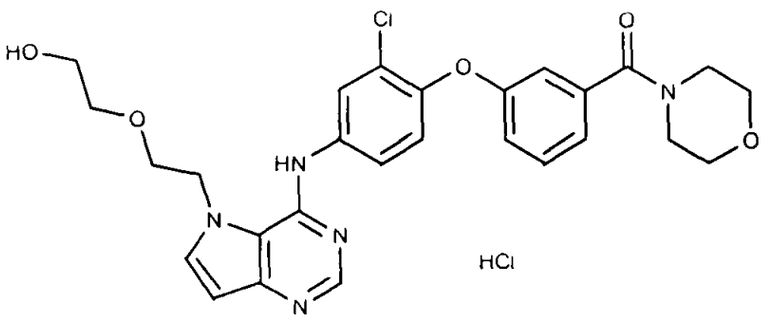
782

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), N,N-dimetilformamida (3 ml), trietilamina (0.050 ml), 1,1'-carbonilbis(1H-imidazol) (58 mg), piperidina (0.059 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-12, se obtuvo 2-{2-[4-({3-cloro-4-[3-(piperidin-1-ilcarbonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol. El compuesto se disolvió en acetato de etilo-etanol y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (126 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.34-1.68 (6H, m), 3.15-3.75 (8H, m), 3.84 (2H, t, J= 4.5 Hz), 4.81 (2H, m), 6.70 (1H, d, J= 3.0 Hz), 6.86 (1H, m), 7.04-7.10 (1H, m), 7.12 (1H, d, J= 7.7 Hz), 7.31 (1H, d, J= 8.8 Hz), 7.44-7.51 (1H, m), 7.64 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.97 (1H, d, J= 2.5 Hz), 8.02 (1H, d, J= 3.3 Hz), 8.74 (1H, s), 9.90 (1H, br s).

783.

Ejemplo C-15



Producción de clorhidrato de 2-{2-[4-({3-cloro-4-[3-(morfolin-4-ilcarbonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), morfolina (0.031 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo 2-{2-[4-({3-cloro-4-[3-(morfolin-4-ilcarbonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol. El compuesto se disolvió en acetato de etilo-etanol, y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (116 mg) en forma de cristales blancos.

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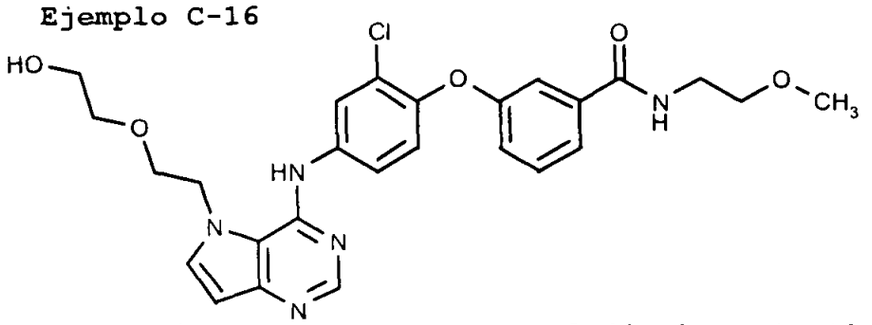
^{1}H-RMN (DMSO-d_6) δ: 3.20-3.80 (12H, m), 3.85 (2H, t, J= 4.4 Hz), 4.81 (2H, t, J= 4.4 Hz), 6.70 (1H, d, J= 3.0 Hz), 6.94 (1H, m), 7.05-7.12 (1H, m), 7.15-7.21 (1H, m), 7.30 (1H, d, J= 8.8 Hz), 7.45-7.53 (1H, m), 7.64 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.97 (1H, d, J= 2.5 Hz), 8.02 (1H, d, J= 3.3 Hz), 8.74 (1H, s), 9.90 (1H, br s).

Ejemplo C-16



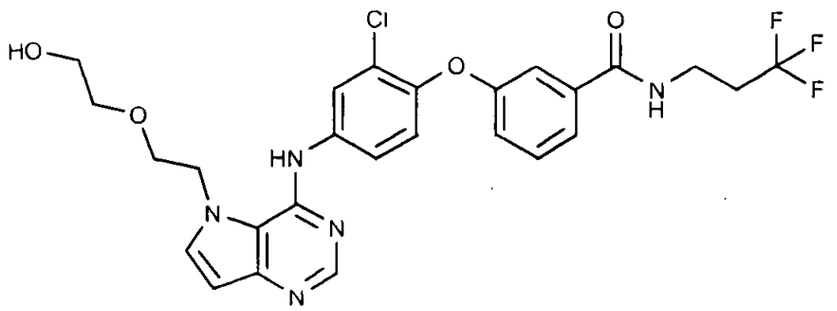
Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2-metoxietil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), 2-metoxietilamina (0.031 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (134 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 2.07-2.31 (1H, m), 3.38 (3H, s),

3.51-3.66 (4H, m), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.54-4.60 (2H, m), 6.51-6.59 (1H, m), 6.62 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 8.8 Hz), 7.08-7.13 (1H, m), 7.21 (1H, d, J= 3.3 Hz), 7.31-7.46 (3H, m), 7.58 (1H, dd, J= 8.8, 2.8 Hz), 7.90 (1H, d, J= 2.8 Hz), 8.51 (1H, s), 8.78 (1H, br s).

Ejemplo C-17



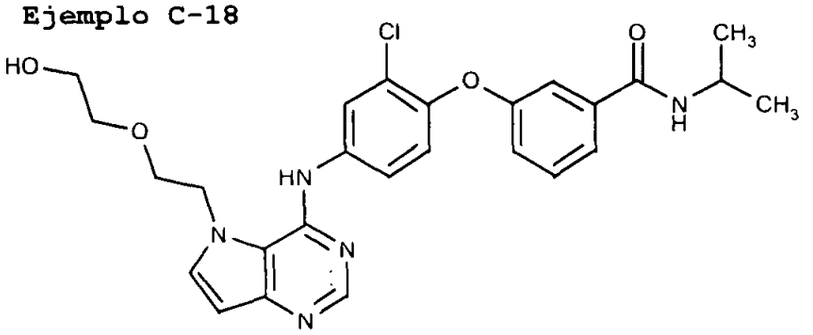
Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(3,3,3-trifluoropropil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), clorhidrato de 3,3,3-trifluoropropilamina (53 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.092 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (150 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 2.08 (1H, br s), 2.37-2.54 (2H,

m), 3.64-3.83 (6H, m), 3.99-4.06 (2H, m), 4.55-4.61 (2H, m), 6.48-6.58 (1H, m), 6.62 (1H, d, J= 3.2 Hz), 7.04 (1H, d, J= 9.0 Hz), 7.11-7.17 (1H, m), 7.22 (1H, d, J= 3.2 Hz), 7.27 (1H, m), 7.34-7.45 (2H, m), 7.57 (1H, dd, J= 2.5 Hz, 9.0 Hz), 7.89 (1H, d, J= 2.5 Hz), 8.50 (1H, s), 8.78 (1H, br s).

Ejemplo C-18



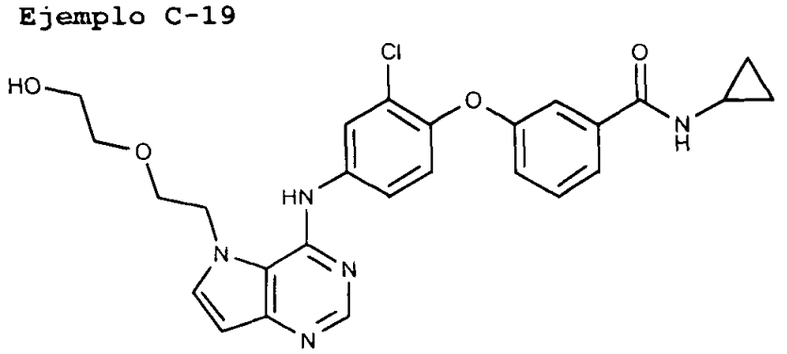
Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-isopropilbenzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), isopropilamina (0.031 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (125 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.25 (6H, d, J= 6.6 Hz), 2.13-2.37

(1H, m), 3.69-3.81 (4H, m), 3.99-4.05 (2H, m), 4.18-4.31 (1H, m), 4.53-4.60 (2H, m), 5.92-6.02 (1H, m), 6.62 (1H, d, J= 3.0 Hz), 7.03 (1H, d, J=8.8 Hz), 7.06-7.12 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.30-7.42 (3H, m), 7.56 (1H, dd, J= 2.8 Hz, 8.8 Hz), 7.90 (1H, d, J= 2.8 Hz), 8.50 (1H, s), 8.78 (1H, br s).

Ejemplo C-19



Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-ciclopropilbenzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), ciclopropilamina (0.025 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (118 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 0.52-0.73 (4H, m), 2.76-2.87

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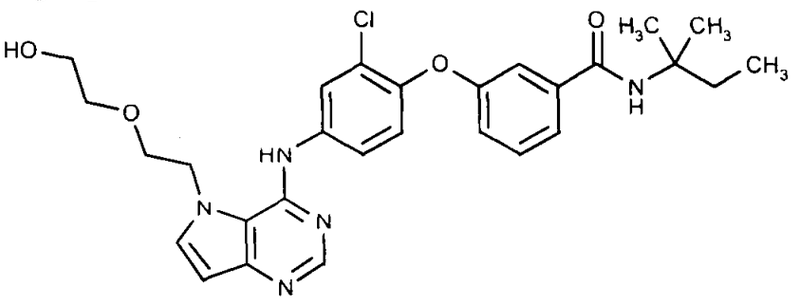
(1H, m), 3.49 (4H, m), 3.84 (2H, t, J= 4.6 Hz), 4.65 (2H, t, J= 4.6 Hz), 4.72 (1H, t, J= 4.6 Hz), 6.52 (1H, d, J= 3.2 Hz), 7.06-7.12 (1H, m), 7.19 (1H, d, J=8.9 Hz), 7.35 (1H, m), 7.44 (1H, t, J= 7.8 Hz), 7.52-7.58 (1H, m), 7.64 (1H, dd, J= 8.9, 2.5 Hz), 7.69 (1H, d, J= 3.2 Hz), 8.00 (1H, d, J= 2.5 Hz), 8.34 (1H, s), 8.49 (1H, d, J= 4.1 Hz), 8.97 (1H, br s).

Ejemplo C-20



Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(1,1-dimetilpropil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), ter-amilamina (0.042 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (135 mg) en forma de cristales blancos.

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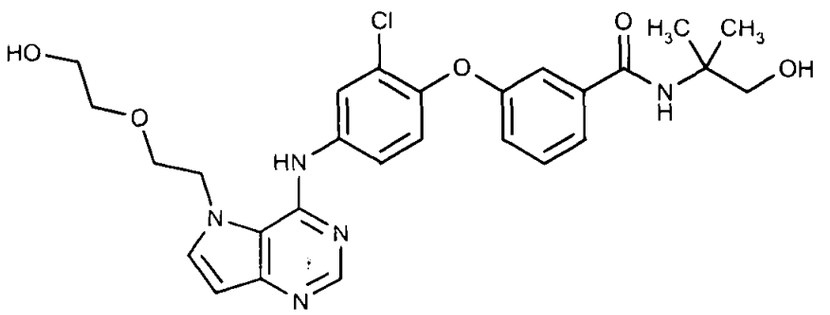
^{1}H-RMN ($CDCl_3$) δ: 0.90 (3H, t, J= 7.5 Hz), 1.40 (6H, s), 1.83 (2H, q, J= 7.5 Hz), 3.70-3.80 (4H, m), 3.99-4.05 (2H, m), 4.54-4.60 (2H, m), 5.84 (1H, br s), 6.63 (1H, d, J= 3.2 Hz), 7.02-7.12 (2H, m), 7.21 (1H, d, J= 3.2 Hz), 7.28-7.39 (3H, m), 7.58 (1H, dd, J= 8.8, 2.7 Hz), 7.91 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.79 (1H, br s).

Ejemplo C-21



Producción de 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2-hidroxi-1,1-dimetiletil)benzamida

Al usar clorhidrato de ácido 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (183 mg), 2-amino-2-metil-1-propanol (0.034 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (69 mg), 1-hidroxibenzotriazol (55 mg), trietilamina (0.050 ml), N,N-dimetilformamida (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y de la misma manera que en el Ejemplo C-9(v), se obtuvo el compuesto del título (106 mg) en forma de cristales blancos.

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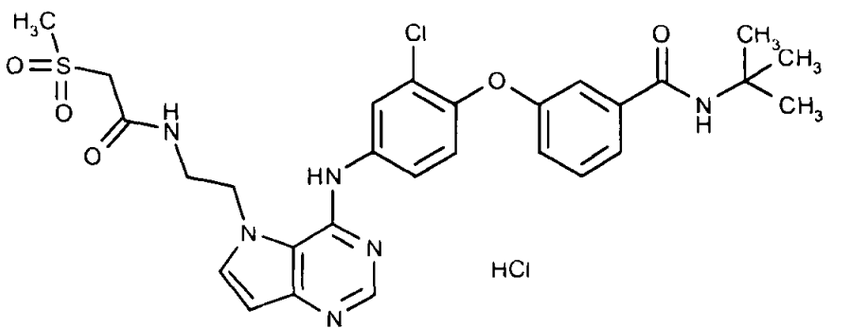
^{1}H-RMN ($CDCl_3$) δ: 1.40 (6H, s), 3.67 (2H, s), 3.69-3.81 (4H, m), 3.98-4.05 (2H, m), 4.54-4.60 (2H, m), 6.23 (1H, br s), 6.62 (1H, d, J= 3.0 Hz), 7.04 (1H, d, J= 8.8 Hz), 7.08-7.15 (1H, m), 7.21 (1H, d, J= 3.0 Hz), 7.28 (1H, m), 7.32-7.40 (2H, m), 7.57 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.90 (1H, d, J= 2.5 Hz), 8.49 (1H, s), 8.80 (1H, br s).

Ejemplo C-22



Producción de clorhidrato de N-(ter-butil)-3-(2-cloro-4-{[5-(2-{[(metilsulfonil)acetil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

(i) Producción de 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoato de metilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (2.08 g), 3-(4-amino-2-clorofenoxi)benzoato de metilo (1.94 g) y alcohol isopropílico (20 ml) se agitó a 80°C durante la noche. A la mezcla de reacción se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y

se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Se añadieron acetato de etilo y éter diisopropílico al residuo, y el sólido precipitado se recogió por filtración para dar el compuesto del título (3.26 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 3.44-3.54 (2H, m), 3.90 (3H, s), 4.43-4.53 (2H, m), 5.12 (1H, t, J= 5.6 Hz), 6.60 (1H, d, J= 3.2 Hz), 7.05 (1H, d, J= 8.9 Hz), 7.16-7.22 (2H, m), 7.39 (1H, t, J= 8.0 Hz), 7.63 (1H, m), 7.74-7.78 (1H, m), 7.89 (1H, dd, J= 2.7 Hz, 8.9 Hz), 8.03 (1H, d, J= 2.7 Hz), 8.52 (1H, s), 8.61 (1H, br s).

(ii) Producción de ácido 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico

A 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoato de metilo (2.96 g) se añadieron metanol (50 ml), tetrahidrofurano (10 ml) y solución acuosa 1 N de hidróxido de sodio (11 ml) y la mezcla se agitó a 60°C durante la noche. Después de concentrar a presión reducida, se añadieron agua y ácido acético (0.63 ml), y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera

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saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en metanol-acetonitrilo-éter dietílico para dar el compuesto del título (2.58 g) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.32 (9H, s), 3.22-3.32 (2H, m), 4.51 (2H, t, J= 6.2 Hz), 6.49 (1H, d, J= 3.0 Hz), 7.10-7.20 (1H, m), 7.24-7.34 (3H, m), 7.52 (1H, t, J= 8.0 Hz), 7.61 (1H, m), 7.67 (1H, d, J= 7.7 Hz), 7.75-7.84 (1H, m), 7.97 (1H, m), 8.33 (1H, s), 8.66 (1H, br s).

(iii) Producción de diclorhidrato de 3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-(ter-butil)benzamida

Una mezcla de ácido 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}benzoico (524 mg), ter-butilamina (0.126 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (230 mg), 1-hidroxibenzotriazol (184 mg) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice

(eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron etanol (2 ml) y solución de cloruro de hidrógeno 4 N/acetato de etilo (2 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió acetato de etilo a la mezcla de reacción, y el sólido precipitado se recogió por filtración para dar el compuesto del título (427 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 3.23-3.37 (2H, m), 4.96-5.06 (2H, m), 6.74 (1H, d, J= 3.3 Hz), 7.17 (1H, dd, J= 2.6 Hz, 8.1 Hz), 7.25 (1H, d, J= 8.8 Hz), 7.35 (1H, m), 7.47 (1H, t, J= 7.8 Hz), 7.58-7.66 (2H, m), 7.85 (1H, s), 7.90 (1H, m), 8.05 (1H, m), 8.27 (3H, br s), 8.74 (1H, s), 10.04 (1H, br s).

(iv) Producción de clorhidrato de N-(ter-butil)-3-(2-cloro-4-{[5-(2-{[(metilsulfonil)acetil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

Una mezcla de diclorhidrato de 3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-(ter-butil)benzamida (166 mg), ácido metilsulfonilacético (62 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y

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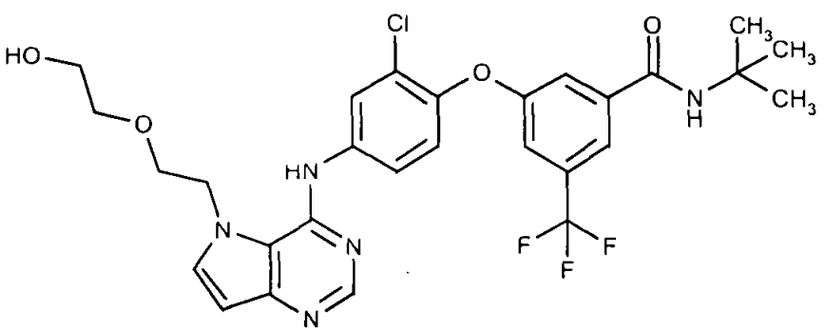
la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (121 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 3.06 (3H, s), 3.50-3.61 (2H, m), 4.07 (2H, s), 4.67-4.77 (2H, m), 6.67 (1H, d, J= 3.1 Hz), 7.13-7.20 (1H, m), 7.25 (1H, d, J= 8.9 Hz), 7.37 (1H, m), 7.47 (1H, t, J= 8.0 Hz), 7.60-7.69 (2H, m), 7.85 (1H, s), 7.93 (1H, d, J= 2.5 Hz), 7.96 (1H, d, J= 3.1 Hz), 8.74 (1H, s), 8.78-8.87 (1H, m), 9.99 (1H, br s).

Ejemplo C-23



Producción de N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-5-(trifluorometil)benzamida

(i) Producción de 3-hidroxi-5-(trifluorometil)benzoato de metilo

Se disolvió ácido 3-amino-5-(trifluorometil)benzoico (2.80 g) en ácido sulfúrico concentrado (50 g) y agua (50 ml) y la mezcla se enfrió hasta -10°C. Se agregó agua (120 ml), y se añadió gota a gota una solución acuosa (20 ml) de nitrito de sodio (0.942 g). Se agregó agua (10 ml), y la mezcla se agitó a -10°C durante 10 min y a 0°C durante 30 min. La mezcla se siguió agitando con calentamiento a reflujo durante 1 h. Después de dejar enfriar, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se disolvió en metanol (30 ml). Se añadió ácido clorhídrico concentrado (0.9 ml) y la mezcla se agitó con calentamiento a reflujo durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió solución acuosa de carbonato ácido de sodio al residuo, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y

el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 10:90→30:70). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (1.86 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.95 (3H, s), 5.49 (1H, s), 7.29 (1H, m), 7.70 (1H, m), 7.87 (1H, m).

(ii) Producción de 3-(4-amino-2-clorofenoxi)-5-(trifluorometil)benzoato de metilo

Una mezcla de 2-cloro-1-fluoro-4-nitrobenceno (1.48 g), 3-hidroxi-5-(trifluorometil)benzoato de metilo (1.86 g), carbonato de potasio (1.75 g) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 5:95→15:85). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron acetato de etilo (30 ml) y platino-carbón activado al 5% (90 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 4 h. El catalizador se filtró, y el filtrado se concentró y el residuo obtenido se sometió a cromatografía en

columna de gel de sílice (eluyente, acetato de etilo:hexano = 15:85→35:65). Las fracciones objeto se concentraron a presión reducida. Se añadió hexano al residuo, y el sólido precipitado se recogió por filtración para dar el compuesto del título (2.50 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 3.76 (2H, br s), 3.92 (3H, s), 6.61 (1H, dd, J= 8.6, 2.7 Hz), 6.81 (1H, d, J= 2.7 Hz), 6.94 (1H, d, J= 8.6 Hz), 7.31 (1H, m), 7.64 (1H, m), 7.95 (1H, m).

(iii) Producción de 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoato de metilo

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (346 mg), 3-(4-amino-2-clorofenoxi)-5-(trifluorometil)benzoato de metilo (346 mg) y alcohol isopropílico (5 ml) se agitó a 80°C durante 5 h. Se añadió benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (69 mg), y la mezcla luego se agitó a 80°C durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió solución acuosa de carbonato ácido de sodio, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se

concentraron a presión reducida para dar el compuesto del título (609 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 3.93 (3H, s), 3.95-4.00 (2H, m), 4.06-4.12 (2H, m), 4.47-4.53 (2H, m), 4.56-4.63 (2H, m), 6.64 (1H, d, J= 3.3 Hz), 6.83 (1H, d, J= 8.8 Hz), 7.24 (1H, d, J= 3.3 Hz), 7.29-7.43 (4H, m), 7.45-7.52 (1H, m), 7.69 (1H, m), 7.77-7.83 (2H, m), 7.92 (1H, d, J= 2.5 Hz), 8.00 (1H, m), 8.52 (1H, s), 8.83 (1H, br s).

(iv) Producción de ácido 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-5-(trifluorometil)benzoico

A 3-{4-[(5-{2-[2-(benzoiloxi)etoxi]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoato de metilo (609 mg) se añadieron metanol (12 ml) y solución acuosa 1 N de hidróxido de sodio (3 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se agregaron agua y ácido clorhídrico 1 N (3 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, se añadió etanol-acetonitrilo-éter dietílico al residuo obtenido, y el sólido precipitado se recogió por filtración para dar el compuesto del título (416 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 3.50 (4H, m), 3.85 (2H, t, J=

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4.4 Hz), 4.56-4.88 (1H, m), 4.68 (2H, t, J= 4.4 Hz), 6.54 (1H, d, J= 3.0 Hz), 7.38 (1H, d, J= 8.7 Hz), 7.52 (1H, m), 7.59-7.80 (3H, m), 7.90 (1H, m), 8.05 (1H, m), 8.40 (1H, s), 9.11 (1H, br s).

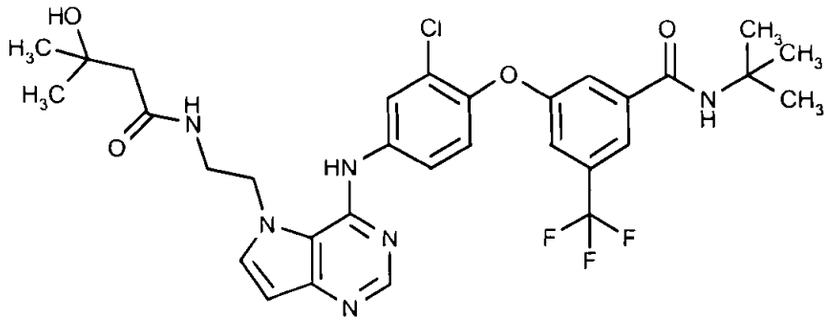
(v) Producción de N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-5-(trifluorometil)benzamida

Una mezcla de ácido 3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-5-(trifluorometil)benzoico (322 mg), ter-butilamina (0.126 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (138 mg), 1-hidroxibenzotriazol (153 mg) y N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter dietílico para dar el compuesto del título (247 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 3.70-4.82 (4H, m), 4.02 (2H, t, J= 4.4 Hz), 4.57 (2H, t, J= 4.4 Hz), 6.00 (1H,

br s), 6.61 (1H, d, J= 3.2 Hz), 7.06 (1H, d, J= 8.8 Hz), 7.21 (1H, d, J= 3.2 Hz), 7.29 (1H, m), 7.44 (1H, m), 7.57 (1H, m), 7.62 (1H, dd, J= 2.8 Hz, 8.8 Hz), 7.93 (1H, d, J= 2.8 Hz), 8.51 (1H, s), 8.87 (1H, br s).

Ejemplo C-24



Producción de N-(ter-butil)-3-{2-cloro-4-[(5-{2-[(3-hidroxi-3-metilbutanoil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}-5-(trifluorometil)benzamida

(i) Producción de 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoato de metilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.48 g), 3-(4-amino-2-clorofenoxi)-5-(trifluorometil)benzoato de metilo (1.73 g) y alcohol isopropílico (20 ml) se agitó a 80°C durante 5 h. Se agregó [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (0.30 g) y la mezcla luego se agitó a 80°C durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió solución acuosa de carbonato ácido de sodio y la mezcla se extrajo con

acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron acetona y éter diisopropílico, y el sólido precipitado se recogió por filtración para dar el compuesto del título (2.06 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 3.45-3.55 (2H, m), 3.93 (3H, s), 4.44-4.54 (2H, m), 5.10-5.18 (1H, m), 6.61 (1H, d, J= 3.2 Hz), 7.11 (1H, d, J= 8.9 Hz), 7.20 (1H, d, J= 3.2 Hz), 7.39 (1H, m), 7.77 (1H, m), 7.96 (1H, dd, J= 8.9, 2.5 Hz), 8.00 (1H, s), 8.07 (1H, d, J= 2.5 Hz), 8.53 (1H, s), 8.67 (1H, br s).

(ii) Producción de ácido 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoico

A 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoato de metilo (2.42 g) se añadieron metanol (10 ml), tetrahidrofurano (10 ml) y solución acuosa 1 N de hidróxido de sodio (8 ml) y la mezcla se agitó a temperatura ambiente durante la noche. A la mezcla de reacción se añadieron agua y ácido clorhídrico 1 N (8 ml), y

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la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en metanol-éter dietílico para dar el compuesto del título (2.03 g) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.32 (9H, s), 3.20-3.36 (2H, m), 4.53 (2H, t, J= 6.4 Hz), 6.51 (1H, d, J= 3.0 Hz), 7.10-7.23 (1H, m), 7.39 (1H, d, J= 8.7 Hz), 7.54 (1H, m), 7.63 (2H, m), 7.80-7.90 (1H, m), 7.90 (1H, m), 8.02 (1H, m), 8.35 (1H, s), 8.73 (1H, br s).

(iii) Producción de diclorhidrato de 3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-(ter-butil)-5-(trifluorometil)benzamida

Una mezcla de ácido 3-{4-[(5-{2-[(ter-butoxicarbonil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-2-clorofenoxi}-5-(trifluorometil)benzoico (888 mg), ter-butilamina (0.189 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (345 mg), 1-hidroxibenzotriazol (276 mg) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el

residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 70:30→100:0→metanol:acetato de etilo = 10:90). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron etanol (1 ml) y solución de cloruro de hidrógeno 4 N/acetato de etilo (5 ml) y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, se añadieron etanol y éter dietílico, y el sólido precipitado se recogió por filtración para dar el compuesto del título (815 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.37 (9H, s), 3.23-3.38 (2H, m), 5.06 (2H, m), 6.76 (1H, d, J= 3.0 Hz), 7.37-7.44 (1H, m), 7.52 (1H, m), 7.59 (1H, m), 7.66-7.75 (1H, m), 7.94-8.55 (7H, m), 8.76 (1H, s), 9.95-10.04 (1H, m).

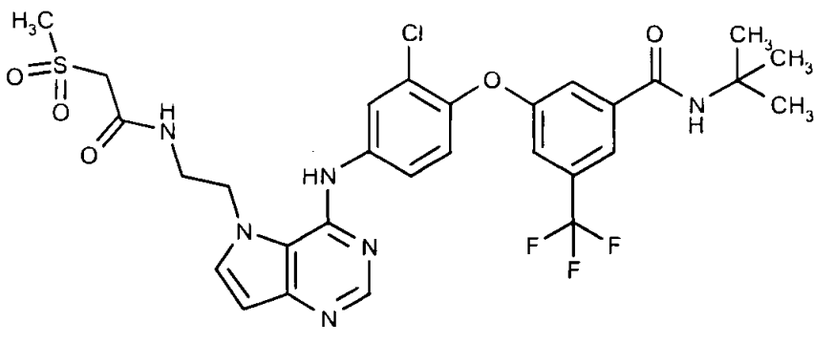
(iv) Producción de N-(ter-butil)-3-{2-cloro-4-[(5-{2-[(3-hidroxi-3-metilbutanoil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}-5-(trifluorometil)benzamida

Una mezcla de diclorhidrato de 3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-(ter-butil)-5-(trifluorometil)benzamida (186 mg), ácido 3-hidroxi-3-metilbutanoico (53 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente

durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (152 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.31 (6H, s), 1.48 (9H, s), 2.48 (2H, s), 3.54-3.66 (2H, m), 4.41-4.53 (2H, m), 6.01 (1H, br s), 6.57 (1H, d, J= 3.3 Hz), 7.07 (1H, d, J= 9.0 Hz), 7.18 (1H, d, J= 3.3 Hz), 7.25-7.35 (2H, m), 7.48 (1H, m), 7.62 (1H, m), 7.78 (1H, dd, J= 2.4 Hz, 9.0 Hz), 8.10 (1H, d, J= 2.4 Hz), 8.49 (1H, s), 8.72 (1H, br s).

Ejemplo C-25



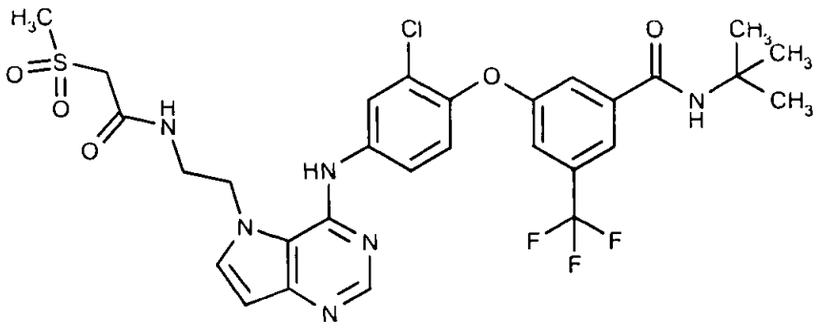
Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-{[(metilsulfonil)acetil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-5-(trifluorometil)benzamida

Una mezcla de diclorhidrato de 3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-(ter-butil)-5-(trifluorometil)benzamida (186 mg), ácido metilsulfonilacético (62 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85) y cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (146 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 3.14 (3H, s), 3.60-3.74 (2H, m), 4.00 (2H, s), 4.40-4.54 (2H, m), 6.06 (1H, br s), 6.58 (1H, d, J= 3.0 Hz), 7.08 (1H, d, J= 8.8 Hz), 7.21

(1H, d, J= 3.0 Hz), 7.35 (1H, m), 7.46 (1H, m), 7.58 (1H, m), 7.78 (1H, dd, J= 2.3 Hz, 8.8 Hz), 7.87-7.96 (1H, m), 7.97 (1H, d, J= 2.3 Hz), 8.29 (1H, br s), 9.46 (1H, s).

Ejemplo C-26



Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

(i) Producción de ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico

Una mezclà de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (1.51 g), 3-(4-amino-2-clorofenoxi)benzoato de metilo (1.39 g) y alcohol isopropílico (20 ml) se agitó a 80°C durante la noche. Se añadió solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato

867.

de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (30 ml) y solución acuosa 1 N de hidróxido de sodio (13.5 ml) y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se concentró a presión reducida, se añadieron agua y ácido clorhídrico 1 N (13.5 ml), y la mezcla se extrajo con acetato de etilo-tetrahidrofurano. El extracto se lavó con agua y el solvente se evaporó a presión reducida. El residuo se cristalizó en acetonitrilo-éter dietílico para dar el compuesto del título (1.88 g) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 3.88 (2H, m), 4.50-4.60 (2H, m), 6.31 (1H, br s), 6.52 (1H, d, J= 3.0 Hz), 7.23-7.34 (3H, m), 7.51 (1H, t, J= 8.0 Hz), 7.59-7.71 (3H, m), 7.99 (1H, d, J= 2.7 Hz), 8.35 (1H, s), 9.90 (1H, br s).

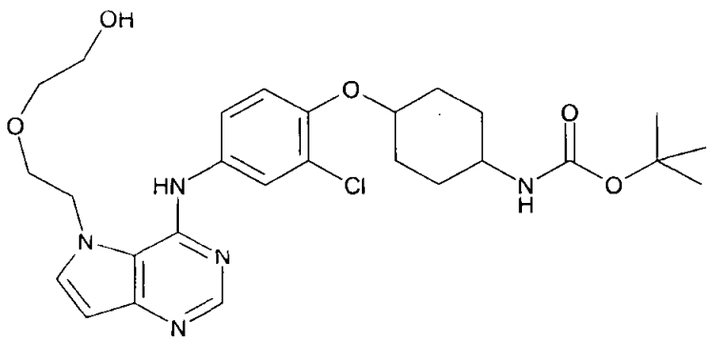
(ii) Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

Una mezcla de ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (850 mg), ter-butilamina (0.420 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (466 mg), 1-hidroxibenzotriazol (368 mg) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a

presión reducida, se añadió agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80) y cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (630 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 1.66 (1H, br s), 4.08-4.16 (2H, m), 4.35-4.42 (2H, m), 5.99 (1H, br s), 6.16 (1H, d, J= 3.3 Hz), 6.98-7.03 (2H, m), 7.04-7.12 (1H, m), 7.30-7.37 (3H, m), 7.41 (1H, dd, J= 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J= 2.6 Hz), 8.23 (1H, s), 9.68 (1H, br s).

Ejemplo C-27



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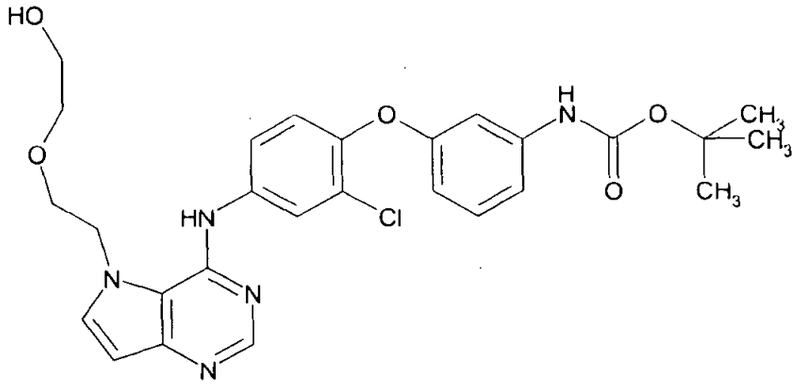
Producción de {4-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]ciclohexil}carbamato de ter-butilo

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (300 mg), [4-(4-amino-2-clorofenoxi)ciclohexil]carbamato de ter-butilo (384 mg) y alcohol isopropílico (7.0 ml) se agitó a 80°C durante la noche. La mezcla de reacción se concentró a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20). Las fracciones objeto se concentraron a presión reducida. El producto crudo se disolvió en metanol (5.0 ml) y tetrahidrofurano (1.0 ml), se añadió solución acuosa 1 N de hidróxido de sodio (2.5 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones

objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo/hexano para dar el compuesto del título (163 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.20-1.52 (4H, m), 1.38 (9H, s), 1.82-2.14 (4H, m), 3.25-3.32 (4H, m), 3.81 (2H, t, J= 4.9 Hz), 4.15-4.29 (1H, m), 4.60-4.72 (3H, m), 6.48 (1H, d, J= 3 Hz), 6.80-6.83 (1H, m), 7.17 (1H, d, J= 9 Hz), 7.46-7.49 (1H, m), 7.63 (1H, d, J= 3 Hz), 7.77 (1H, d, J= 3 Hz), 8.26 (1H, s), 8.68 (1H, br s).

Ejemplo C-28



Producción de {3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}carbamato de ter-butilo

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (165 mg), [3-(4-amino-2-clorofenoxi)fenil]carbamato de ter-butilo (200 mg), alcohol isopropílico (7.0 ml), metanol (5.0 ml), tetrahidrofurano (1.0 ml) y solución acuosa 1 N de hidróxido de sodio (2.5 ml) y de la misma manera que en el Ejemplo C-27, se obtuvo el compuesto del título (90 mg) en forma de cristales.

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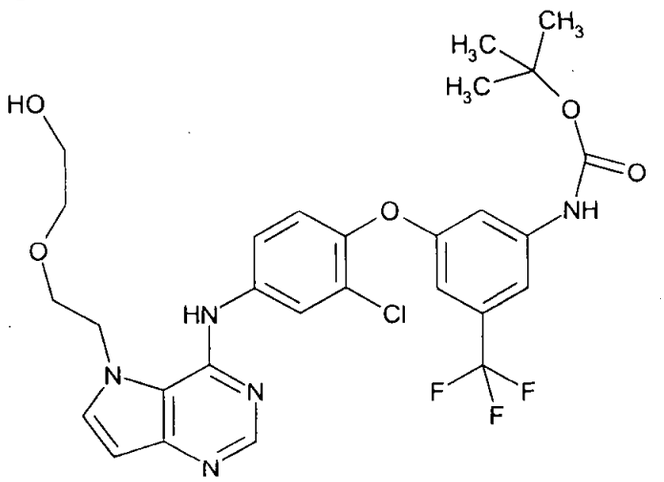
^{1}H-RMN (DMSO-d_6) δ: 1.45 (9H, s), 3.49 (4H, s), 3.83 (2H, t, J= 4.7 Hz), 4.63-4.72 (3H, m), 6.51 (2H, d, J= 3 Hz), 7.12-7.24 (4H, m), 7.63-7.69 (2H, m), 7.99 (1H, s), 8.34 (1H, s), 8.93 (1H, s), 9.43 (1H, s).

Ejemplo C-29



Producción de [3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-5-(trifluorometil)fenil]carbamato de ter-butilo

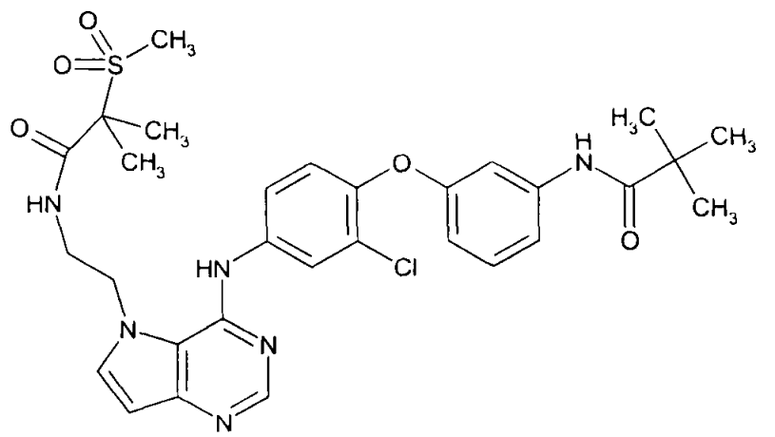
Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (206 mg), [3-(4-amino-2-clorofenoxi)-5-(trifluorometil)fenil]carbamato de ter-butilo (300 mg), alcohol isopropílico (10 ml), metanol (2.0 ml), tetrahidrofurano (1.0 ml) y solución acuosa 1 N de hidróxido de sodio (2.0 ml) y de la misma manera que en el Ejemplo C-27, se obtuvo el compuesto del título (53 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 1.53 (9H, s), 3.72-3.82 (5H, m),

612.

4.02 (2H, t, J= 4.9 Hz), 4.58 (2H, t, J= 4.9 Hz), 6.36 (1H, d, J= 2.1 Hz), 6.58 (2H, d, J= 4.7 Hz), 6.66 (1H, d, J= 3.2 Hz), 7.07 (1H, d, J= 8.9 Hz), 7.23-7.25 (2H, m), 7.62 (1H, dt, J= 8.9, 2.1 Hz), 7.87 (1H, s), 8.54 (1H, s), 8.79 (1H, s).

Ejemplo C-30



Producción de N-[3-(2-cloro-4-{[5-(2-{[2-metil-2-(metilsulfonil)propanoil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2,2-dimetilpropanamida

(i) Producción de triclorhidrato de 5-(2-aminoetil)-N-[4-(3-aminofenoxi)-3-clorofenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (267 mg) y [3-(4-amino-2-clorofenoxi)fenil]carbamato de ter-butilo (430 mg) en 1-metil-2-pirrolidona (15 ml) se agitó a 120°C durante 5 h. Tras enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de

etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 19:1→3:2→acetato de etilo) para dar un sólido marrón. A una solución del sólido obtenido en tetrahidrofurano (20 ml) se añadió ácido clorhídrico 2 N (10 ml) a temperatura ambiente, y la mezcla se agitó a 60°C durante 20 h. Después de concentrar a presión reducida, se añadió etanol y la mezcla luego se concentró. Se agregó éter diisopropílico al residuo y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con éter diisopropílico para dar el compuesto del título (342 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.26-3.34 (2H, m), 5.04-5.13 (2H, m), 6.76-7.05 (4H, m), 7.28-7.69 (3H, m), 7.94 (1H, s), 8.11 (1H, s), 8.45 (3H, br s), 8.76 (1H, s), 10.39 (2H, br s).

(ii) Producción de N-[3-(2-cloro-4-{[5-(2-{[2-metil-2-(metilsulfonil)propanoil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2,2-dimetilpropanamida

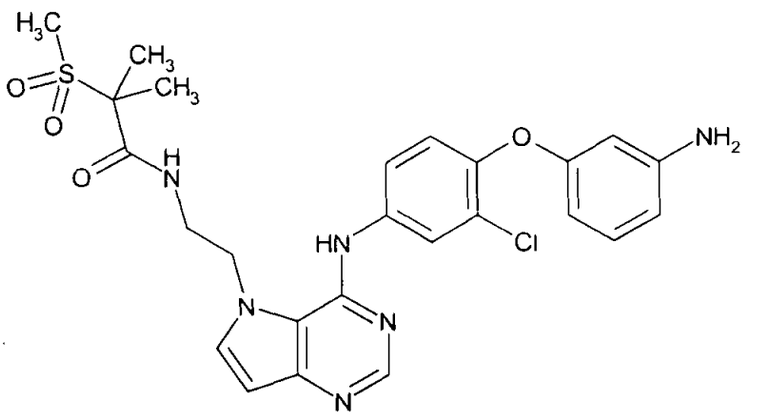
Una mezcla de triclorhidrato de 5-(2-aminoetil)-N-[4-(3-aminofenoxi)-3-clorofenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (114 mg), ácido 2-metil-2-(metilsulfonil)propanoico (210 mg), clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (380 mg), 1-hidroxibenzotriazol (41 mg), trietilamina (1.0 ml) y tetrahidrofurano (5.0 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El producto crudo obtenido se disolvió en tetrahidrofurano (5.0 ml), se añadieron N-metilmorfolina (1.0 ml) y cloruro de 2,2-dimetilpropanoílo (0.25 ml), y la mezcla se agitó durante 1 h. Bajo enfriamiento con hielo, se añadió carbonato ácido de sodio acuoso saturado, y la mezcla se extrajo con diclorometano. El extracto se secó sobre sulfato de magnesio y se concentró, y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→acetato de etilo:metanol = 80:20), y se cristalizó en éter dietílico/acetato de etilo para dar el compuesto del título (82 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.19 (9H, s), 1.14 (6H, s), 2.96 (3H, s), 3.39-3.50 (2H, m), 4.55-4.59 (2H, m), 6.49 (1H, d, J= 3.2 Hz), 6.66-6.68 (1H, m), 7.17-7.74 (6H, m), 7.97 (1H,

s), 8.22 (1H, br s), 8.34 (1H, s), 8.65 (1H, s), 9.26 (1H, s).

Ejemplo C-31



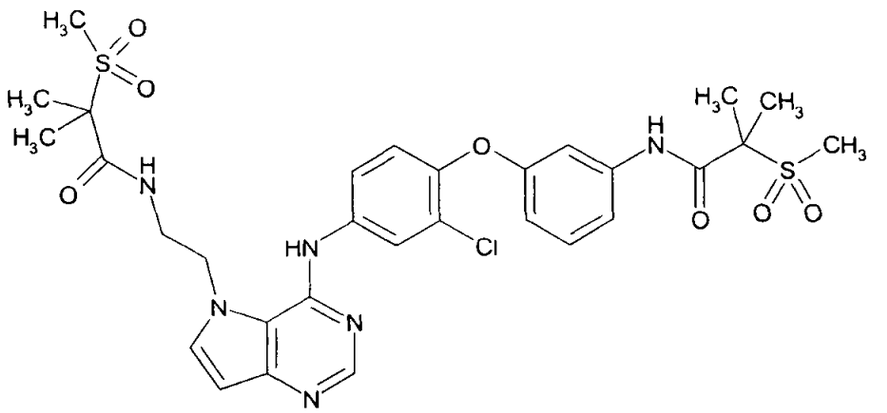
Producción de N-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Una mezcla de triclorhidrato de 5-(2-aminoetil)-N-[4-(3-aminofenoxi)-3-clorofenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (860 mg), ácido 2-metil-2-(metilsulfonil)propanoico (700 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.10 g), 1-hidroxibenzotriazol (50 mg), trietilamina (3.0 ml) y tetrahidrofurano (30 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo =

0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El producto crudo obtenido se cristalizó en éter dietílico/acetato de etilo para dar el compuesto del título (850 mg).

^{1}H-RMN (DMSO-d_6) δ: 1.41(6H, s), 2.96 (3H, s), 3.39-3.51 (2H, m), 4.54-4.59 (2H, m), 5.32 (2H, m), 6.07-6.11 (2H, m), 6.29 (1H, d, J= 8.8 Hz), 6.53 (1H, d, J= 3.0 Hz), 6.94-6.71 (1H, m), 7.11 (1H, d, J= 8.8 Hz), 7.56-7.60 (2H, m), 7.70 (1H, d, J= 3.0 Hz), 8.10 (1H, br s), 8.34 (1H, s), 8.91 (1H, s).

Ejemplo C-32



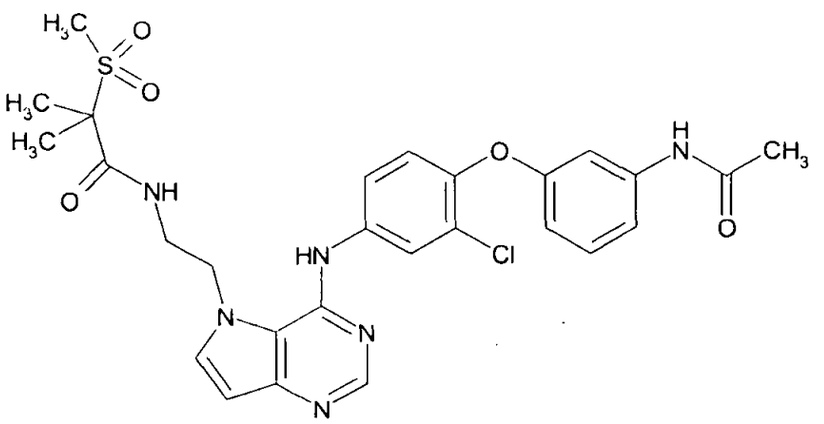
Producción de N-[3-(2-cloro-4-{[5-(2-{[2-metil-2-(metilsulfonil)propanoil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2-metil-2-(metilsulfonil)propanamida

Al usar triclorhidrato de 5-(2-aminoetil)-N-[4-(3-aminofenoxi)-3-clorofenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (80 mg), ácido 2-metil-2-(metilsulfonil)propanoico (87 mg),

clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (210 mg), 1-hidroxibenzotriazol (71 mg), trietilamina (0.9 ml) y tetrahidrofurano (8.0 ml) y de la misma manera que en el Ejemplo C-31, se obtuvo el compuesto del título (89 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.41 (6H, s), 1.64 (6H, s), 2.96 (3H, s), 3.03 (3H, s), 3.41-3.52 (2H, m), 4.55-4.59 (2H, m), 6.49 (1H, d, J= 3.2 Hz), 6.73-6.76 (1H, m), 7.17-7.76 (6H, m), 7.99 (1H, d. J= 3.2 Hz), 8.22 (1H, br s), 8.34 (1H, s), 8.66 (1H, s), 9.52 (1H, s).

Ejemplo C-33



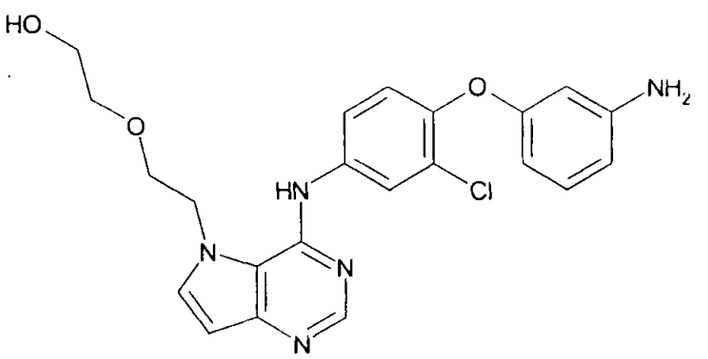
Producción de N-{2-[4-({4-[3-(acetilamino)fenoxi]-3-clorofenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-metil-2-(metilsulfonil)propanamida

Una mezcla de N-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida (91 mg), trietilamina (0.2 ml), anhídrido acético (0.3 ml) y tetrahidrofurano (7.0 ml)

se agitó a temperatura ambiente durante 1 h. Bajo enfriamiento con hielo, se añadió carbonato ácido de sodio acuoso saturado, y la mezcla se extrajo con diclorometano. El extracto se secó sobre sulfato de magnesio y se concentró, y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20), y se cristalizó en éter dietílico/acetato de etilo para dar el compuesto del título (84 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.41(6H, s), 2.00 (3H, s), 2.96 (3H, s), 3.39-3.50 (2H, m), 4.55-4.59 (2H, m), 6.49 (1H, d, J= 3.2 Hz), 6.63-6.68 (1H, m), 7.23-7.30 (4H, m), 7.59 (1H, s), 7.72-7.75 (1H, m), 7.96 (1H, s), 8.20 (1H, br s), 8.34 (1H, s), 8.65 (1H, s), 10.00 (1H, s).

Ejemplo C-34



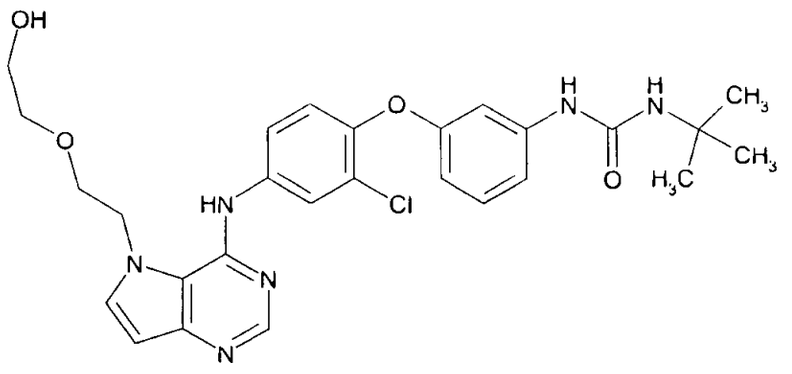
Producción de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

Se disolvió {3-[2-cloro-4-({5-[2-(2-

hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}carbamato de ter-butilo (120 mg) en metanol (7.0 ml), se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (8.0 ml) y la mezcla se agitó durante 5 h. Se agregaron solución acuosa 8 N de hidróxido de sodio (8.0 ml) y agua (10 ml), y la mezcla se extrajo con diclorometano. El extracto se secó sobre sulfato de magnesio y se concentró, y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20), y se cristalizó en éter dietílico/acetato de etilo para dar el compuesto del título (59 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.49 (4H, s), 3.81-3.85 (2H, m), 4.62-4.65 (2H, t, J= 4.8Hz), 4.71 (1H, m), 5.32 (2H, m), 6.06-6.09 (2H, m), 6.27 (1H, d, J= 8.8 Hz), 6.51 (1H, d, J= 3.0 Hz), 6.94-6.70 (1H, m), 7.11 (1H, d, J= 8.8 Hz), 7.56-7.60 (1H, m), 7.70 (1H, d, J= 3.0 Hz), 7.95 (1H, s), 8.34 (1H, s), 8.93 (1H, s).

Ejemplo C-35



Producción de N-(ter-butil)-N'-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}urea

(i) Producción de diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (206 mg), [3-(4-amino-2-clorofenoxi)fenil]carbamato de ter-butilo (300 mg) y alcohol isopropílico (7.0 ml) se agitó a 80°C durante 12 h. La mezcla de reacción se concentró a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→0:100). Las fracciones objeto se concentraron a presión reducida. El producto crudo se disolvió en metanol (8.0 ml), y al usar solución de cloruro de hidrógeno 4 N/acetato de etilo (8.0 ml) y de la misma manera que en el Ejemplo C-34, se obtuvo el compuesto del título (370 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.76-3.80 (2H, m), 3.87-3.94 (2H, m), 4.22-4.35 (2H, m), 4.85-4.93 (2H, m), 6.62-6.77 (3H,

m), 6.87-7.18 (3H, m), 7.30-7.71 (8H, m), 7.90 (1H, s), 8.01 (1H, s), 8.65 (1H, s).

(ii) Producción de N-(ter-butil)-N'-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}urea

Se suspendió diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (200 mg) en tolueno (10 ml), se añadieron trietilamina (0.9 ml) y 2-isocianato-2-metilpropano (0.4 ml), y la mezcla se agitó a 120°C durante 6 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en metanol (6.0 ml) y tetrahidrofurano (6.0 ml). Se añadió solución acuosa 1 N de hidróxido de sodio (3.0 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel

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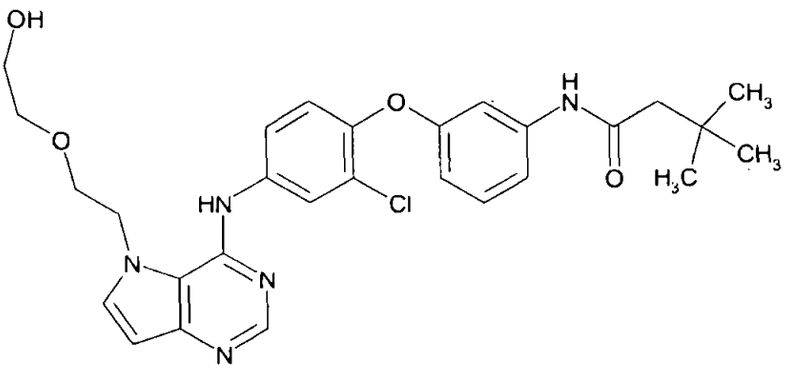
de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (74 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.26 (9H, s), 3.49 (4H, s), 3.83 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 5.93 (1H, s), 6.43-6.52 (2H, m), 6.96-7.21 (4H, m), 7.60-7.69 (2H, m), 7.98 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.35 (1H, s), 8.92 (1H, s).

Ejemplo C-36



Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-3,3-dimetilbutanamida

Una mezcla de diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (270 mg), trietilamina (1.9 ml), cloruro de 3,3-dimetilbutanoílo (0.3 ml) y tetrahidrofurano (20 ml) se agitó a temperatura ambiente

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durante 1 h. Bajo enfriamiento con hielo, se añadió carbonato ácido de sodio acuoso saturado, y la mezcla se extrajo con diclorometano. El extracto se secó sobre sulfato de magnesio y se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en metanol (6.0 ml) y tetrahidrofurano (6.0 ml). Se añadió solución acuosa 1 N de hidróxido de sodio (2.0 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (126 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.00 (9H, s), 2.15 (2H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.68-6.70 (1H, m), 7.16-7.37 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.85 (1H, s).

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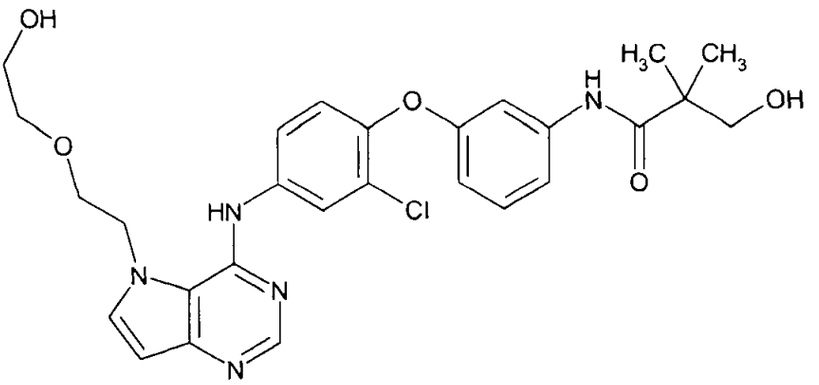
Ejemplo C-37



Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-3-hidroxi-2,2-dimetilpropanamida

Una mezcla de diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (260 mg), ácido 3-hidroxi-2,2-dimetilpropanoico (200 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (621 mg), 1-hidroxibenzotriazol (70 mg), trietilamina (2.0 ml) y tetrahidrofurano (15 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El producto crudo obtenido se disolvió en

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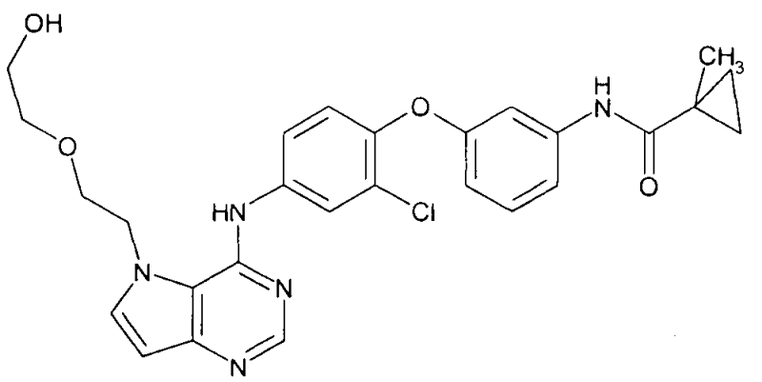
metanol (6.0 ml) y tetrahidrofurano (6.0 ml), se añadió solución acuosa 1 N de hidróxido de sodio (2.0 ml), y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (84 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.30 (6H, s), 3.49 (4H, s), 3.56 (2H, br s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, s), 4.73 (1H, m), 6.50 (1H, d, J= 3.2 Hz), 6.64 (1H, d, J= 7.7 Hz), 7.15-7.38 (4H, m), 7.62-7.70 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.90 (1H, s).

Ejemplo C-38

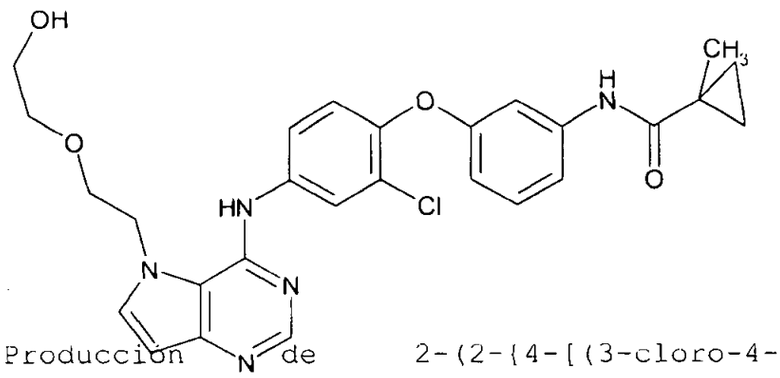


Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-1-metilciclopropancarboxamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (200 mg), ácido 1-metilciclopropancarboxílico (179 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (600 mg), 1-hidroxibenzotriazol (70 mg), trietilamina (2.3 ml), tetrahidrofurano (20 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml), tetrahidrofurano (6.0 ml) y etanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (69 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.59-0.62 (2H, m), 1.04-1.08 (2H, m), 1.37 (3H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.60-6.70 (1H, m), 7.15 (1H, d, J= 6.0 Hz), 7.23-7.41 (3H, m), 7.60-7.64 (1H, m), 7.70 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.36 (1H, s), 8.98 (1H, s), 9.22 (1H, s).

Ejemplo C-39



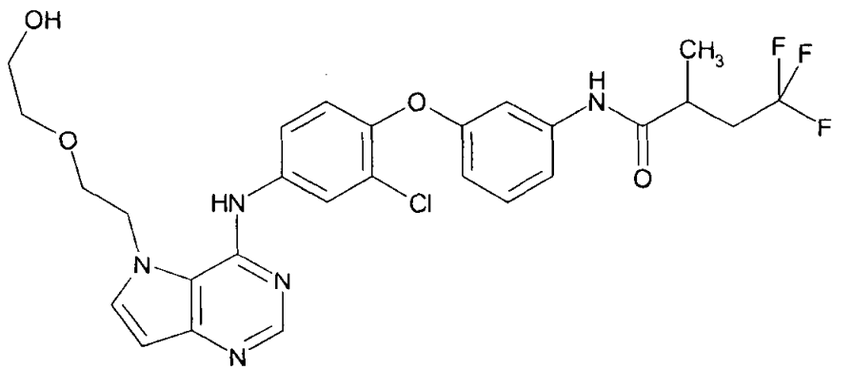
Producción de 2-(2-{4-[(3-cloro-4-{3-[(2,2-dimetilpropil)amino]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol

Se suspendió diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (220 mg) en diclorometano (7.0 ml), y se añadieron ácido acético (0.7 ml), tamices moleculares 4A (300 mg) y pivalaldehido (120 mg), y la mezcla se agitó durante 30 min. Se agregó triacetoxiborohidruro de sodio (470 mg), y la mezcla se siguió agitando durante 3 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en metanol (6.0 ml) y tetrahidrofurano (6.0 ml). Se añadió solución acuosa 1 N de

hidróxido de sodio (2.0 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (67 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 0.93 (9H, s), 2.77 (2H, d, J= 6.0 Hz), 3.49 (4H, s), 3.83 (2H, t, J= 4.7 Hz), 4.63-4.72 (3H, m), 5.63 (1H, t, J= 6.0 Hz), 6.02-6.05 (1H, m), 6.24 (1H, t, J= 3.0 Hz), 6.34-6.36 (1H, m), 6.51 (1H, d, J= 3.0 Hz), 7.00 (1H, t, J= 6.0 Hz), 7.08 (1H, d, J= 9.0 Hz), 7.56-7.60 (1H, m), 7.68 (1H, d, J= 3.0 Hz), 7.95 (1H, d, J= 3.0 Hz), 8.33 (1H, s), 8.91 (1H, s).

Ejemplo C-40

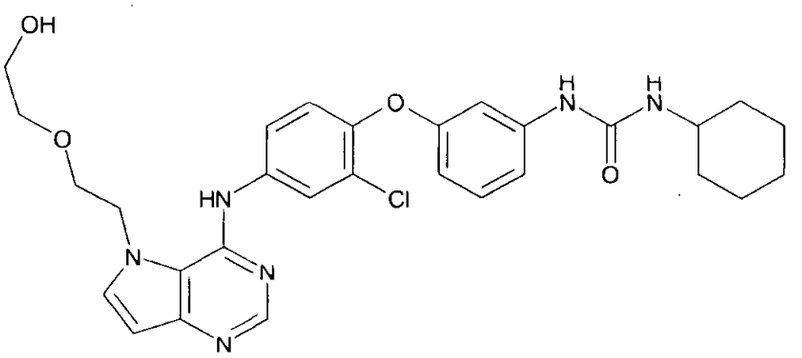


Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-4,4,4-trifluoro-2-metilbutanamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (50 mg), ácido 4,4,4-trifluoro-2-metilbutanoico (47 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (125 mg), 1-hidroxibenzotriazol (5 mg), trietilamina (0.7 ml), tetrahidrofurano (7.0 ml), solución acuosa 1 N de hidróxido de sodio (1.5 ml), tetrahidrofurano (3.0 ml) y metanol (2.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (25 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.18 (3H, d, J= 6.0 Hz), 2.26-2.85 (3H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.68-6.70 (1H, m), 7.14-7.38 (4H, m), 7.62-7.70 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.95 (1H, s), 10.14 (1H, s).

Ejemplo C-41

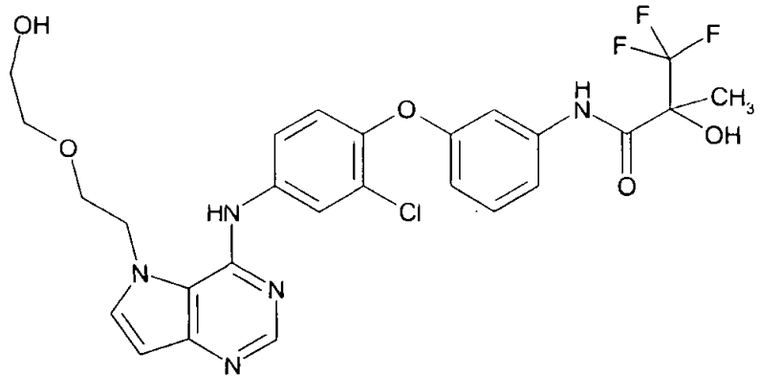


Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-N'-ciclohexilurea

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (240 mg), tolueno (15 ml), trietilamina (2.0 ml), ciclohexilisocianato (137 mg), solución acuosa 1 N de hidróxido de sodio (3.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-35(ii), se obtuvo el compuesto del título (56 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.09-1.82 (10H, m), 3.34-3.51 (1H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.00 (1H, d, J= 9.0 Hz), 6.46-6.52 (2H, m), 6.96-7.21 (4H, m), 7.61-7.69 (2H, m), 7.98 (1H, d, J= 2.7 Hz), 8.34 (1H, s), 8.41 (1H, s), 8.93 (1H, s).

Ejemplo C-42



Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-3,3,3-trifluoro-2-hidroxi-2-metilpropanamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (201 mg), ácido 3,3,3-trifluoro-2-hidroxi-2-metilpropanoico (175 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (415 mg), 1-hidroxibenzotriazol (47 mg), trietilamina (1.8 ml), tetrahidrofurano (28 ml), solución acuosa 1 N de hidróxido de sodio (4.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (47 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.01 (3H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.65 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.60-6.70 (1H, m), 7.14 (1H, d, J= 6.0 Hz), 7.22-7.45 (3H, m), 7.60-7.65 (1H, m), 7.71 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.36 (1H, s), 8.98 (1H, s), 9.22 (1H, s).

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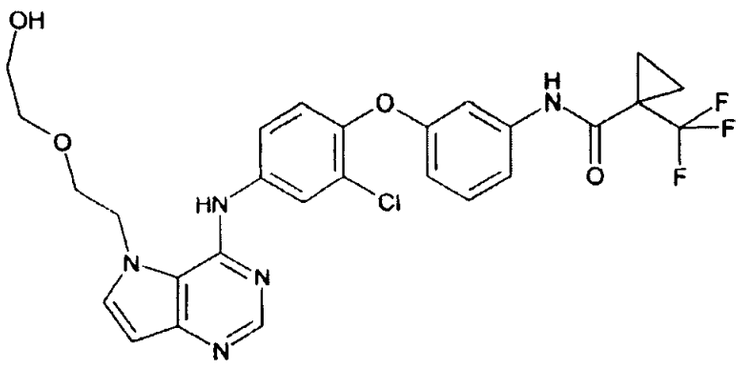
Ejemplo C-43



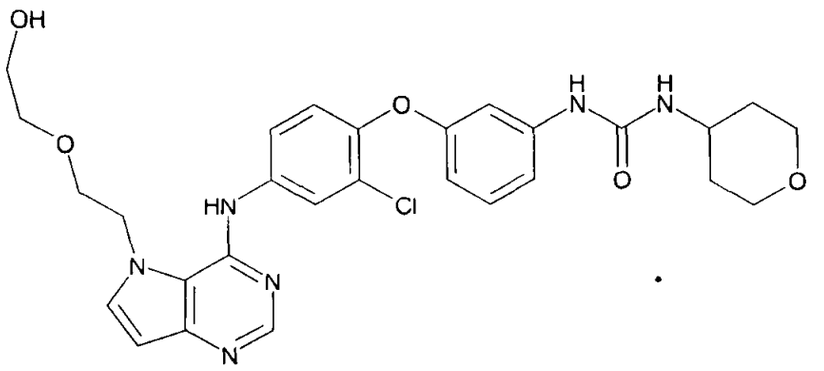
Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-1-(trifluorometil)ciclopropancarboxamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (220 mg), ácido 1-(trifluorometil)ciclopropancarboxílico (300 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (450 mg), 1-hidroxibenzotriazol (110 mg), trietilamina (2.6 ml), tetrahidrofurano (15 ml), solución acuosa 1 N de hidróxido de sodio (4.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (23 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.14-1.31 (2H, m), 1.42-1.45 (2H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.51 (1H, d, J= 3.0 Hz), 6.70-6.73 (1H, m), 7.15-7.41 (4H, m), 7.60-7.69 (2H, m), 7.99 (1H, d,

J= 3.0 Hz), 8.34 (1H, s), 8.95 (1H, s), 9.84 (1H, s).

Ejemplo C-44



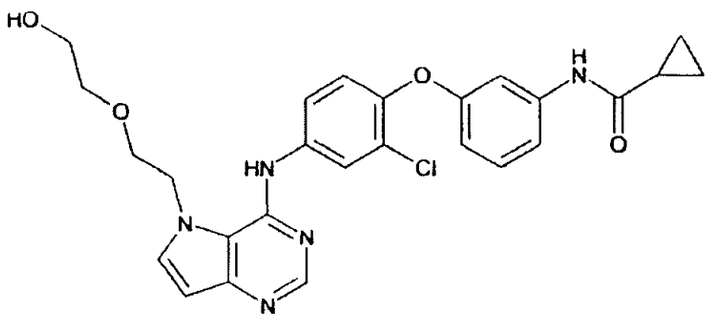
Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-N'-(tetrahidro-2H-piran-4-il)urea

A una solución de 1,1'-carbonilbis(1H-imidazol) (401 mg) en tolueno (10 ml) se añadió tetrahidro-2H-piran-4-amina (250 mg) y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadieron diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (220 mg) y trietilamina (2.0 ml), y la mezcla se agitó a 70°C durante 30 min. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se disolvió en metanol (8.0 ml) y tetrahidrofurano (2.0 ml). Se añadió solución acuosa 1 N de hidróxido de sodio (3.0 ml) y la mezcla se agitó a temperatura ambiente durante la noche.

Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en acetato de etilo-hexano para dar el compuesto del título (12 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.09-1.82 (4H, m), 3.20-3.63 (4H, m), 3.33-3.55 (1H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.00 (1H, d, J= 9.0 Hz), 6.45-6.52 (2H, m), 6.97-7.21 (4H, m), 7.59-7.71 (2H, m), 7.99 (1H, d, J= 2.7 Hz), 8.34 (1H, s), 8.41 (1H, s), 8.94 (1H, s).

Ejemplo C-45



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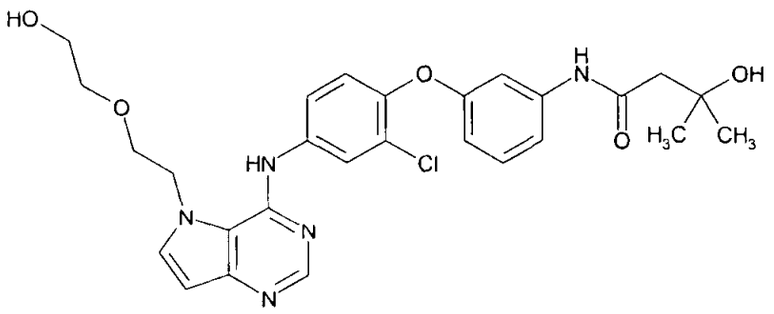
Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}ciclopropancarboxamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (200 mg), ácido ciclopropancarboxílico (200 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (470 mg), 1-hidroxibenzotriazol (42 mg), trietilamina (2.0 ml), tetrahidrofurano (29 ml), solución acuosa 1 N de hidróxido de sodio (3.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (98 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.76-0.78 (2H, m), 1.04 (2H, d, J= 6.0 Hz), 1.71-1.75 (1H, m), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.66 (2H, t, J= 6.0 Hz), 4.71 (1H, m), 6.52 (1H, d, J= 3.0 Hz), 6.62-6.66 (1H, m), 7.17 (1H, d, J= 9.0 Hz), 7.23-7.31 (3H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.0 Hz), 8.34 (1H, s), 8.94 (1H, s), 10.25 (1H, s).

Ejemplo C-46



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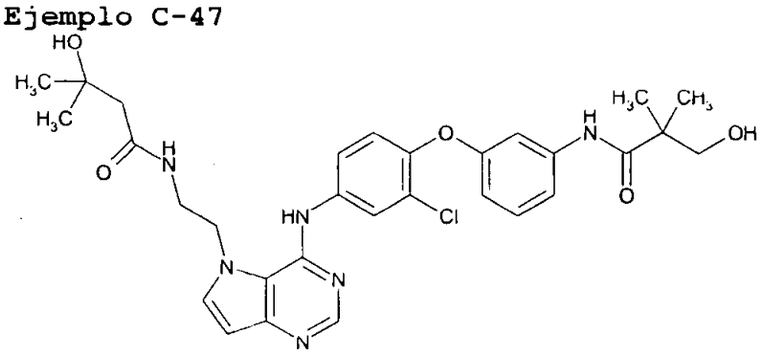
Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-3-hidroxi-3-metilbutanamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (200 mg), ácido 3-hidroxi-3-metilbutanoico (200 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (470 mg), 1-hidroxibenzotriazol (41 mg), trietilamina (1.8 ml), tetrahidrofurano(28 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (53 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.21 (6H, s), 2.38 (2H, s), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.71 (1H, s), 4.73 (1H, m), 6.51 (1H, d, J= 3.2 Hz), 6.63 (1H, d, J= 7.7 Hz), 7.15-7.37 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s), 9.87 (1H, s).

Ejemplo C-47

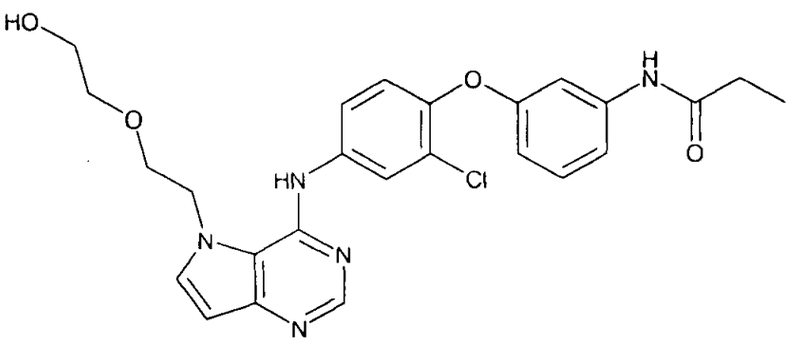


Producción de N-(2-{4-[(3-cloro-4-{3-[(3-hidroxi-2,2-dimetilpropanoil)amino]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

Al usar triclorhidrato de 5-(2-aminoetil)-N-[4-(3-aminofenoxi)-3-clorofenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (150 mg), ácido 3-hidroxi-3-metilbutanoico (42 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (357 mg), 1-hidroxibenzotriazol (18 mg) y trietilamina (0.9 ml) en tetrahidrofurano (4.0 ml) y de la misma manera que en el Ejemplo C-31, se llevó a cabo la reacción. Al usar el producto crudo obtenido y ácido 3-hidroxi-2,2-dimetilpropanoico (200 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (460 mg), 1-hidroxibenzotriazol (150 mg), trietilamina (2.0 ml) en tetrahidrofurano (7.0 ml) y de la misma manera que en el Ejemplo C-31, se obtuvo el compuesto del título (90 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 1.25 (6H, s), 1.32 (6H, s), 2.48 (2H, s), 2.80 (2H, br s), 3.59 (2H, s), 3.57-3.65 (2H, m), 4.45-4.51 (2H, m), 6.62 (1H, d, J= 3.0 Hz), 7.05-7.44(8H, m), 7.73 (1H, dd, J= 8.7 Hz, 2.7 Hz), 8.03 (1H, d, J= 2.7 Hz), 8.30 (1H, s), 8.50 (1H, s).

Ejemplo C-48



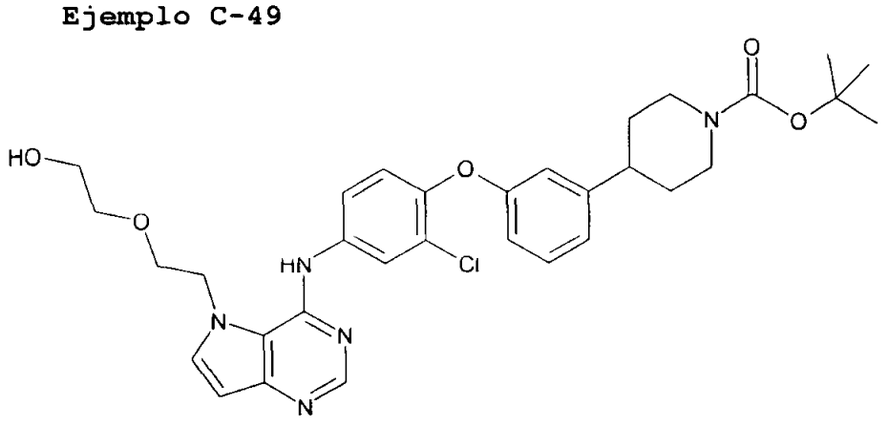
Producción de N-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}propanamida

Al usar diclorhidrato de benzoato de 2-[2-(4-{[4-(3-aminofenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (200 mg), ácido propiónico (0.5 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (560 mg), 1-hidroxibenzotriazol (67 mg), trietilamina (2.1 ml), tetrahidrofurano (10 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml), tetrahidrofurano (6.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-37, se obtuvo el compuesto del título (70 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.04 (3H, t, J= 7.5 Hz), 2.28 (2H, dd, J= 7.5 Hz), 3.49 (4H, s), 3.84 (2H, t, J= 6.0 Hz), 4.64 (2H, t, J= 6.0 Hz), 4.73 (1H, m), 6.51 (1H, d, J= 3.2 Hz), 6.63 (1H, d, J= 7.7 Hz), 7.15-7.32 (4H, m), 7.61-7.69 (2H, m), 7.99 (1H, d, J= 3.2 Hz), 8.34 (1H, s), 8.94 (1H, s),

9.92 (1H, s).

Ejemplo C-49



Producción de 4-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}piperidin-1-carboxilato de ter-butilo

(i) Producción de 4-[3-(2-cloro-4-nitrofenoxi)fenil]piperidin-1-carboxilato de ter-butilo

Se disolvieron 2-cloro-1-fluoro-4-nitrobenceno (7.27 g) y 4-(3-hidroxifenil)piperidin-1-carboxilato de ter-butilo (11.5 g) en N,N-dimetilformamida (42 ml), se añadió carbonato de potasio (8.28 g) y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con acetato de etilo (300 ml) y se lavó con agua (300 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro, y se evaporó a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano/acetato de etilo = 100/0→60/40) para dar el compuesto del título (17.6 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (9H, s), 1.50-1.70 (2H, m),

840.

1.84 (2H, d, J= 13 Hz), 2.60-2.90 (3H, m), 4.23 (2H, m), 6.87 (1H, d, J= 9 Hz), 6.92 (2H, m), 7.12 (1H, d, J= 8 Hz), 7.37 (1H, m), 8.04 (1H, dd, J= 3 Hz, 9 Hz), 8.38 (1H, d, J= 3 Hz).

(ii) Producción de 4-[3-(4-amino-2-clorofenoxi)fenil]piperidin-1-carboxilato de ter-butilo

Se suspendió 4-[3-(2-cloro-4-nitrofenoxi)fenil]piperidin-1-carboxilato de ter-butilo (1.9 g) en etanol (43 ml)/agua (4.81 ml), a ello se añadió cloruro de calcio (270 mg) y la mezcla se disolvió con calentamiento agitando a 90°C durante 10 min. Se agregó hierro reducido (1.63 g), y la mezcla se agitó con calentamiento a 90°C durante 16 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de celite, y el filtrado se concentró a presión reducida. El sólido residual se diluyó con acetato de etilo (150 ml) y se lavó con salmuera saturada (80 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se purificó por cromatografía en gel de silice (hexano/acetato de etilo = 80/20→60/40) para dar el compuesto del título (1.71 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 1.50-1.70 (2H, m), 1.80 (2H, d, J= 13 Hz), 2.58 (1H, m), 2.77 (2H, t, J= 13 Hz), 3.69 (2H, br s), 4.22 (2H, m), 6.57 (1H, dd, J= 3 Hz, 9 Hz), 6.60-6.90 (5H, m), 7.20 (1H, t, J= 8 Hz).

(iii) Producción de 4-{3-[2-cloro-4-({5-[2-(2-

hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}piperidin-1-carboxilato de ter-butilo

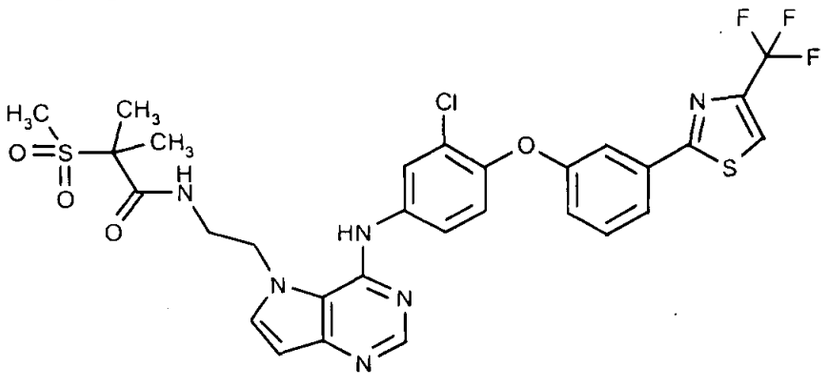
Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (150 mg), 4-[3-(4-amino-2-clorofenoxi)fenil]piperidin-1-carboxilato de ter-butilo (260 mg) y alcohol isopropílico (1.5 ml) se agitó con calentamiento a 80°C durante 16 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml), y se lavó con bicarbonato de sodio acuoso (40 ml). La capa orgánica se separó, se secó sobre sulfato de magnesio anhidro, y se evaporó a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 90/10→0/100), y las fracciones objeto se concentraron a presión reducida. El residuo obtenido se disolvió en metanol (1.89 ml), a ello se añadió solución acuosa 1 N de hidróxido de sodio (0.433 ml) y la mezcla se agitó a temperatura ambiente durante 2 h. Se agregó ácido clorhídrico 1 N (0.433 ml), y la mezcla se diluyó con acetato de etilo (30 ml), y se lavó con salmuera saturada (30 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida, y el residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→85/15) para dar el compuesto del título (88 mg) en forma de polvo.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (9H, s), 1.50-1.80 (2H, m),

842.

1.81 (2H, m), 2.61 (1H, m), 2.77 (2H, m), 3.72 (2H, m), 3.79 (2H, m), 4.01 (2H, t, J= 5 Hz), 4.21 (2H, m), 4.55 (2H, t, J= 5 Hz), 6.59 (1H, d, J= 3 Hz), 6.79 (2H, m), 6.90 (1H, d, J= 7.5 Hz), 7.00 (1H, d, J= 9 Hz), 7.18-7.30 (2H, m), 7.55 (1H, dd, J= 3 Hz, 9 Hz), 7.86 (1H, d, J= 3 Hz), 8.49 (1H, s), 8.78 (1H, br s).

Ejemplo C-50



Producción de N-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-metil-2-(metilsulfonil)propanamida

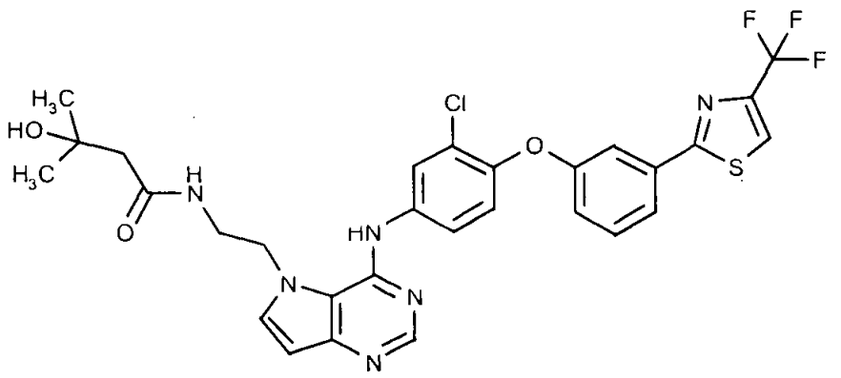
Al usar diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 2-metil-2-(metilsulfonil)propanoico (83 mg), 1-hidroxibenzotriazol (75 mg), trietilamina (0.23 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (105 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo C-8(iii), se obtuvo el compuesto del título (171 mg)

843

en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.70 (6H, s), 2.93 (3H, s), 3.6-3.75 (2H, m), 4.40-4.55 (2H, m), 6.63 (1H, d, J = 3.3 Hz), 7.00-7.10 (1H, m), 7.09 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.25-7.45 (2H, m), 7.60-7.70 (2H, m), 7.75 (1H, s), 7.80-7.95 (1H, m), 8.04 (1H, d, J = 2.4 Hz), 8.36 (1H, s), 8.53 (1H, s).

Ejemplo C-51



Producción de N-(2-{4-[(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

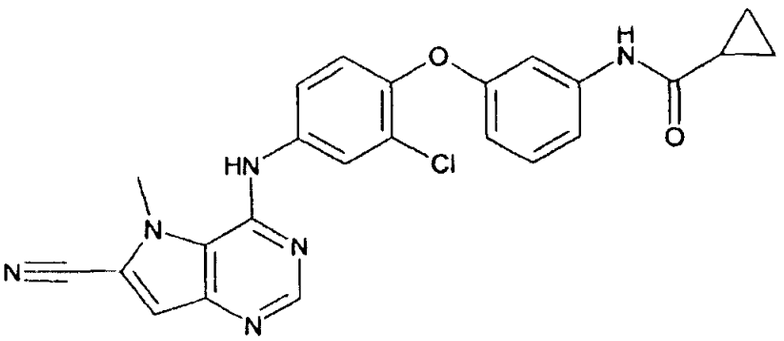
Al usar diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[4-(trifluorometil)-1,3-tiazol-2-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 3-hidroxi-3-metilbutanoico (59 mg), 1-hidroxibenzotriazol (75 mg), trietilamina (0.23 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (105 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el

844

Ejemplo C-8(iii), se obtuvo el compuesto del título (95.3 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.33 (6H, s), 2.48 (2H, s), 3.60-3.70 (2H, m), 4.40-4.50 (2H, m), 6.60 (1H, d, J = 3.0 Hz), 6.85-6.95 (1H, m), 7.00-7.10 (2H, m), 7.18 (1H, d, J = 3.0 Hz), 7.40 (1H, t, J = 9.0 Hz), 7.60-7.80 (4H, m), 8.07 (1H, s), 8.52 (1H, s), 8.63 (1H, s).

Ejemplo C-52



Producción de N-(3-{2-cloro-4-[(6-ciano-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida

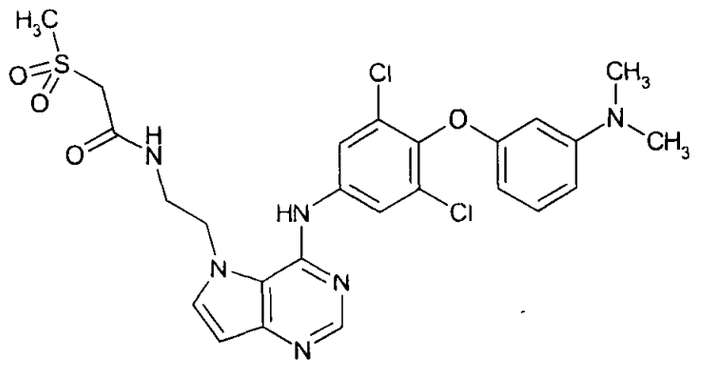
A una solución de diisopropilamina (545 mg) en tetrahidrofurano (15 ml) se añadió n-butil-litio (2.9 ml) a 0°C. Tras agitar durante 30 min, la mezcla se enfrió hasta -78°C, y a ello se agregó 4-cloro-5-metil-5H-pirrolo[3,2-d]pirimidina (603 mg). La mezcla se agitó durante 1 h, se agregó cianuro de p-toluensulfonilo (1300 mg), y la mezcla se calentó hasta -40°C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera

845

saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→30:70). Después de concentrar a presión reducida, los cristales resultantes se disolvieron en alcohol isopropílico (7.0 ml). A ello se agregó N-[3-(4-amino-2-clorofenoxi)fenil]ciclopropancarboxamida (232 mg), y la mezcla se agitó a 80°C durante 3 h. Después de concentrar a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→0:100). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (103 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.77(4H, d, J= 6.1 Hz), 1.73-1.81 (1H, m), 4.31 (3H, s), 6.66-6.70 (1H, m), 7.21-7.40 (4H, m), 7.53 (1H, s), 7.62 (1H, d, J= 8.7 Hz), 7.90 (1H, s), 8.64 (1H, s), 9.87 (1H, br s), 10.25 (1H, s).

Ejemplo C-53



Producción de N-{2-[4-({3.5-dicloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 3,5-dicloro-4-[3-(dimetilamino)fenoxi]anilina

A una solución de 3-(dimetilamino)fenol (470 mg) y 1,3-dicloro-2-yodo-5-nitrobenceno (1.00 g) en N,N-dimetilformamida (15 ml) se añadió carbonato de potasio (850 mg) y la mezcla se agitó a temperatura ambiente durante 18 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) y el producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (23 ml). Se agregaron hierro reducido (750 mg) y cloruro de calcio (120 mg), y la mezcla se agitó a 80°C

durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1) para dar el compuesto del título (402 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 2.85 (6H, s), 5.58 (2H, s), 5.88 (1H, dd, J = 1.9 Hz, 8.0 Hz), 6.19 (1H, t, J = 2.2 Hz), 6.37 (1H, dd, J = 1.9 Hz, 8.0 Hz), 6.69 (2H, s), 7.04 (1H, t, J = 8.3 Hz).

(ii) Producción de N-{2-[4-({3,5-dicloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

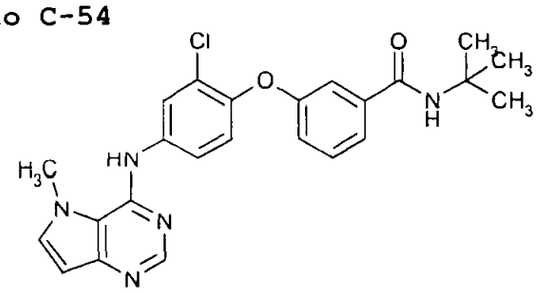
Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (150 mg), 3,5-dicloro-4-[3-(dimetilamino)fenoxi]anilina (150 mg) y alcohol isopropílico (8.0 ml) se agitó a 80°C durante 12 h. Bajo enfriamiento con hielo, a la mezcla de reacción se añadió bicarbonato de sodio acuoso, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por

cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0), el producto crudo obtenido (150 mg) se disolvió en tetrahidrofurano (10 ml), se agregó solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), y la mezcla se agitó a 70°C durante 20 h. El solvente se evaporó a presión reducida, se añadieron etanol y éter diisopropílico al residuo, y el polvo precipitado se recogió por filtración y se disolvió en N,N-dimetilformamida (7.0 ml). Se agregaron ácido metilsulfonilacético (70 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (160 mg), 1-hidroxibenzotriazol (70 mg) y trietilamina (0.15 ml) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 90:10), y se cristalizó en éter diisopropílico para dar el compuesto del título (74 mg).

^{1}H-RMN (DMSO-d_6) δ: 2.89 (6H, s), 3.11 (3H, s), 3.44-3.49 (2H, m), 4.06 (2H, s), 4.55-4.59 (2H, m), 5.89-7.11 (5H, m), 7.66-8.69 (5H, m), 8.77 (1H, s).

849

Ejemplo C-54



Producción de N-(ter-butil)-3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzamida

(i) Producción de 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzoato de metilo

Una mezcla de 4-cloro-5-metil-5H-pirrolo[3,2-d]pirimidina (1.01 g), 3-(4-amino-2-clorofenoxi)benzoato de metilo (1.39 g) y alcohol isopropílico (10 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). Las fracciones objeto se concentraron a presión reducida. Se añadió acetato de etilo-éter dietílico al residuo, y el sólido precipitado se recogió por filtración para dar el compuesto del título (1.77 g) en forma de un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ: 3.90 (3H, s), 4.15 (3H, s), 6.56 (1H, d, J = 3.3 Hz), 6.83 (1H, br s), 7.06 (1H, d, J = 8.8

Hz), 7.16-7.22 (2H, m), 7.40 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.56-7.60 (1H, m), 7.74-7.79 (1H, m), 7.81 (1H, d, J = 2.5 Hz), 8.51 (1H, s).

(ii) Producción de ácido 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzoico

A 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzoato de metilo (1.68 g) se añadieron metanol (20 ml), tetrahidrofurano (5 ml) y solución acuosa 1 N de hidróxido de sodio (8.2 ml), y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, ácido clorhídrico 1 N (8.2 ml), se añadieron acetato de etilo y éter diisopropílico. El sólido precipitado se recogió por filtración, se lavó con agua y éter diisopropílico para dar el compuesto del título (1.62 g) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 4.16 (3H, s), 6.45 (1H, d, J = 3.0 Hz), 7.24-7.32 (3H, m), 7.51 (1H, t, J = 8.0 Hz), 7.60 (1H, d, J = 3.0 Hz), 7.64-7.73 (2H, m), 7.96 (1H, d, J = 2.4 Hz), 8.32 (1H, s), 8.62 (1H, br s).

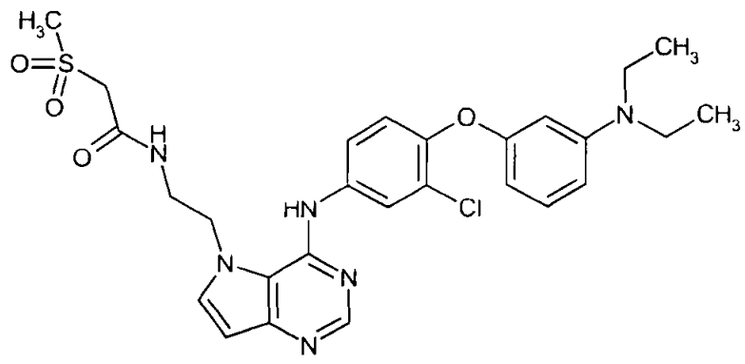
(iii) Producción de N-(ter-butil)-3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzamida

Una mezcla de ácido 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzoico (197 mg), ter-butilamina (0.105 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), monohidrato de 1-

hidroxibenzotriazol (92 mg) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (215 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 4.15 (3H, s), 5.96 (1H, br s), 6.56 (1H, d, J = 3.0 Hz), 6.85 (1H, br s), 7.02 (1H, d, J = 8.5 Hz), 7.05-7.10 (1H, m), 7.18 (1H, d, J = 3.0 Hz), 7.31-7.44 (4H, m), 7.80 (1H, d, J = 2.5 Hz), 8.50 (1H, s).

Ejemplo C-55



Producción de N-{2-[4-({3-cloro-4-[3-(dietilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 3-(4-amino-2-clorofenoxi)-N,N-dietilanilina

Al usar 3-(dietilamino)fenol (920 mg), 3-cloro-4-fluoronitrobenceno (1.01 g), carbonato de potasio (1.38 g), N,N-dimetilformamida (20 ml), platino-carbón activado al 5% (300 mg), acetato de etilo (10 ml) y metanol (5.0 ml) y de la misma manera que en el Ejemplo C-6(iv) y (v), se obtuvo el compuesto del título (954 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.06-1.12 (6H, m), 3.25-3.34 (4H, m), 5.26 (2H, s), 5.94-6.57 (4H, m), 6.68 (1H, d, J = 2.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.12 (1H, t, J = 8.3 Hz).

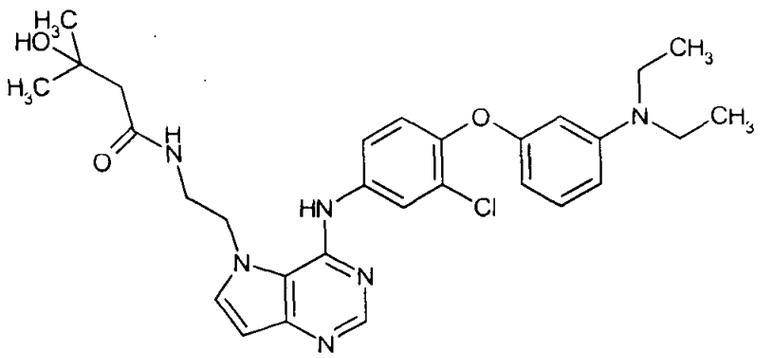
(ii) Producción de N-{2-[4-({3-cloro-4-[3-(dietilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3-(4-amino-2-clorofenoxi)-N,N-dietilanilina (150 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (150 mg), alcohol isopropílico (10 ml), tetrahidrofurano (15 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), ácido metilsulfonilacético (190 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (290 mg), 1-hidroxibenzotriazol (10 mg), trietilamina (4.0 ml) y N,N-

dimetilformamida (15 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (117 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.05-1.10 (6H, m), 3.10 (3H, s), 3.27-3.34 (4H, m), 3.44-3.49 (2H, m), 4.05 (2H, s), 4.53-4.57 (2H, m), 6.00-6.49 (4H, m), 7.07-7.91 (5H, m), 8.32 (1H, s), 8.62-8.68 (2H, m).

Ejemplo C-56



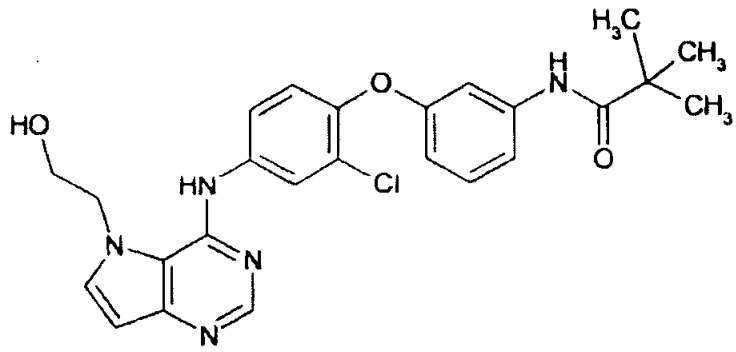
Producción de N-{2-[4-({3-cloro-4-[3-(dietilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

Al usar 3-(4-amino-2-clorofenoxi)-N,N-dietilanilina (150 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (150 mg), alcohol isopropílico (10 ml), tetrahidrofurano (15 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), ácido 3-hidroxi-3-metilbutanoico (75 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (191 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (0.3 ml) y N,N-

dimetilformamida (6 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (94 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.05-1.17 (12H, m), 2.20 (2H, s), 3.24-3.34 (4H, m), 3.37-3.44 (2H, m), 4.48-4.53 (2H, m), 4.65 (1H, s), 6.01-6.48 (4H, m), 7.06-7.97 (5H, m), 8.22-8.26 (1H, m), 8.31 (1H, s), 8.80 (1H, s).

Ejemplo C-57



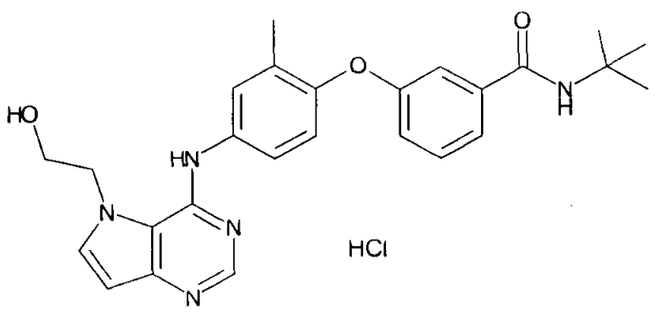
Producción de N-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2,2-dimetilpropanamida

Una mezcla de N-[3-(4-amino-2-clorofenoxi)fenil]-2,2-dimetilpropanamida (70 mg) y benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (63 mg) se disolvió en alcohol isopropílico (3 ml), a ello se añadió clorhidrato de piridina (5 mg), y la mezcla se agitó a 80°C durante 16 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se adicionó solución acuosa 1 N de hidróxido de sodio (2 ml), y la mezcla se agitó a temperatura ambiente durante 9 h. Una solución acuosa saturada de cloruro de amonio se añadió a la

dimetilformamida (5 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (178 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.10-1.82 (8H, m), 1.95-2.07 (2H, m), 3.86-4.01 (1H, m), 4.01-4.18 (2H, m), 4.37-4.44 (2H, m), 6.03 (1H, d, J= 8.1 Hz), 6.04-6.12 (1H, m), 6.22 (1H, d, J= 3.0 Hz), 6.98-7.11 (3H, m), 7.32-7.44 (4H, m), 7.79 (1H, d, J= 2.7 Hz), 8.28 (1H, s), 9.57 (1H, br s).

Ejemplo C-61



Producción de clorhidrato de N-(ter-butil)-3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)benzamida

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(i) Producción de 3-(2-metil-4-nitrofenoxi)benzoato de metilo

Una mezcla de 3-hidroxibenzoato de metilo (3.04 g), 2-fluoro-5-nitrotolueno (3.10 g), carbonato de potasio (4.15 g) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 5:95→15:85). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (5.66 g) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.41 (3H, s), 3.91 (3H, s), 6.78 (1H, d, J = 8.9 Hz), 7.21-7.27 (1H, m), 7.49 (1H, t, J = 7.8 Hz), 7.65-7.68 (1H, m), 7.86-7.91 (1H, m), 8.01 (1H, dd, J = 2.8 Hz, 8.9 Hz), 8.17 (1H, d, J = 2.8 Hz).

(ii) Producción de ácido 3-(2-metil-4-nitrofenoxi)benzoico

A 3-(2-metil-4-nitrofenoxi)benzoato de metilo (5.66 g) se añadieron alcohol isopropílico (100 ml) y solución acuosa 1 N de hidróxido de sodio (22 ml) y la mezcla se agitó a temperatura ambiente durante la noche. A la mezcla de

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reacción se añadió ácido clorhídrico 1 N (25 ml) y el sólido precipitado se recogió por filtración, y se lavó con agua para dar el compuesto del título (4.54 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.41 (3H, s), 6.81 (1H, d, J = 8.9 Hz), 7.26-7.32 (1H, m), 7.52 (1H, t, J = 7.9 Hz), 7.70-7.74 (1H, m), 7.92-7.97 (1H, m), 8.02 (1H, dd, J = 2.9 Hz, 8.9 Hz), 8.17 (1H, d, J = 2.9 Hz).

(iii) Producción de N-(ter-butil)-3-(2-metil-4-nitrofenoxi)benzamida

Una mezcla de ácido 3-(2-metil-4-nitrofenoxi)benzoico (820 mg), cloruro de tionilo (0.438 ml), N,N-dimetilformamida (una gota) y tolueno (10 ml) se agitó a 80°C durante 2 h. Se adicionó cloruro de tionilo (0.656 ml) y la mezcla se siguió agitando durante 1 h. La mezcla de reacción se concentró a presión reducida, se añadió tolueno, y la mezcla se volvió a concentrar a presión reducida. Una solución del residuo en tetrahidrofurano (5 ml) se añadió a una solución de ter-butilamina (439 mg) y trietilamina (0.627 ml) en tetrahidrofurano (10 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a

cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 10:90→30:70). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (948 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (9H, s), 2.40 (3H, s), 5.93 (1H, br s), 6.79 (1H, d, J = 8.9 Hz), 7.14 (1H, ddd, J = 1.2 Hz, 2.5 Hz, 7.8 Hz), 7.40-7.53 (3H, m), 8.00 (1H, dd, J = 2.8 Hz, 8.9 Hz), 8.15 (1H, d, J = 2.8 Hz).

(iv) Producción de 3-(4-amino-2-metilfenoxi)-N-(ter-butil)benzamida

A una solución de N-(ter-butil)-3-(2-metil-4-nitrofenoxi)benzamida (948 mg) en acetato de etilo (20 ml) se añadió platino-carbón activado al 5% (50 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. El catalizador se filtró, el filtrado se concentró y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 25:75→45:55). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (892 mg) en forma de un aceite de color púrpura rojizo.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 2.08 (3H, s), 3.56 (2H, br s), 5.89 (1H, br s), 6.51 (1H, dd, J = 2.5 Hz, 8.4 Hz), 6.58 (1H, d, J = 2.5 Hz), 6.77 (1H, d, J = 8.4 Hz), 6.87-6.94 (1H, m), 7.22-7.30 (3H, m).

(v) Producción de clorhidrato de N-(ter-butil)-3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)benzamida

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (121 mg), 3-(4-amino-2-metilfenoxi)-N-(ter-butil)benzamida (119 mg) y alcohol isopropílico (5 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico, y se recogió por filtración. Al polvo obtenido se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo =

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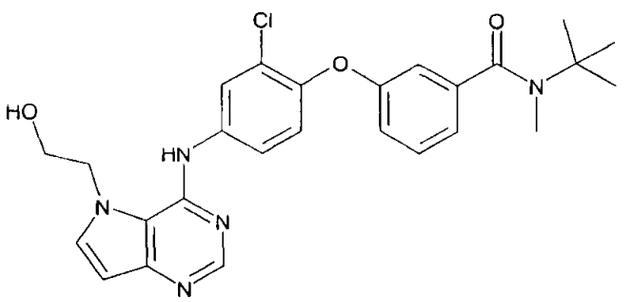
0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol y se agregó solución de cloruro de hidrógeno 1 N/acetato de etilo (0.4 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (139 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 2.20 (3H, s), 3.90 (2H, t, J = 4.4 Hz), 4.69 (2H, t, J = 4.4 Hz), 6.30-6.55 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 7.02-7.12 (2H, m), 7.28-7.32 (1H, m), 7.43 (1H, t, J = 8.0 Hz), 7.48-7.59 (3H, m), 7.81 (1H, br s), 7.99 (1H, d, J = 3.0 Hz), 8.72 (1H, s), 10.77 (1H, br s).

Ejemplo C-62



Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-metilbenzamida

(i) Producción de 3-(2-cloro-4-nitrofenoxi)benzoato de metilo

Al usar 3-hidroxibenzoato de metilo (8.20 g), 2-

cloro-1-fluoro-4-nitrobenceno (9.46 g), carbonato de potasio (11.2 g) y N,N-dimetilformamida (50 ml) y de la misma manera que en el Ejemplo C-61(i), se obtuvo el compuesto del título (16.0 g) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.92 (3H, s), 6.91 (1H, d, J = 9.1 Hz), 7.29 (1H, ddd, J = 0.8 Hz, 2.6 Hz, 8.0 Hz), 7.52 (1H, t, J = 8.0 Hz), 7.70-7.73 (1H, m), 7.91-7.97 (1H, m), 8.07 (1H, dd, J = 2.8 Hz, 9.1 Hz), 8.39 (1H, d, J = 2.8 Hz).

(ii) Producción de ácido 3-(2-cloro-4-nitrofenoxi)benzoico

Al usar 3-(2-cloro-4-nitrofenoxi)benzoato de metilo (7.08 g), alcohol isopropílico (150 ml), tetrahidrofurano (50 ml) y solución acuosa 1 N de hidróxido de sodio (25.3 ml) y de la misma manera que en el Ejemplo C-61(ii), se obtuvo el compuesto del título (5.31 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 6.94 (1H, d, J = 9.0 Hz), 7.31-7.37 (1H, m), 7.56 (1H, t, J = 8.0 Hz), 7.76-7.79 (1H, m), 7.97-8.03 (1H, m), 8.09 (1H, dd, J = 2.6 Hz, 9.0 Hz), 8.40 (1H, d, J = 2.6 Hz).

(iii) Producción de N-(ter-butil)-3-(2-cloro-4-nitrofenoxi)-N-metilbenzamida

Al usar ácido 3-(2-cloro-4-nitrofenoxi)benzoico (881 mg), cloruro de tionilo (1.09 ml), N,N-dimetilformamida (una gota), tolueno (10 ml), tetrahidrofurano (5 ml), N-metil-ter-butilamina (523 mg), trietilamina (0.627 ml) y

tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-61(iii), se obtuvo el compuesto del título (1.14 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 2.87 (3H, s), 6.92 (1H, d, J = 9.1 Hz), 7.08-7.16 (2H, m), 7.30-7.35 (1H, m), 7.45 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.38 (1H, d, J = 2.6 Hz).

(iv) Producción de 3-(4-amino-2-clorofenoxi)-N-(ter-butil)-N-metilbenzamida

Al usar N-(ter-butil)-3-(2-cloro-4-nitrofenoxi)-N-metilbenzamida (1.14 g), acetato de etilo (20 ml) y platino-carbón activado al 5% (50 mg) y de la misma manera que en el Ejemplo C-61(iv), se obtuvo el compuesto del título (868 mg) en forma de un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 2.84 (3H, s), 3.69 (2H, br s), 6.55 (1H, dd, J = 2.8 Hz, 8.7 Hz), 6.76 (1H, d, J = 2.8 Hz), 6.86-6.93 (3H, m), 7.03-7.08 (1H, m), 7.27 (1H, t, J = 7.8 Hz).

(v) Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-metilbenzamida

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (121 mg), 3-(4-amino-2-clorofenoxi)-N-(ter-butil)-N-metilbenzamida (133 mg) y alcohol isopropílico (5 ml) se agitó a 80°C durante la noche.

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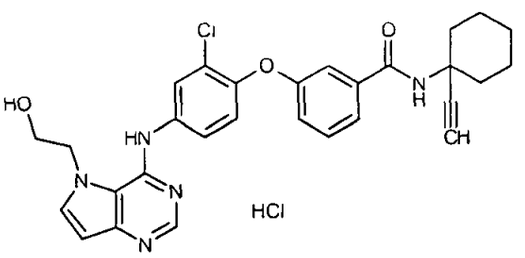
Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml), y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (173 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 2.86 (3H, s), 4.09 (2H, t, J = 4.5 Hz), 4.38 (2H, t, J = 4.5 Hz), 6.19 (1H, d, J = 3.3 Hz), 6.50-6.90 (1H, m), 6.95-7.03 (4H, m), 7.04-7.09 (1H, m), 7.26-7.39 (2H, m), 7.82 (1H, d, J = 2.5 Hz), 8.26 (1H, s), 9.73 (1H, br s).

867.

Ejemplo C-63



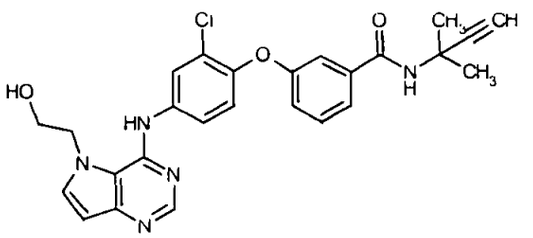
Producción de clorhidrato de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-etinilciclohexil)benzamida

Una mezcla de ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), 1-etinilciclohexanoamina (148 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), monohidrato de 1-hidroxibenzotriazol (92 mg) y N,N-dimetilformamida (5 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol, y a ello se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.4 ml). El solvente se evaporó a presión

reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (160 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.20-1.37 (1H, m), 1.43-1.64 (5H, m), 1.71-1.88 (2H, m), 2.04-2.18 (2H, m), 3.16 (1H, s), 3.85-3.95 (2H, m), 4.64-4.74 (2H, m), 6.20-6.40 (1H, m), 6.70 (1H, d, J = 3.0 Hz), 7.17 (1H, dd, J = 2.3 Hz, 8.1 Hz), 7.27-7.35 (2H, m), 7.48 (1H, t, J = 8.0 Hz), 7.57-7.65 (2H, m), 7.94 (1H, d, J = 2.5 Hz), 7.98-8.03 (1H, m), 8.17 (1H, br s), 8.76 (1H, s), 10.76-10.86 (1H, m).

Ejemplo C-64



Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1,1-dimetilprop-2-in-1-il)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), 3-amino-3-metil-1-butina (120 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), monohidrato de 1-hidroxibenzotriazol (92 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-59, se obtuvo el compuesto del título (155 mg) en forma de un polvo blanco.

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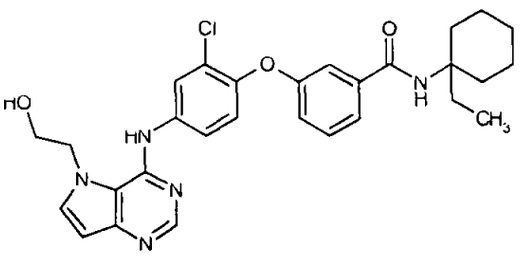
^{1}H-RMN ($CDCl_3$) δ: 1.75 (6H, s), 2.37 (1H, s), 4.13 (2H, t, J = 4.3 Hz), 4.39 (2H, t, J = 4.3 Hz), 6.15 (1H, d, J = 3.3 Hz), 6.25 (1H, br s), 6.45 (1H, br s), 6.98-7.03 (2H, m), 7.08-7.14 (1H, m), 7.31-7.45 (4H, m), 7.78 (1H, d, J = 2.5 Hz), 8.23 (1H, s), 9.62 (1H, br s).

Ejemplo C-65



Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-etilciclohexil)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), 1-etilciclohexanoamina (153 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), monohidrato de 1-hidroxibenzotriazol (92 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-59, se obtuvo el compuesto del título (136 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.84 (3H, t, J = 7.4 Hz), 1.20-1.70 (8H, m), 1.88 (2H, q, J = 7.4 Hz), 2.10-2.21 (2H, m), 4.12 (2H, t, J = 4.5 Hz), 4.38 (2H, t, J = 4.5 Hz), 5.70 (1H, br s), 6.15 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.99 (1H, d, J = 3.0 Hz), 7.02 (1H, d, J = 8.8 Hz), 7.04-7.11 (1H, m),

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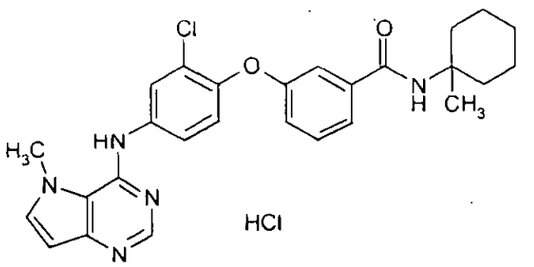
7.30-7.44 (4H, m), 7.80 (1H, d, J = 2.5 Hz), 8.23 (1H, s), 9.64 (1H, br s).

Ejemplo C-66



Producción de clorhidrato de 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}-N-(1-metilciclohexil)benzamida

Al usar ácido 3-{2-cloro-4-[(5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzoico (197 mg), clorhidrato de 1-metilciclohexanoamina (150 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (144 mg), monohidrato de 1-hidroxibenzotriazol (115 mg), trietilamina (0.139 ml) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-63, se obtuvo el compuesto del título (178 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.18-1.57 (8H, m), 1.31 (3H, s), 2.13-2.29 (2H, m), 4.29 (3H, s), 6.62-6.65 (1H, m), 7.16 (1H, dd, J = 2.6 Hz, 8.1 Hz), 7.28 (1H, d, J = 8.8 Hz), 7.33 (1H, m), 7.48 (1H, t, J = 8.0 Hz), 7.55-7.68 (3H, m), 7.91-7.98 (2H, m), 8.71 (1H, s), 9.78-9.94 (1H, m).

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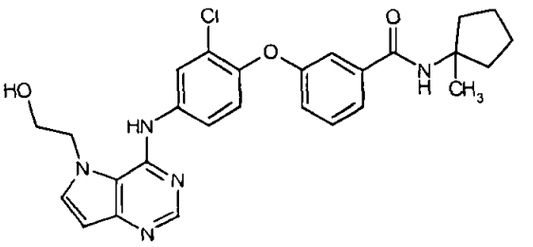
Ejemplo C-67



Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-metilciclopentil)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (212 mg), clorhidrato de 1-metilciclopentanoamina (136 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (144 mg), 1-hidroxibenzotriazol (101 mg), trietilamina (0.139 ml) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-59, se obtuvo el compuesto del título (162 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (3H, s), 1.65-1.82 (6H, m), 1.98-2.13 (2H, m), 4.12 (2H, t, J = 4.4 Hz), 4.39 (2H, t, J = 4.4 Hz), 6.06 (1H, br s), 6.17 (1H, d, J = 3.0 Hz), 6.52 (1H, br s), 7.00 (1H, d, J = 3.0 Hz), 7.01 (1H, d, J = 8.8 Hz), 7.05-7.12 (1H, m), 7.30-7.37 (3H, m), 7.41 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.6 Hz), 8.24 (1H, s), 9.66 (1H, br s).

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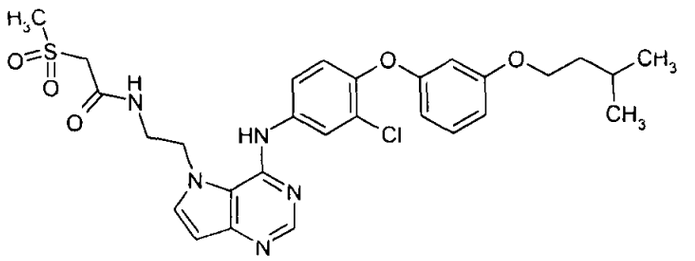
Ejemplo C-68



Producción de N-{2-[4-({3-cloro-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 3-cloro-4-[3-(3-metilbutoxi)fenoxi]anilina

A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (1.0 g) y 1-yodo-3-metilbutano (1.0 ml) en N,N-dimetilformamida (20 ml) se añadió carbonato de cesio (1.6 g) y la mezcla se agitó a temperatura ambiente durante 2 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (25 ml), se añadieron hierro reducido (1.60 g) y cloruro de calcio (220 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al

residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1) para dar el compuesto del título (806 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 0.89-0.92 (6H, m), 1.53-1.60 (2H, m), 1.70-1.79 (1H, m), 3.91-3.95 (2H, m), 5.33 (2H, s), 6.31-6.33 (2H, m), 6.53-6.60 (2H, m), 6.71-6.72 (1H, m), 6.88-6.91 (1H, m), 7.14-7.20 (1H, m).

(ii) Producción de N-{2-[4-({3-cloro-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-[3-(3-metilbutoxi)fenoxi]anilina (250 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (250 mg), alcohol isopropílico (20 ml), acetato de etilo (10 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (15 ml), ácido metilsulfonilacético (72 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (187 mg), 1-hidroxibenzotriazol (10 mg), trietilamina (1.5 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (277 mg) en forma de cristales.

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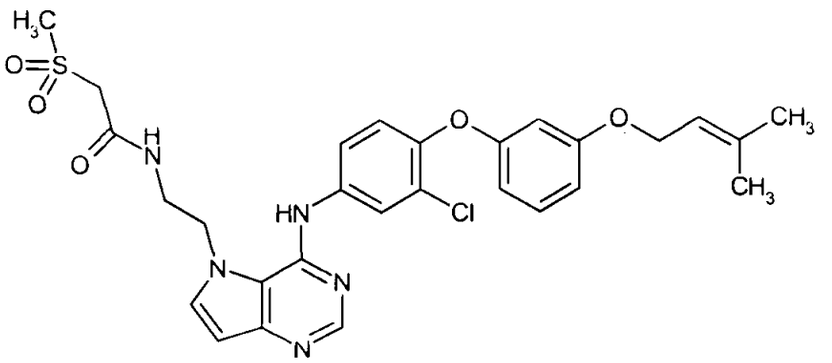
^{1}H-RMN (DMSO-d_6) δ: 0.91-0.93 (6H, m), 1.56-1.78 (3H, m), 3.10 (3H, s), 3.42-3.49 (2H, m), 3.95-4.05 (4H, m), 4.52-4.60 (2H, m), 6.43-6.70 (4H, m), 7.16-7.94 (5H, m), 8.34 (1H, s), 8.64-8.68 (2H, m).

Ejemplo C-69



Producción de N-(2-{4-[(3-cloro-4-{3-[(3-metilbut-2-en-1-il)oxi]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de 3-cloro-4-{3-[(3-metilbut-2-en-1-il)oxi]fenoxi}anilina

A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (1.0 g) y 1-bromo-3-metilbut-2-eno (1.5 ml) en N,N-dimetilformamida (20 ml) se añadió carbonato de cesio (1.8 g) y la mezcla se agitó a temperatura ambiente durante 2 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel

de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (25 ml), se añadieron hierro reducido (1.60 g) y cloruro de calcio (220 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1) para dar el compuesto del título (730 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 1.62-1.71 (6H, m), 4.42-4.47 (2H, m), 5.32-5.36 (1H, m), 6.32-6.35 (2H, m), 6.56-6.59 (2H, m), 6.71-6.72 (1H, m), 6.87-6.90 (1H, m), 7.13-7.19 (1H, m).

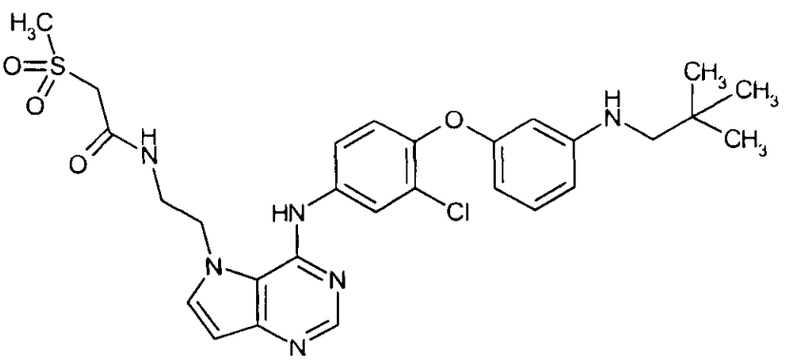
(ii) Producción de N-(2-{4-[(3-cloro-4-{3-[(3-metilbut-2-en-1-il)oxi]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-{3-[(3-metilbut-2-en-1-il)oxi]fenoxi}anilina (150 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (150 mg), alcohol isopropílico (16 ml), acetato de etilo (10 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5 ml), ácido metilsulfonilacético (120 mg), clorhidrato de 1-etil-3-

(3-dimetilaminopropil)carbodiimida (470 mg), 1-hidroxibenzotriazol (10 mg), trietilamina (1.5 ml) y N,N-dimetilformamida (15 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (108 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.75-1.79 (6H, m), 3.10 (3H, s), 3.40-3.52 (2H, m), 4.03 (2H, s), 4.47-4.60 (4H, m), 5.40-5.51 (1H, m), 6.40-6.70 (4H, m), 7.15-7.95 (5H, m), 8.35 (1H, s), 8.62-8.70 (2H, m).

Ejemplo C-70



Producción de N-(2-{4-[(3-cloro-4-{3-[(2,2-dimetilpropil)amino]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de 3-(2-cloro-4-nitrofenoxi)-N-(2,2-dimetilpropil)anilina

Se suspendió clorhidrato de 3-(2-cloro-4-nitrofenoxi)anilina (1.98 g) en tetrahidrofurano (80 ml), y a ello se añadieron trietilamina (0.87 ml), ácido acético (6.0 ml) y pivalaldehido (2.10 g), y la mezcla se agitó durante 30

min. Se agregó triacetoxiborohidruro de sodio (470 mg), y la mezcla se siguió agitando durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 95:5→1:1) para dar el compuesto del título (1.79 g) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 0.99 (9H, s), 2.89 (2H, s), 6.31-6.54 (3H, m), 6.89-7.26 (3H, m), 8.01-8.09 (1H, m), 8.37 (1H, s).

(ii) Producción de 3-cloro-4-{3-[(2,2-dimetilpropil)amino]fenoxi}anilina

Se disolvió 3-(2-cloro-4-nitrofenoxi)-N-(2,2-dimetilpropil)anilina (1.0 g) en 15% de etanol con contenido de agua (30 ml), se añadieron hierro reducido (800 mg) y cloruro de calcio (100 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente,

hexano:acetato de etilo = 4:1→1:1) para dar el compuesto del titulo (737 mg) en forma de un aceite marrón.

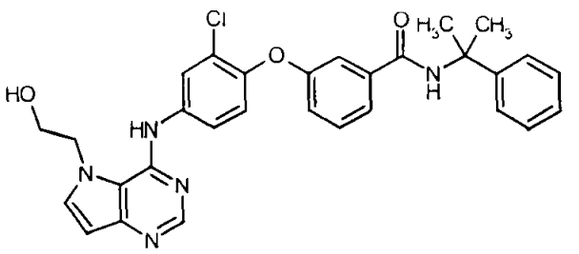
^{1}H-RMN (DMSO-d_6) δ: 0.95 (9H, s), 2.78-2.82 (2H, m), 6.31-6.54 (3H, m), 6.89-7.26 (3H, m), 8.01-8.09 (1H, m), 8.37 (1H, s).

(iii) Producción de N-(2-{4-[(3-cloro-4-{3-[(2,2-dimetilpropil)amino]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-{3-[(2,2-dimetilpropil)amino]fenoxi}anilina (73 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (71 mg), alcohol isopropílico (5 ml), acetato de etilo (10 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (10 ml), ácido metilsulfonilacético (61 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (220 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (1.5 ml) y N,N-dimetilformamida (7.0 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del titulo (48 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.93 (9H, s), 2.76-2.79 (2H, m), 3.10 (3H, s), 3.42-3.48 (2H, m), 4.05 (2H, s), 4.53-4.59 (2H, m), 5.61-6.50 (5H, m), 6.98-7.12 (2H, m), 7.61-7.91 (3H, m), 8.33 (1H, s), 8.64-8.68 (2H, m).

Ejemplo C-71

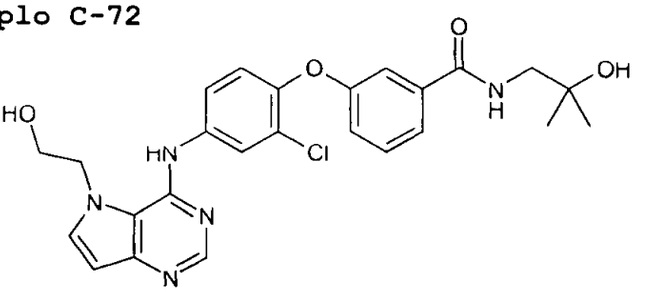


Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-metil-1-feniletil)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), cumilamina (108 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), 1-hidroxibenzotriazol (81 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-59, se obtuvo el compuesto del título (139 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.79 (6H, s), 4.02 (2H, t, J = 4.5 Hz), 4.32 (2H, t, J = 4.5 Hz), 6.16 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.95-7.00 (2H, m), 7.07-7.13 (1H, m), 7.17-7.46 (9H, m), 7.77 (1H, d, J = 2.5 Hz), 8.22 (1H, s), 9.66 (1H, br s).

Ejemplo C-72



Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(2-hidroxi-2-metilpropil)benzamida

(i) Producción de 3-(2-cloro-4-nitrofenoxi)-N-(2-hidroxi-2-metilpropil)benzamida

Se disolvió ácido 3-(2-cloro-4-nitrofenoxi)benzoico (500 mg) en un solvente mixto de tetrahidrofurano (5 ml)/N,N-dimetilformamida (5 ml), y 1-amino-2-metilpropan-2-ol (199 mg), se añadieron sucesivamente 1-hidroxibenzotriazol (347 mg), trietilamina (0.7 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (496 mg), y la mezcla se agitó a temperatura ambiente durante 2.5 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 33:67→0:100) para dar el compuesto del título (448 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.30 (6H, s), 3.48 (2H, d, J= 5.8 Hz), 6.60 (1H, br s), 6.92 (1H, d, J= 9.1 Hz), 7.19-7.25 (1H, m), 7.47-7.58 (2H, m), 7.61-7.69 (1H, m), 8.07 (1H, dd, J= 2.8 Hz, 9.1 Hz), 8.39 (1H, d, J= 2.8 Hz).

(ii) Producción de 3-(4-amino-2-clorofenoxi)-N-(2-hidroxi-2-metilpropil)benzamida

Se disolvió 3-(2-cloro-4-nitrofenoxi)-N-(2-hidroxi-2-metilpropil)benzamida (446 mg) en un solvente mixto de etanol (13.5 ml)/agua (1.5 ml), se añadieron hierro reducido (347 mg) y cloruro de calcio (68 mg), y la mezcla se agitó con calentamiento a reflujo durante 15 h. La mezcla de reacción se filtró a través de celite, y el filtrado se concentró a presión reducida. El residuo se disolvió en acetato de etilo, y la solución se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 33:67→0:100) para dar el compuesto del título (349 mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.27 (6H, s), 2.38 (1H, br s), 3.44 (2H, d, J= 6.0 Hz), 3.71 (2H, br s), 6.53-6.64 (1H, m), 6.57 (1H, dd, J= 2.8 Hz, 8.7 Hz), 6.78 (1H, d, J= 2.8 Hz), 6.90 (1H, d, J= 8.7 Hz), 6.97-7.03 (1H, m), 7.29-7.37 (2H, m), 7.38-7.44 (1H, m).

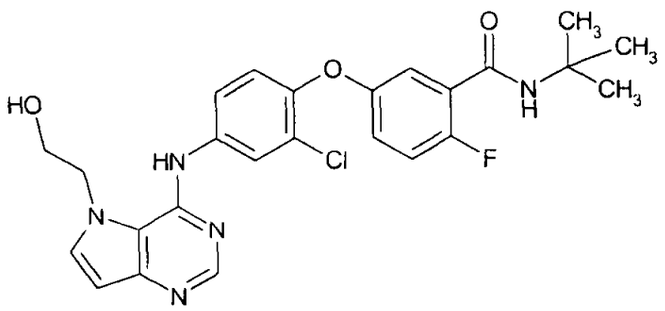
(iii) Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(2-hidroxi-2-metilpropil)benzamida

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (84.3 mg) y 3-(4-amino-2-clorofenoxi)-N-(2-hidroxi-2-metilpropil)benzamida (110 mg) se disolvió en alcohol isopropílico (2 ml), se añadió una

cantidad catalítica de clorhidrato de piridina, y la mezcla se agitó a 70°C durante 16 h. Tras enfriar hasta temperatura ambiente, se agregó solución acuosa 1 N de hidróxido de sodio (1 ml), y la mezcla se agitó a temperatura ambiente durante 9 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 10:90→0:100→acetato de etilo:metanol = 90:10), y se cristalizó en éter diisopropílico/acetato de etilo para dar el compuesto del título (99.7 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.09 (6H, s), 3.23 (2H, d, J= 6.0 Hz), 3.87 (2H, t, J= 4.5 Hz), 4.47-4.61 (3H, m), 6.30 (1H, br s), 6.51 (1H, d, J= 3.0 Hz), 7.05-7.13 (1H, m), 7.24 (1H, d, J= 8.9 Hz), 7.36-7.42 (1H, m), 7.46 (1H, t, J= 7.9 Hz), 7.56-7.64 (2H, m), 7.66 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 2.6 Hz), 8.31 (1H, t, J= 6.0 Hz), 8.34 (1H, s), 9.87 (1H, br s).

Ejemplo C-73

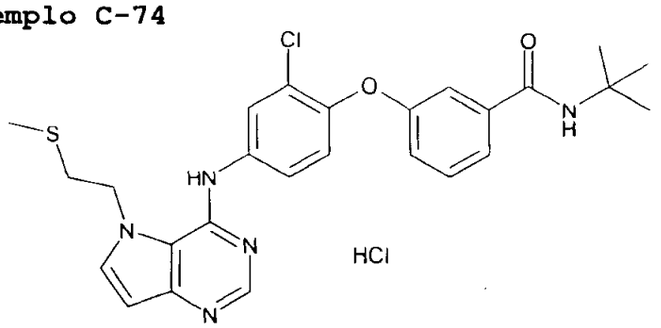


Producción de N-(ter-butil)-5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida

Al usar 5-(4-amino-2-clorofenoxi)-N-(ter-butil)-2-fluorobenzamida (260 mg), benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (150 mg), alcohol isopropílico (7.0 ml), solución acuosa 1 N de hidróxido de sodio (4.0 ml) y metanol (10 ml) y de la misma manera que en el Ejemplo C-57, se obtuvo el compuesto del título (285 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.33 (9H, s), 3.85-3.89 (2H, m), 4.51-4.54 (2H, m), 6.50-7.29 (5H, m), 7.58-7.97 (4H, m), 8.33 (1H, s), 9.76(1H, br s).

Ejemplo C-74



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Producción de clorhidrato de N-(ter-butil)-3-[2-cloro-4-({5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

(i) Producción de 4-cloro-5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidina

Una mezcla de 4-cloro-5H-pirrolo[3,2-d]pirimidina (768 mg), 2-cloroetilmetilsulfuro (664 mg), carbonato de cesio (1.95 g) y N,N-dimetilformamida (10 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida. A una mezcla del residuo obtenido, carbonato de cesio (3.91 g) y N,N-dimetilformamida (10 ml) se añadió gota a gota una solución de 2-cloroetilmetilsulfuro (553 mg) en N,N-dimetilformamida (3 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Una solución de 2-cloroetilmetilsulfuro (553 mg) en N,N-dimetilformamida (3 ml) se añadió nuevamente gota a gota y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice

885.

(eluyente, acetato de etilo:hexano = 40:60→60:40). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (880 mg) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.04 (3H, s), 2.95 (2H, t, J = 6.9 Hz), 4.67 (2H, t, J = 6.9 Hz), 6.75 (1H, d, J = 3.2 Hz), 7.56 (1H, d, J = 3.2 Hz), 8.71 (1H, s).

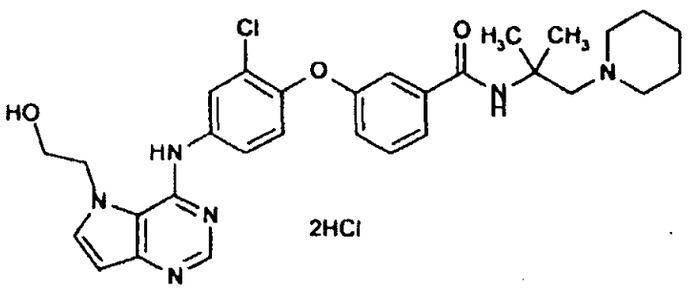
(ii) Producción de clorhidrato de N-(ter-butil)-3-[2-cloro-4-({5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

Una mezcla de 4-cloro-5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidina (455 mg), 3-(4-amino-2-clorofenoxi)-N-(ter-butil)benzamida (638 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida para dar N-(ter-butil)-3-[2-cloro-4-({5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida (1.00 g) en forma de un polvo amorfo. La N-(ter-butil)-3-[2-cloro-4-({5-[2-(metiltio)etil]-

5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida obtenida (200 mg) se disolvió en acetato de etilo-etanol, y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.5 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (138 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 1.99 (3H, s), 2.88 (2H, t, J = 6.4 Hz), 4.92 (2H, t, J = 6.4 Hz), 6.69 (1H, d, J = 3.2 Hz), 7.16 (1H, dd, J = 3.0 Hz, 7.7 Hz), 7.24 (1H, d, J = 8.8 Hz), 7.36-7.39 (1H, m), 7.47 (1H, t, J = 8.0 Hz), 7.57-7.65 (2H, m), 7.84 (1H, br s), 7.92 (1H, d, J = 2.5 Hz), 8.06 (1H, d, J = 3.2 Hz), 8.73 (1H, s), 10.06 (1H, br s).

Ejemplo C-75



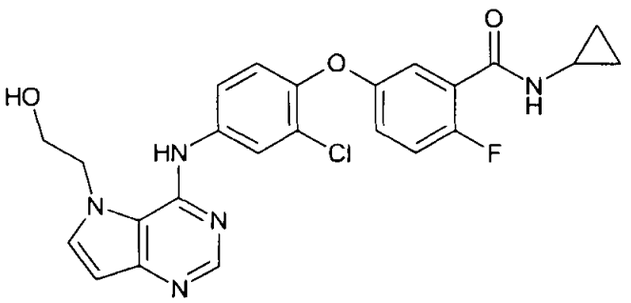
Producción de diclorhidrato de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1,1-dimetil-2-(piperidin-1-il)etil)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), 2-metil-1-(piperidin-1-il)propan-2-amina (125 mg),

clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), 1-hidroxibenzotriazol (81 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-63, se obtuvo el compuesto del título (136 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.33-2.00 (6H, m), 1.51 (6H, s), 2.91-3.09 (2H, m), 3.27-3.62 (4H, m), 3.90 (2H, t, J = 4.5 Hz), 4.71 (2H, t, J = 4.5 Hz), 6.30-6.65 (1H, m), 6.71 (1H, d, J = 3.0 Hz), 7.15 (1H, dd, J = 2.3, 7.8 Hz), 7.30 (1H, d, J = 8.9 Hz), 7.45-7.53 (2H, m), 7.62 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.73 (1H, d, J = 7.7 Hz), 7.96 (1H, d, J = 2.5 Hz), 8.02 (1H, d, J = 3.0 Hz), 8.17 (1H, br s), 8.76 (1H, s), 9.70 (1H, br s), 10.88 (1H, br s).

Ejemplo C-76



Producción de 5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-ciclopropil-2-fluorobenzamida

(i) Producción de 5-[4-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-2-fluorobenzoato de metilo

Al usar 5-(4-amino-2-clorofenoxi)-2-fluorobenzoato de metilo (1.50 g), benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (1.53 g) y alcohol isopropílico (15 ml) y de la misma manera que en el Ejemplo C-2(v), se obtuvo el compuesto del título (2.12 g) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.80 (3H, s), 4.54-4.57 (2H, m), 4.94-4.97 (2H, m), 6.56 (1H, s), 7.21-7.79 (12H, m), 8.32 (1H, s), 8.78 (1H, br s).

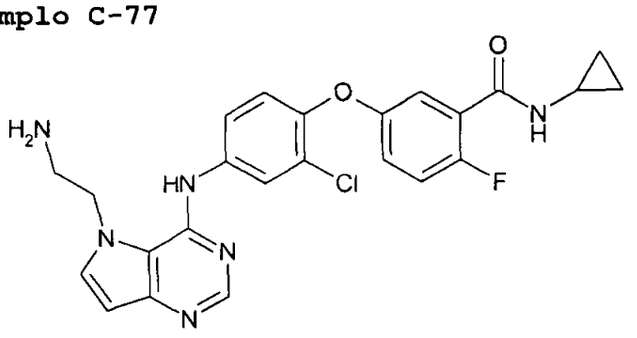
(ii) Producción de 5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-ciclopropil-2-fluorobenzamida

Al usar 5-[4-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-2-fluorobenzoato de metilo (200 mg), solución acuosa 1 N de hidróxido de sodio (3.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-2(v), se obtuvo un compuesto. El compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-9(v) y se usó ciclopropanamina (60 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (200 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (1.5 ml) y N,N-dimetilformamida (5.0 ml) para dar el compuesto del título (101 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.52-0.71 (4H, m), 2.77-2.83 (1H, m), 3.86-3.89 (2H, m), 4.52-4.55 (2H, m), 6.15-6.51 (2H,

m), 7.01-7.97 (7H, m), 8.33 (1H, s), 8.37-8.38 (1H, m), 9.84(1H, br s).

Ejemplo C-77



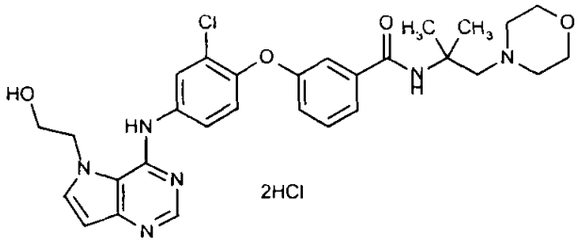
Producción de 5-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-ciclopropil-2-fluorobenzamida

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (286 mg), 5-(4-amino-2-clorofenoxi)-N-ciclopropil-2-fluorobenzamida (310 mg) y alcohol isopropílico (5.0 ml) se agitó a 80°C durante 12 h. Bajo enfriamiento con hielo, se añadió bicarbonato de sodio acuoso a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). El producto crudo obtenido se disolvió en metanol (10 ml), se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), y la mezcla se agitó a 70°C durante 20 h. Se agregaron acetato de etilo e carbonato ácido de sodio acuoso

saturado, y la capa orgánica se secó sobre sulfato de magnesio. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 10:90→0:100→acetato de etilo:metanol = 90:10), y se cristalizó en éter diisopropílico/acetato de etilo para dar el compuesto del título (356 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.53-0.70 (4H, m), 2.77-2.85 (1H, m), 3.06 (2H, br s), 4.36 (2H, br s), 5.95 (2H, br s), 6.48-8.01 (8H, m), 8.31 (1H, s), 8.37-8.38 (1H, m).

Ejemplo C-78



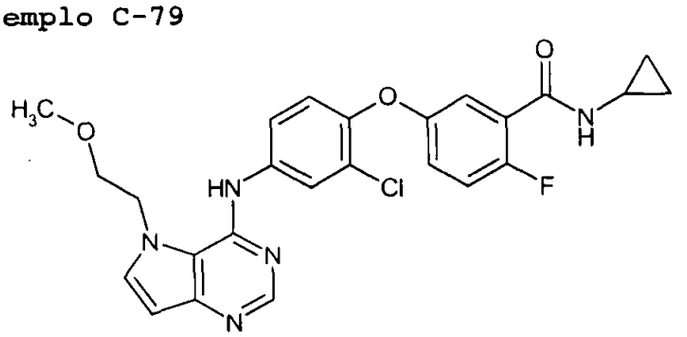
Producción de diclorhidrato de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1,1-dimetil-2-(morfolin-4-il)etil)benzamida

Al usar ácido 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico (170 mg), 2-metil-1-(morfolin-4-il)propan-2-amina (127 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (115 mg), 1-hidroxibenzotriazol (81 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-63, se obtuvo el compuesto del título (128 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.52 (6H, s), 3.00-4.20 (12H,

m), 4.70 (2H, m), 6.20-6.70 (1H, m), 6.71 (1H, d, J = 3.0 Hz), 7.15 (1H, dd, J = 2.5 Hz, 7.8 Hz), 7.29 (1H, d, J = 8.8 Hz), 7.44-7.54 (2H, m), 7.62 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.68-7.76 (1H, m), 7.95 (1H, d, J = 2.7 Hz), 8.01 (1H, d, J = 2.7 Hz), 8.15 (1H, br s), 8.75 (1H, s), 10.38 (1H, br s), 10.85 (1H, br s).

Ejemplo C-79

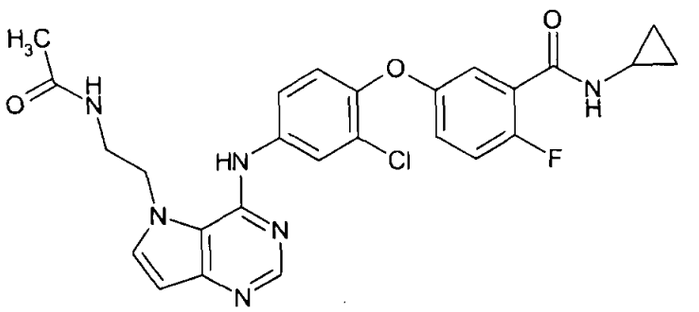


Producción de 5-(2-cloro-4-{[5-(2-metoxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-ciclopropil-2-fluorobenzamida

Al usar 5-(4-amino-2-clorofenoxi)-N-ciclopropil-2-fluorobenzamida (100 mg), 4-cloro-5-(2-metoxietil)-5H-pirrolo[3,2-d]pirimidina (66 mg) y alcohol isopropílico (5.0 ml) y de la misma manera que en el Ejemplo C-22(i), se obtuvo el compuesto del título (131 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.52-0.71 (4H, m), 2.77-2.83 (1H, m), 3.31 (3H, s), 3.72-3.75 (2H, m), 4.64-4.67 (2H, m), 6.50-7.95 (8H, m), 8.34 (1H, s), 8.37-8.39 (1H, m), 9.97(1H, br s).

Ejemplo C-80



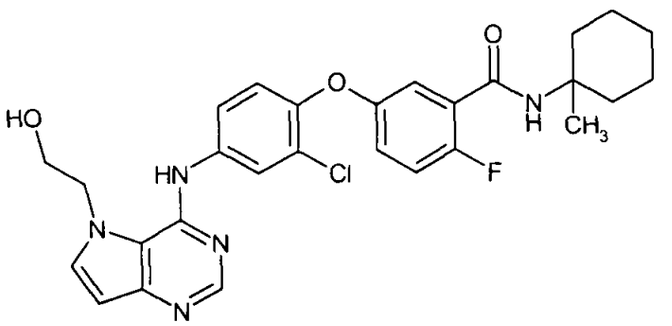
Producción de 5-[4-({5-[2-(acetilamino)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-N-ciclopropil-2-fluorobenzamida

Al usar 5-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)-N-ciclopropil-2-fluorobenzamida (100 mg), ácido acético (40 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (120 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (0.5 ml) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo C-23(v), se obtuvo el compuesto del título (71 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.52-0.71 (4H, m), 1.79 (3H, s), 2.79-2.82 (1H, m), 3.33-3.39 (2H, m), 4.48-4.53 (2H, m), 6.49-6.50 (1H, m), 7.02-7.32 (4H, m), 7.63-8.43 (6H, m), 8.79(1H, s).

893.

Ejemplo C-81

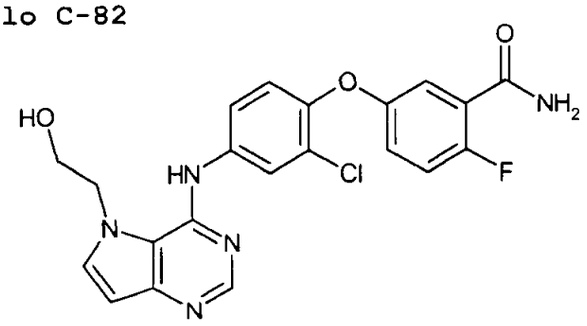


Producción de 5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluoro-N-(1-metilciclohexil)benzamida

Al usar 5-[4-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-2-fluorobenzoato de metilo (150 mg), solución acuosa 1 N de hidróxido de sodio (3.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-2(v), se obtuvo un compuesto. El compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-9(v) y se usó 1-metilciclohexanoamina (110 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (250 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (1.5 ml) y N,N-dimetilformamida (5.0 ml) para dar el compuesto del título (82 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.20-1.51 (13H, m), 2.14-2.18 (1H, m), 3.86-3.89 (2H, m), 4.52-4.56 (2H, m), 6.49-6.51 (1H, m), 7.17-7.68 (7H, m), 7.98 (1H, s), 8.34(1H, br s), 9.85 (1H, br s).

Ejemplo C-82

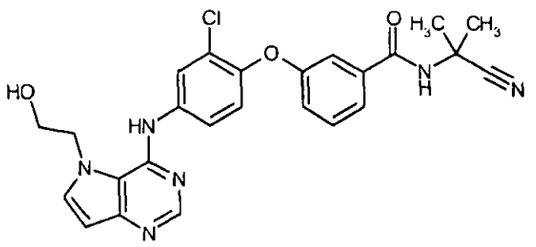


Producción de 5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida

Al usar 5-[4-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-2-fluorobenzoato de metilo (150 mg), solución acuosa 1 N de hidróxido de sodio (3.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-2(v), se obtuvo un compuesto. El compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-9(v) y se usó solución al 30% de amoníaco/metanol (5.0 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (300 mg), 1-hidroxibenzotriazol (30 mg), trietilamina (1.5 ml) y N,N-dimetilformamida (10 ml) para dar el compuesto del título (58 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.86-3.89 (2H, m), 4.52-4.56 (2H, m), 6.50-6.51 (1H, m), 7.22-8.04 (9H, m), 8.34(1H, br s), 9.86 (1H, br s).

Ejemplo C-83



Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-ciano-1-metiletil)benzamida

(i) Producción de N-[3-(2-cloro-4-nitrofenoxi)benzoil]-2-metilalaninato de metilo

Una mezcla de ácido 3-(2-cloro-4-nitrofenoxi)benzoico (1.47 g), cloruro de tionilo (1.00 ml), N,N-dimetilformamida (una gota) y tolueno (20 ml) se agitó a 80°C durante 2 h. Después de concentrar a presión reducida, se añadió tolueno, y la mezcla se volvió a concentrar a presión reducida. Una solución del residuo en tetrahidrofurano (5 ml) se añadió a una mezcla de clorhidrato de 2-aminoisobutirato de metilo (922 mg), trietilamina (1.67 ml) y tetrahidrofurano (10 ml) bajo enfriamiento con hielo, y la mezcla se agitó bajo enfriamiento con hielo durante 1 h y a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a

cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (1.72 g) en forma de un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.69 (6H, s), 3.79 (3H, s), 6.84 (1H, br s), 6.92 (1H, d, J = 9.2 Hz), 7.20-7.25 (1H, m), 7.48-7.54 (2H, m), 7.61-7.66 (1H, m), 8.08 (1H, dd, J = 2.7 Hz, 9.2 Hz), 8.40 (1H, d, J = 2.7 Hz).

(ii) Producción de N-[3-(2-cloro-4-nitrofenoxi)benzoil]-2-metilalanina

A N-[3-(2-cloro-4-nitrofenoxi)benzoil]-2-metilalaninato de metilo (1.72 g) se añadieron alcohol isopropílico (20 ml), tetrahidrofurano (5 ml) y solución acuosa 1 N de hidróxido de sodio (6 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió ácido clorhídrico 1 N (6.6 ml) a la mezcla de reacción, y el solvente se evaporó a presión reducida. Se añadió agua y el sólido precipitado se recogió por filtración, y se lavó con agua para dar el compuesto del título (1.53 g) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.45 (6H, s), 7.08 (1H, d, J = 9.1 Hz), 7.39 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.68 (1H, m), 7.83 (1H, d, J = 8.0 Hz), 8.20 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.50 (1H, d, J = 2.7 Hz), 8.55 (1H, br s).

(iii) Producción de 3-(2-cloro-4-nitrofenoxi)-N-(1-ciano-1-metiletil)benzamida

A una solución de N-[3-(2-cloro-4-nitrofenoxi)benzoil]-2-metilalanina (1.52 g) en N,N-dimetilformamida (20 ml) se añadieron clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (920 mg) y 1-hidroxibenzotriazol (649 mg) bajo enfriamiento con hielo, y la mezcla se agitó durante 1 h bajo enfriamiento con hielo. Se añadió amoníaco acuoso al 28% (1.4 ml) a la mezcla de reacción, y la mezcla se agitó bajo enfriamiento con hielo durante 1 h y a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con solución acuosa de hidróxido de sodio y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en acetato de etilo. El polvo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo). Las fracciones objeto se concentraron a presión reducida para dar N-(2-amino-1,1-dimetil-2-oxoetil)-3-(2-cloro-4-nitrofenoxi)benzamida (0.95 g) en forma de un polvo blanco. A una solución de la N-(2-amino-1,1-dimetil-2-oxoetil)-3-(2-cloro-4-nitrofenoxi)benzamida obtenida (0.95 g) y trietilamina (1.12 ml) en tetrahidrofurano (30 ml) se añadió

gota a gota una solución de anhídrido trifluoroacético (0.556 ml) en tetrahidrofurano (5 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante la noche. Se volvieron a agregar trietilamina (0.697 ml) y anhídrido trifluoroacético (0.348 ml) a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 15:85→50:50). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (419 mg) en forma de un polvo amorfo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.82 (6H, s), 6.21 (1H, br s), 6.93 (1H, d, J = 9.1 Hz), 7.22-7.27 (1H, m), 7.48-7.55 (2H, m), 7.58-7.63 (1H, m), 8.08 (1H, dd, J = 2.6, 9.1 Hz), 8.39 (1H, d, J = 2.6 Hz).

(iv) Producción de 3-(4-amino-2-clorofenoxi)-N-(1-ciano-1-metiletil)benzamida

A una solución de 3-(2-cloro-4-nitrofenoxi)-N-(1-ciano-1-metiletil)benzamida (419 mg) en acetato de etilo (10 ml) se añadió platino-carbón activado al 5% (20 mg) bajo una atmósfera de hidrógeno y la mezcla se agitó a temperatura

ambiente durante 6 h. El catalizador se filtró, el filtrado se concentró y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 30:70→60:40). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (283 mg) en forma de un polvo amorfo verde amarillento.

^{1}H-RMN ($CDCl_3$) δ: 1.80 (6H, s), 3.72 (2H, br s), 6.15 (1H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.4 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 8.4 Hz), 7.00-7.10 (1H, m), 7.25-7.40 (3H, m).

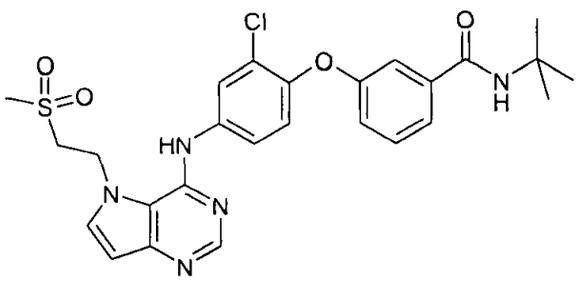
(v) Producción de 3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-N-(1-ciano-1-metiletil)benzamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (121 mg), 3-(4-amino-2-clorofenoxi)-N-(1-ciano-1-metiletil)benzamida (132 mg), alcohol isopropílico (5 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.8 ml) y de la misma manera que en el Ejemplo C-62(v), se obtuvo el compuesto del título (68 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.80 (6H, s), 4.13 (2H, t, J = 4.3 Hz), 4.38 (2H, t, J = 4.3 Hz), 6.24 (1H, d, J = 3.0 Hz), 6.50 (1H, br s), 6.97 (1H, d, J = 9.1 Hz), 7.06 (1H, d, J = 3.0 Hz), 7.13-7.20 (1H, m), 7.28-7.44 (4H, m), 7.76 (1H, d, J =

2.7 Hz), 8.24 (1H, s), 9.58 (1H, br s).

Ejemplo C-84



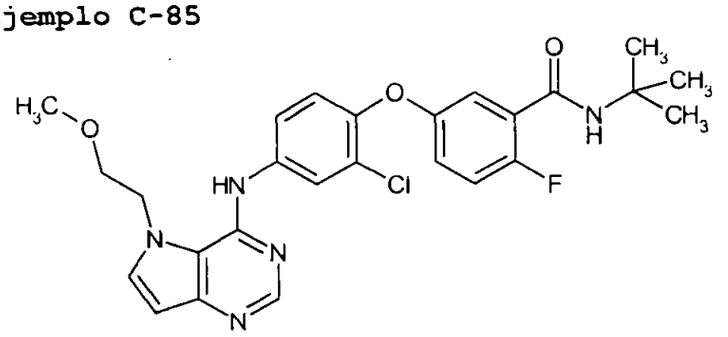
Producción de N-(ter-butil)-3-[2-cloro-4-({5-[2-(metilsulfonil)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida

A una solución de N-(ter-butil)-3-[2-cloro-4-({5-[2-(metiltio)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida (255 mg) en metanol (2 ml) se añadió una solución de compuesto OXONE® monopersulfatado (615 mg) en agua (1 ml) bajo enfriamiento con hielo. Se añadieron metanol (18 ml) y agua (9 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con solución acuosa al 5% de tiosulfato de sodio y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0→metanol:acetato de etilo→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se

cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (207 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 2.73 (3H, s), 3.67 (2H, t, J = 6.2 Hz), 4.87 (2H, t, J = 6.2 Hz), 5.95 (1H, br s), 6.74 (1H, d, J = 3.4 Hz), 7.00-7.12 (2H, m), 7.31-7.40 (4H, m), 7.48 (1H, dd, J = 2.7 Hz, 8.7 Hz), 7.86 (1H, d, J = 2.7 Hz), 7.97 (1H, br s), 8.56 (1H, s).

Ejemplo C-85



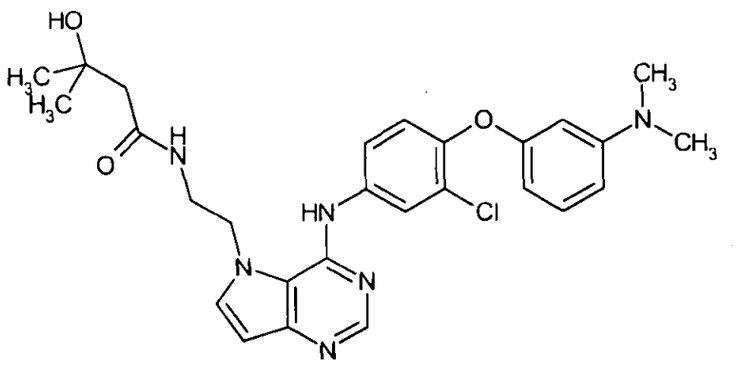
Producción de N-(ter-butil)-5-(2-cloro-4-{[5-(2-metoxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida

Al usar 5-(4-amino-2-clorofenoxi)-N-(ter-butil)-2-fluorobenzamida (60 mg), 4-cloro-5-(2-metoxietil)-5H-pirrolo[3,2-d]pirimidina (38 mg) y alcohol isopropílico (3.0 ml) y de la misma manera que en el Ejemplo C-22(i), se obtuvo el compuesto del título (84 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.32 (9H, s), 3.72-3.76 (2H, m), 3.80 (3H, s), 4.64-4.68 (2H, m), 6.51-7.99 (8H, m), 8.36 (1H, s), 9.01 (1H, s), 9.97(1H, br s).

962

Ejemplo C-86



Producción de N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

(i) Producción de 3-(4-amino-2-clorofenoxi)-N,N-dimetilanilina

Al usar 3-(dimetilamino)fenol (5.0 g), 3-cloro-4-fluoronitrobenceno (6.38 g), carbonato de potasio (5.38 g), N,N-dimetilformamida (100 ml), platino-carbón activado al 5% (0.73 g) y acetato de etilo (75 ml) y de la misma manera que en el Ejemplo C-1(i) y (ii), se obtuvo el compuesto del título (8.95 g).

^{1}H-RMN (DMSO-d_6) δ: 2.84 (6H, s), 5.27 (2H, s), 5.95-6.55 (4H, m), 6.69 (1H, d, J = 2.0 Hz), 6.86 (1H, d, J = 8.0 Hz), 7.04 (1H, t, J = 8.3 Hz).

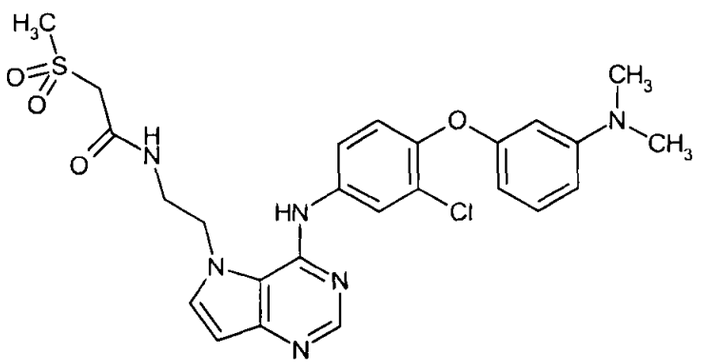
(ii) Producción de N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

Al usar 3-(4-amino-2-clorofenoxi)-N,N-

dimetilanilina (100 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (89 mg), alcohol isopropílico (5.0 ml), acetato de etilo (5.0 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), ácido 3-hidroxi-3-metilbutanoico (54 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (136 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (1.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (67 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.13 (6H, s), 2.20 (2H, s), 2.89 (6H, s), 3.38-3.44 (2H, m), 4.49-4.53 (2H, m), 4.66 (1H, s), 6.09-7.15 (6H, m), 7.62-8.26 (4H, m), 8.31 (1H, s), 8.81 (1H, s).

Ejemplo C-87



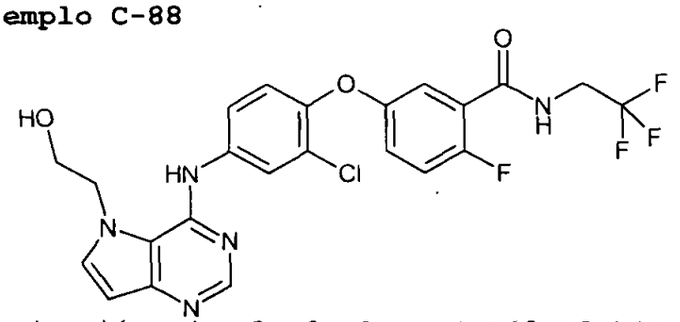
Producción de N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3-(4-amino-2-clorofenoxi)-N,N-

dimetilanilina (100 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (89 mg), alcohol isopropílico (5.0 ml), acetato de etilo (5.0 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), ácido metilsulfonilacético (52 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (141 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (1.0 ml) y tetrahidrofurano (10 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (74 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 2.89 (6H, s), 3.09 (3H, s), 3.44-3.47 (2H, m), 4.04 (2H, s), 4.51-4.59 (2H, m), 6.08-7.16 (6H, m), 7.60-7.91 (3H, m), 8.32 (1H, s), 8.61-8.69 (2H, m).

Ejemplo C-88



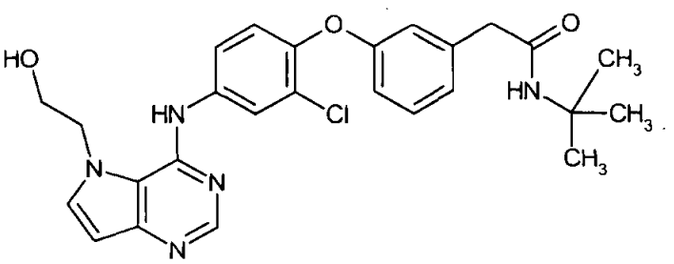
Producción de 5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluoro-N-(2,2,2-trifluoroetil)benzamida

Al usar 5-[4-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-2-clorofenoxi]-2-fluorobenzoato de metilo (100 mg), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y tetrahidrofurano (5.0 ml) y de

la misma manera que en el Ejemplo C-2(v), se obtuvo un compuesto. El compuesto obtenido se hizo reaccionar de la misma manera que en el Ejemplo C-9(v) y se usó 2,2,2-trifluoroetanoamina (70 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (220 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (0.5 ml) y N,N-dimetilformamida (5.0 ml) para dar el compuesto del título (52 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.86-3.90 (2H, m), 3.99-4.10 (2H, m), 4.52-4.56 (2H, m), 6.15-6.52 (1H, m), 7.24-7.99 (7H, m), 8.34 (1H, s), 9.13-9.17 (1H, m), 9.87(1H, br s).

Ejemplo C-89



Producción de N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]acetamida

(i) Producción de [3-(2-cloro-4-nitrofenoxi)fenil]acetato de bencilo

Al usar (3-hidroxifenil)acetato de bencilo (2.50 g), 3-cloro-4-fluoronitrobenceno (1.83 g), carbonato de potasio (1.90 g) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo C-1(i), se obtuvo el compuesto del

título (1.21 g) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 3.81(2H, s), 5.12 (2H, s), 7.00-7.25 (4H, m), 7.31-7.37 (5H, m), 7.43-7.48 (1H, m), 8.14-8.18 (1H, m), 8.46-8.47 (1H, m).

(ii) Producción de 2-[3-(4-amino-2-clorofenoxi)fenil]-N-(ter-butil)acetamida

A [3-(2-cloro-4-nitrofenoxi)fenil]acetato de bencilo (1.00 g) se añadieron solución acuosa 1 N de hidróxido de sodio (5.3 ml) y tetrahidrofurano (4 ml) y la mezcla se agitó a temperatura ambiente durante 21 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo obtenido, 2-metilpropan-2-amina (1.1 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (2.11 g), 1-hidroxibenzotriazol (30 mg), trietilamina (3.5 ml) y N,N-dimetilformamida (10 ml) se hicieron reaccionar de la misma manera que en el Ejemplo C-9(v), y el compuesto obtenido, platino-carbón activado al 5% (130 mg) y acetato de etilo (10 ml) se hicieron reaccionar de la misma manera que en el Ejemplo C-1(ii) para dar el compuesto del título (340 mg) en forma de un aceite de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.21 (9H, s), 3.61(2H, s), 5.27

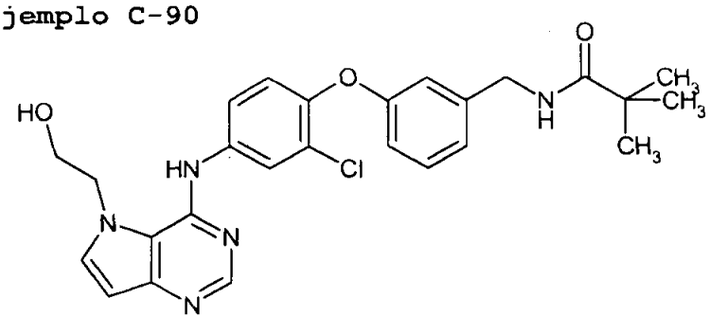
(2H, s), 5.92-6.59 (4H, m), 6.65-6.69 (1H, m), 6.87 (1H, d, J = 8.0 Hz), 7.13 (1H, t, J = 8.3 Hz).

(iii) Producción de N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]acetamida

Al usar 2-[3-(4-amino-2-clorofenoxi)fenil]-N-(ter-butil)acetamida (330 mg), benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (270 mg), alcohol isopropílico (20 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo C-57, se obtuvo el compuesto del título (115 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.22 (9H, s), 3.34-3.40 (2H, m), 3.84-3.92 (2H, m), 4.51-4.57 (2H, m), 6.30 (1H, br s), 6.51-7.30 (6H, m), 7.56-7.96 (4H, m), 8.36 (1H, s), 9.91(1H, br s).

Ejemplo C-90



Producción de N-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)bencil]-2,2-dimetilpropanamida

(i) Producción de N-[3-(4-amino-2-

clorofenoxi)bencil]-2,2-dimetilpropanamida

Al usar N-(3-hidroxibencil)-2,2-dimetilpropanamida (2.07 g), 3-cloro-4-fluoronitrobenceno (1.79 g), N,N-dimetilformamida (40 ml), carbonato de potasio (1.78 g), 15% de etanol con contenido de agua (23 ml), hierro reducido (750 mg) y cloruro de calcio (120 mg) y de la misma manera que en el Ejemplo C-53(i), se obtuvo el compuesto del título (1.73 g) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 1.09 (9H, s), 4.21-4.25 (2H, m), 5.26 (2H, s), 5.90-6.58 (4H, m), 6.64-6.68 (1H, m), 6.85-6.98 (1H, m), 7.13 (1H, t, J = 8.3 Hz).

(ii) Producción de N-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)bencil]-2,2-dimetilpropanamida

Al usar N-[3-(4-amino-2-clorofenoxi)bencil]-2,2-dimetilpropanamida (190 mg), benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (172 mg), alcohol isopropílico (5.0 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y metanol (5.0 ml) y de la misma manera que en el Ejemplo C-57, se obtuvo el compuesto del título (121 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.07 (9H, s), 3.86-3.89 (2H, m), 4.21-4.23 (2H, m), 4.51-4.55 (2H, m), 6.51-7.32 (6H, m), 7.56-8.06 (4H, m), 8.33 (1H, s), 9.82(1H, br s).

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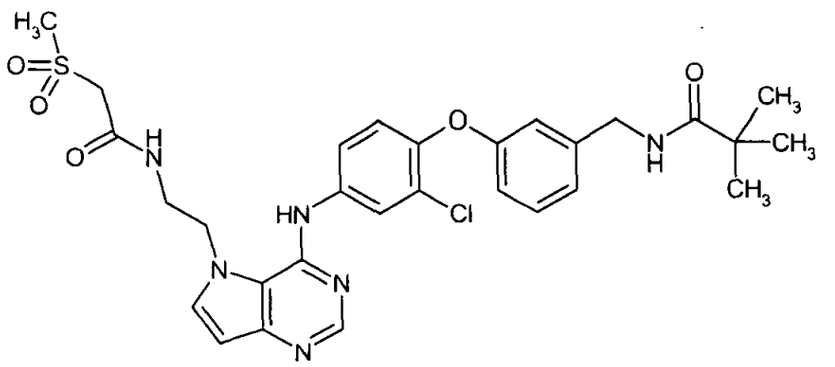
Ejemplo C-91

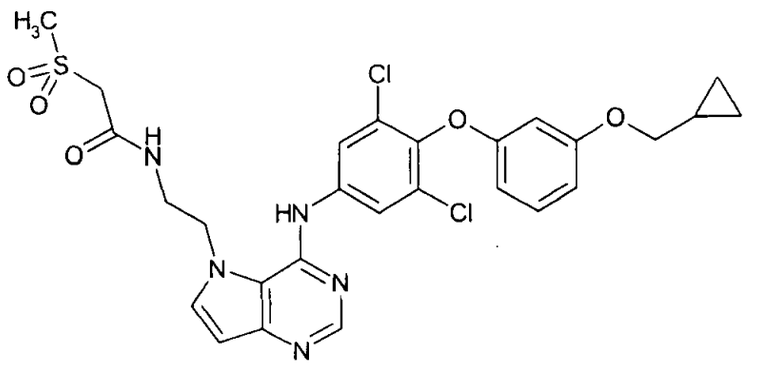


Producción de N-[3-(2-cloro-4-{[5-(2-{[(metilsulfonil)acetil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)bencil]-2,2-dimetilpropanamida

Al usar N-[3-(4-amino-2-clorofenoxi)bencil]-2,2-dimetilpropanamida (350 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (312 mg), alcohol isopropílico (11 ml), tetrahidrofurano (17 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (7.0 ml), ácido metilsulfonilacético (220 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (380 mg), 1-hidroxibenzotriazol (20 mg), trietilamina (4.0 ml) y N,N-dimetilformamida (15 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (263 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.08 (9H, s), 3.10 (3H, s), 3.45-3.49 (2H, m), 4.04 (2H, s), 4.22-4.24 (2H, m), 4.54-4.59 (2H, m), 6.48-7.33 (6H, m), 7.62-8.08 (4H, m), 8.34 (1H, s), 8.67(1H, br s).

Ejemplo C-92



Producción de N-{2-[4-({3,5-dicloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de benzoato de 3-(2.6-dicloro-4-nitrofenoxi)fenilo

A una solución de benzoato de 3-hidroxifenilo (675 mg) y 1,3-dicloro-2-yodo-5-nitrobenceno (1.0 g) en N,N-dimetilformamida (15 ml) se añadió carbonato de potasio (1.25 g) y la mezcla se agitó a temperatura ambiente durante 18 h. Bajo enfriamiento con hielo, a la mezcla de reacción se añadió salmuera, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1) para dar el compuesto del título (269 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 6.90-6.97 (2H, m), 7.07-7.10

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(1H, m), 7.44-7.77 (4H, m), 8.10-8.12 (2H, m), 8.55(2H, s).

(ii) Producción de 3,5-dicloro-4-[3-(ciclopropilmetoxi)fenoxi]anilina

Al benzoato de 3-(2.6-dicloro-4-nitrofenoxi)fenilo (269 mg) se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida. A una solución del residuo obtenido y 1-(bromometil)ciclopropano (0.78 ml) en N,N-dimetilformamida (15 ml) se añadió carbonato de potasio (430 mg) y la mezcla se agitó a temperatura ambiente durante 18 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (10 ml), se añadieron hierro reducido (250 mg) y cloruro de calcio (70 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se

añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→0:1) para dar el compuesto del título (112 mg) en forma de un aceite marrón.

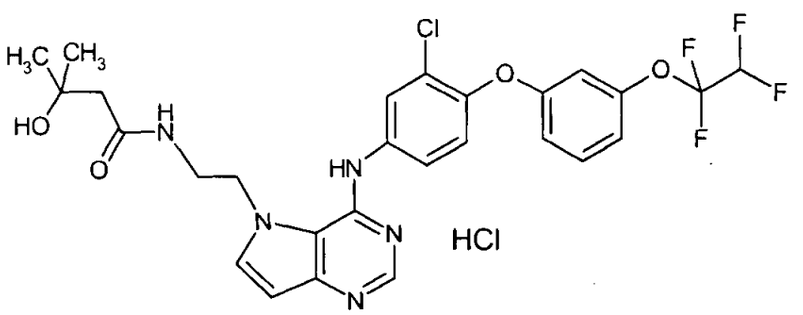
^{1}H-RMN (DMSO-d_6) δ: 0.30-0.57 (4H, m), 1.11-1.35 (1H, m), 3.79-3.81 (2H, m), 5.56 (2H, s), 5.90 (1H, dd, J = 2.0 Hz, 8.0 Hz), 6.22 (1H, t, J = 2.2 Hz), 6.36 (1H, dd, J = 2.0 Hz, 8.0 Hz), 6.71 (2H, s), 7.05 (1H, t, J = 8.3 Hz).

(iii) Producción de N-{2-[4-({3,5-dicloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3,5-dicloro-4-[3-(ciclopropilmetoxi)fenoxi]anilina (110 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (101 mg), alcohol isopropílico (5.0 ml), metanol (10 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml), ácido metilsulfonilacético (90 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (120 mg), 1-hidroxibenzotriazol (5.0 mg), trietilamina (0.8 ml) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (43 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.30-0.57 (4H, m), 1.11-1.35 (1H, m), 3.11 (3H, s), 3.40-3.50 (2H, m), 3.79-3.81 (2H, m), 4.07 (2H, s), 4.54-4.59 (2H, m), 6.32-6.67 (4H, m), 7.19-7.67 (2H, m), 8.02 (2H, s), 8.41 (1H, s), 8.68(1H, br s), 8.80 (1H, s).

Ejemplo C-93



Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

(i) Producción de 2-cloro-4-nitro-1-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]benceno

Una mezcla de 3-cloro-4-fluoronitrobenceno (5 g) y 3-(1,1,2,2-tetrafluoroetoxi)fenol (6 g) se disolvió en N,N-dimetilformamida (28 ml), se añadió carbonato de potasio (5.92 g), y la mezcla se agitó a temperatura ambiente durante 15 h. Se agregó agua (200 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (200 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se

purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→60:40) para dar el compuesto del título (10 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 5.91 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.90-7.10 (3H, m), 7.10-7.15 (1H, m), 7.44 (1H, t, J= 8.0 Hz), 8.10 (1H, dd, J= 3.0 Hz, 9.0 Hz), 8.39 (1H, d, J= 3.0 Hz).

(ii) Producción de 3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina

Una mezcla de 2-cloro-4-nitro-1-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]benceno (10 g), hierro reducido (10.2 g) y cloruro de calcio (1.7 g) en etanol (270 ml)/agua (30 ml) se agitó con calentamiento a 90°C durante 16 h. Tras enfriar hasta temperatura ambiente, la mezcla se filtró a través de celite. El filtrado se concentró a presión reducida, y el residuo se dividió en acetato de etilo (300 ml)/salmuera saturada (200 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→60:40) para dar el compuesto del título (7.91 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.70 (2H, br s), 5.87 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.58 (1H, dd, J= 3.0 Hz, 8.0 Hz), 6.70-6.85 (3H, m), 6.85-7.00 (2H, m), 7.26 (1H, t, J= 8.0 Hz).

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(iii) Producción de {2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Se disolvieron [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.0 g) y 3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina (1.70 g) en alcohol isopropílico (10 ml), y la mezcla se agitó a 80°C durante 20 h. Se añadió una solución saturada acuosa de carbonato ácido de sodio (50 ml) a la mezcla de reacción y la mezcla se extrajo con acetato de etilo (100 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 80:20→0:100) para dar el compuesto del título (2.04 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 1.49 (9H, s), 3.40-3.60 (2H, m), 4.40-4.60 (2H, m), 5.11 (1H, t, J= 6.0 Hz), 5.89 (1H, tt, J= 3.0 Hz, 53.0 Hz), 6.60 (1H, d, J= 3.0 Hz), 6.80-7.00 (3H, m), 7.09 (1H, d, J= 9.0 Hz), 7.19 (1H, d, J= 3.0 Hz), 7.31 (1H, t, J= 8.0 Hz), 7.89 (1H, dd, J= 3.0 Hz, 9.0 Hz), 8.03 (1H, d, J= 3.0 Hz), 8.52 (1H, s), 8.64 (1H, br s).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

9L6

Se disolvió {2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (1.98 g) en tetrahidrofurano (47.2 ml), se agregó ácido clorhídrico 2 N (23.6 ml), y la mezcla se agitó a 60°C durante 15 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en etanol (50 ml), y la mezcla se volvió a concentrar a presión reducida. Esta operación se repitió dos veces. El sólido residual se filtró con alcohol isopropílico y se secó para dar el compuesto del título (1.65 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.20-3.40 (2H, m), 5.00-5.10 (2H, m), 6.60-7.00 (4H, m), 7.35 (1H, d, J= 9.0 Hz), 7.51 (1H, t, J= 9.0 Hz), 7.60-7.70 (1H, m), 7.94 (1H, d, J= 2.4 Hz), 8.11 (1H, d, J= 3.0 Hz), 8.40 (3H, br s), 8.75 (1H, s).

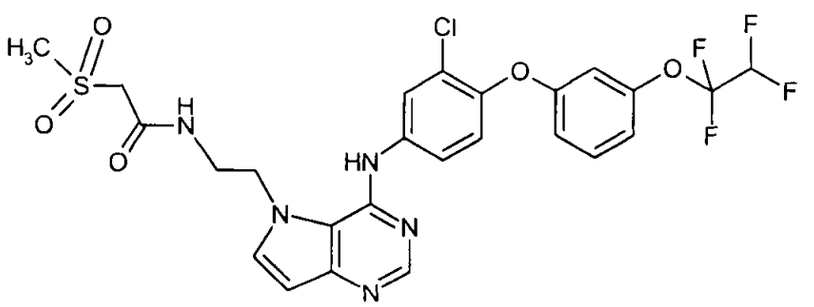
(v) Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

Se agitaron diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (204 mg), ácido 3-hidroxi-3-metilbutanoico (63.5 mg), N,N-dimetilformamida (6.9 ml), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida

(103 mg) a temperatura ambiente durante 16 h. La mezcla se dividió en acetato de etilo (80 ml)/agua (50 ml), la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15) y cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15). El residuo se disolvió en acetato de etilo (5 ml), se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo (0.18 ml), y se cristalizó en éter diisopropílico/acetato de etilo para dar el compuesto del título (134 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.11 (6H, s), 2.20 (2H, s), 3.44-3.56 (2H, m), 4.68 (2H, t, J= 6.0 Hz), 6.60-7.10 (5H, m), 7.35 (1H, d, J= 9.0 Hz), 7.51 (1H, t, J= 8.0 Hz), 7.73 (1H, dd, J= 3.0 Hz, 9.0 Hz), 7.98 (2H, dd, J= 3.0 Hz, 7.0 Hz), 8.43 (1H, m), 8.74 (1H, s).

Ejemplo C-94



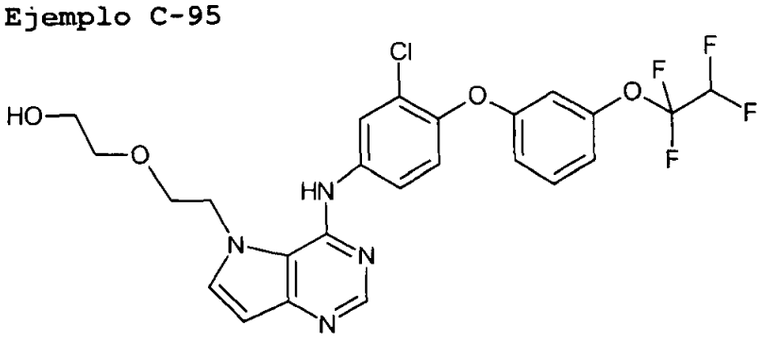
Producción de N-{2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-

d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Se agitaron diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (204 mg), ácido metilsulfonilacético (74.2 mg), N,N-dimetilformamida (6.9 ml), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg) a temperatura ambiente durante 16 h. La mezcla se dividió en acetato de etilo (80 ml)/agua (50 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15) y cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15) para dar el compuesto del título (140 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.10 (3H, s), 3.40-3.50 (2H, m), 4.05 (2H, s), 4.56 (2H, t, J= 7.0 Hz), 6.50 (1H, d, J= 3.0 Hz), 6.60-7.10 (4H, m), 7.29 (1H, d, J= 9.0 Hz), 7.47 (1H, t, J= 8.0 Hz), 7.63 (1H, d, J= 3.0 Hz), 7.76 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.35 (1H, s), 8.68 (1H, m), 8.71 (1H, br s).

Ejemplo C-95



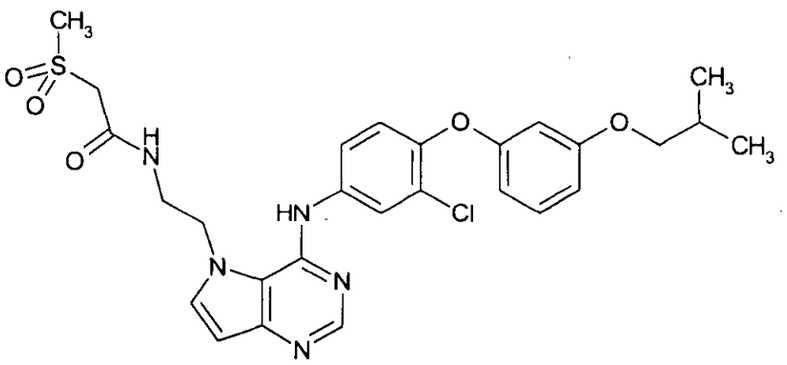
Producción de 2-{2-[4-({3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Se agitaron benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (150 mg) y 3-cloro-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina (217 mg) en alcohol isopropílico (3 ml) a 80°C durante 16 h. una solución saturada acuosa de carbonato ácido de sodio (40 ml) se añadió a la mezcla de reacción y la mezcla se extrajo con acetato de etilo (80 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→0:100). El residuo oleoso obtenido se disolvió en metanol (1.89 ml), se añadió solución acuosa 1 N de hidróxido de sodio (0.433 ml) y la mezcla se agitó a temperatura ambiente y se agitó durante 1 h. Se adicionó ácido clorhídrico 1 N (0.433 ml) a la mezcla y la mezcla se dividió en acetato de etilo (50 ml) y salmuera saturada (20 ml). La capa orgánica se secó sobre sulfato de

magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→90:10) y cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→90:10) para dar el compuesto del título (136 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6)δ: 3.49 (4H, br s), 3.83 (2H, t, J= 4.5 Hz), 4.64 (2H, t, J= 4.5 Hz), 4.73 (1H, t, J= 4.5 Hz), 6.52 (1H, d, J= 3.0 Hz), 6.76 (1H, m), 6.79 (1H, tt, J= 3.0 Hz, 52.0 Hz), 6.91 (1H, dd, J= 2.0 Hz, 8.0 Hz), 7.02 (1H, d, J= 9.0 Hz), 7.27 (1H, d, J= 9.0 Hz), 7.47 (1H, t, J= 8.0 Hz), 7.60-7.70 (2H, m), 8.01 (1H, d, J= 2.0 Hz), 8.34 (1H, s), 8.99 (1H, br s).

Ejemplo C-96



Producción de N-[2-(4-{[3-cloro-4-(3-isobutoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

(i) Producción de 3-cloro-4-(3-isobutoxifenoxi)anilina

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A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (1.00 g) y 1-yodo-2-metilpropano (1.5 ml) en N,N-dimetilformamida (15 ml) se añadió carbonato de potasio (1.50 g) y la mezcla se agitó a temperatura ambiente durante 12 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (30 ml), se añadieron hierro reducido (750 mg) y cloruro de calcio (70 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→0:1) para dar el compuesto del título (390 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 0.94-0.96 (6H, m), 1.90-2.01 (1H, m), 3.67-3.69 (2H, m), 5.33 (2H, s), 6.32-7.34 (2H, m), 6.53-6.59 (2H, m), 6.71-6.72 (1H, m), 6.89-6.91 (1H, m),

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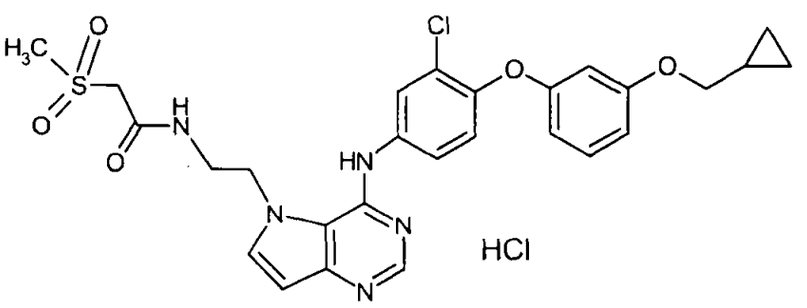
7.14-7.20 (1H, m).

(ii) Producción de N-[2-(4-{[3-cloro-4-(3-isobutoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-(3-isobutoxifenoxi)anilina (1.00 g), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-carbamato de ter-butilo (1.02 g), alcohol isopropílico (25 ml), metanol (35 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (10 ml), ácido metilsulfonilacético (870 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (2.50 g), 1-hidroxibenzotriazol (100 mg), trietilamina (4.1 ml) y N,N-dimetilformamida (100 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (933 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.95-0.97 (6H, m), 1.95-2.04 (1H, m), 3.09 (3H, s), 3.40-3.50 (2H, m), 3.72-3.74 (2H, m), 4.04 (2H, s), 4.54-4.59 (2H, m), 6.44-7.27 (6H, m), 7.61-7.75 (2H, m), 7.94 (1H, s), 8.33 (1H, s), 8.66 (2H, s).

Ejemplo C-97



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Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 2-cloro-1-[3-(ciclopropilmetoxi)fenoxi]-4-nitrobenceno

A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (2.92 g) en N,N-dimetilformamida (10.9 ml) se añadieron carbonato de cesio (5.39 g) y 1-(bromometil)ciclopropano (1.6 ml) y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla se dividió en acetato de etilo (150 ml)/agua (80 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 100:0→70:30) para dar el compuesto del título (3.17 g) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 0.30-0.40 (2H, m), 0.60-0.70 (2H, m), 1.20-1.40 (1H, m), 3.79 (2H, d, J= 7.0 Hz), 6.60-6.70 (2H, m), 6.70-6.82 (1H, m), 6.92(1H, d, J= 9.0 Hz), 7.29 (1H, m), 8.00-8.10 (1H, m), 8.36 (1H, d, J= 3.0 Hz).

(ii) Producción de 3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]anilina

Se disolvió 2-cloro-1-[3-(ciclopropilmetoxi)fenoxi]-4-nitrobenceno (3.1 g) en etanol (97 ml)/agua (11 ml), se añadieron hierro reducido (3.61 g) y cloruro de calcio (717 mg), y la mezcla se agitó a 90°C

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durante 16 h. El sólido se eliminó por filtración a través de celite, y el filtrado se concentró a presión reducida. Se añadió acetato de etilo (150 ml) al residuo, y la mezcla se lavó con salmuera saturada (100 ml). La capa orgánica se secó sobre sulfato de magnesio, se concentró a presión reducida, y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 90:10→60:40) para dar el compuesto del título (2.50 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 0.20-0.40 (2H, m), 0.50-0.70 (2H, m), 1.10-1.30 (1H, m), 3.66 (2H, br s), 3.74 (2H, d, J= 7.0 Hz), 6.40-6.50 (2H, m), 6.50-6.60 (2H, m), 6.76 (1H, d, J= 3.0 Hz), 6.85 (1H, d, J= 9.0 Hz), 7.10-7.20 (1H, m).

(iii) Producción de {2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Se disolvieron [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (0.5 g) y 3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]anilina (732 mg) en alcohol isopropílico (5 ml), y la mezcla se agitó a 80°C durante 20 h. Se añadió una solución saturada acuosa de carbonato ácido de sodio (60 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (80 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se

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purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→0:100) para dar el compuesto del título (742 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.30-0.40 (2H, m), 0.60-0.70 (2H, m), 1.10-1.30 (1H, m), 1.49 (9H, s), 3.40-3.60 (2H, m), 3.76 (2H, d, J= 7.0 Hz), 4.40-4.50 (2H, m), 5.21 (1H, t, J= 5.0 Hz), 6.50-6.70 (4H, m), 7.04 (1H, d, J= 9.0 Hz), 7.10-7.30 (2H, m), 7.82 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.98 (1H, d, J= 3.0 Hz), 8.49 (1H, s), 8.59 (1H, br s).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Se disolvió {2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (700 mg) en tetrahidrofurano (18 ml), se añadió ácido clorhídrico 2 N (9.0 ml), y la mezcla se agitó a 60°C durante 15 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en etanol (50 ml), y la solución se volvió a concentrar a presión reducida. Esta operación se repitió dos veces. El sólido precipitado se recogió con alcohol isopropílico y se secó para dar el compuesto del título (599 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 0.20-0.40 (2H, m), 0.50-0.60 (2H, m), 1.10-1.40 (1H, m), 3.20-3.40 (2H, m), 3.80 (2H, d,

J= 7.0 Hz), 5.00-5.10 (2H, m), 6.40-6.60 (2H, m), 6.60-6.80 (2H, m), 7.10-7.30 (2H, m), 7.50-7.70 (1H, m), 7.88 (1H, m), 8.08 (1H, m), 8.37 (3H, br s), 8.73 (1H, s), 10.19 (1H, br s).

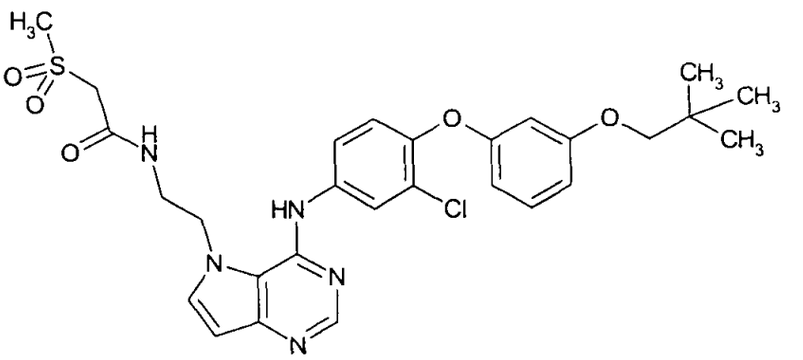
(v) Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Se agitaron diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (187 mg), ácido metilsulfonilacético (74.2 mg), N,N-dimetilformamida (6.9 ml), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg) a temperatura ambiente durante 16 h. La mezcla se dividió en acetato de etilo (80 ml)/agua (50 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15) y cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15). El compuesto obtenido se disolvió en acetato de etilo (4 ml), se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo (0.18 ml), y se cristalizó en éter diisopropílico/acetato de etilo para dar el compuesto del título (167 mg) en forma de cristales blancos.

927.

^{1}H-RMN (DMSO-d_6) δ: 0.20-0.40 (2H, m), 0.50-0.60 (2H, m), 1.10-1.40 (1H, m), 3.05 (3H, s), 3.50-3.60 (2H, m), 3.80 (2H, d, J= 7.0 Hz), 4.07 (2H, s), 4.73 (1H, t, J= 7.0 Hz), 6.40-6.55 (2H, m), 6.60-6.75 (2H, m), 7.20-7.30 (2H, m), 7.63 (1H, dd, J= 2.0 Hz, 9.0 Hz), 7.90 (1H, d, J= 2.0 Hz), 7.96 (1H, d, J= 3.0 Hz), 8.72 (1H, s), 8.87 (1H, m), 10.05 (1H, br s).

Ejemplo C-98



Producción de N-{2-[4-({3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 2-cloro-1-[3-(2,2-dimetilpropoxi)fenoxi]-4-nitrobenceno

A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (1.0 g) en N,N-dimetilformamida (10 ml) se añadieron hidróxido de potasio (423 mg) y hexafluorofosfato de tris(dimetilamino)(2,2-dimetilpropoxi)fosfonio (2.99 g) y la mezcla se agitó a 180°C durante 30 min. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se

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extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1) para dar el compuesto del título (180 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 1.03 (9H, s), 3.58(2H, s), 6.63-6.65 (2H, m), 6.80-6.94 (2H, m), 7.30-7.34 (1H, m), 8.04-8.08 (1H, m), 8.37-8.38 (1H, m).

(ii) Producción de 3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]anilina

Se disolvió 2-cloro-1-[3-(2,2-dimetilpropoxi)fenoxi]-4-nitrobenceno (210 mg) en 15% de etanol con contenido de agua (7 ml), se añadieron hierro reducido (150 mg) y cloruro de calcio (20 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→0:1) para dar el compuesto del título (75 mg) en forma de un aceite marrón.

^{1}H-RMN (DMSO-d_6) δ: 0.98 (9H, s), 3.92 (2H, s), 5.34

929

(2H, s), 6.31-7.33 (2H, m), 6.52-6.58 (2H, m), 6.70-6.72 (1H, m), 6.88-6.92 (1H, m), 7.13-7.20 (1H, m).

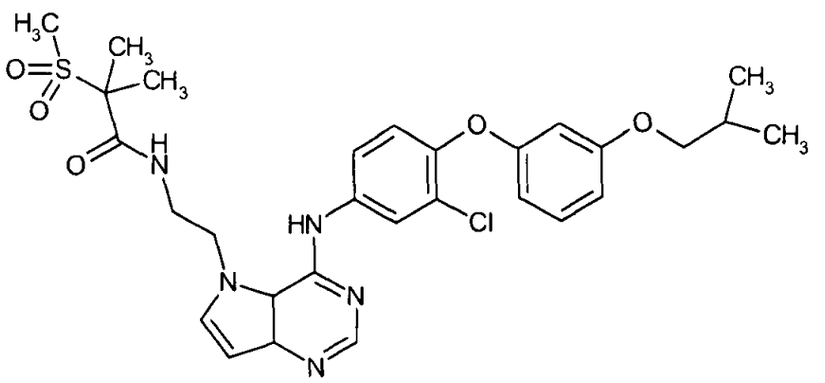
(iii) Producción de N-{2-[4-({3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]-anilina (75 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (73 mg), alcohol isopropílico (10 ml), metanol (10 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (5 ml), ácido metilsulfonilacético (50 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (120 mg), 1-hidroxibenzotriazol (10 mg), trietilamina (0.7 ml) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (62 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.98 (9H, s), 3.09 (3H, s), 3.45-3.49 (2H, m), 3.62 (2H, s), 4.05 (2H, s), 4.54-4.59 (2H, m), 6.44-7.28 (6H, m), 7.66-7.94 (3H, m), 8.39 (1H, s), 8.67 (1H, br s), 8.81 (1H, s).

930.

Ejemplo C-99



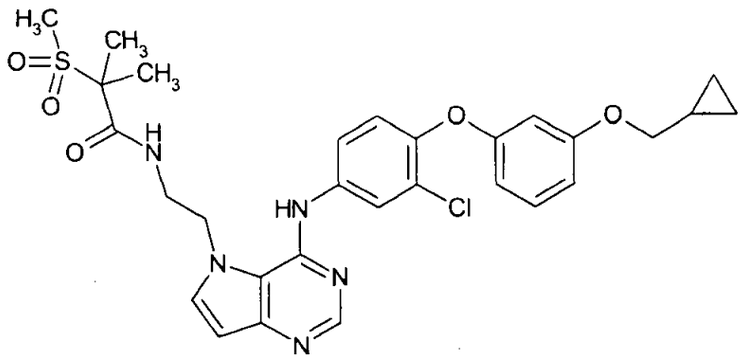
Producción de N-[2-(4-{[3-cloro-4-(3-isobutoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Al usar 3-cloro-4-(3-isobutoxifenoxi)anilina (180 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (185 mg), alcohol isopropílico (5.0 ml), metanol (6.0 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml), ácido 2-metil-2-(metilsulfonil)propanoico (160 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (320 mg), 1-hidroxibenzotriazol (20 mg), trietilamina (1.0 ml) y N,N-dimetilformamida (25 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (146 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.95-0.97 (6H, m), 1.41 (6H, s), 1.95-2.04 (1H, m), 2.95 (3H, s), 3.40-3.50 (2H, m), 3.72-3.74 (2H, m), 4.54-4.59 (2H, m), 6.44-7.27 (6H, m), 7.56-7.97 (3H, m), 8.19-8.22 (1H, m), 8.33 (1H, s), 8.65(1H, s).

931

Ejemplo C-100



Producción de N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-metil-2-(metilsulfonil)propanamida

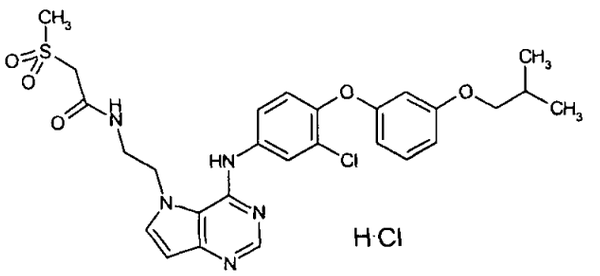
A una solución de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 2-metil-2-(metilsulfonil)propanoico (170 mg) y 1-hidroxibenzotriazol (20 mg) en N,N-dimetilformamida (25 ml) se añadieron trietilamina (0.87 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (320 mg) bajo enfriamiento con hielo y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→90:10) y luego se recristalizó en acetato de etilo/éter diisopropílico para

932

dar el compuesto del título (160 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 0.29-0.58 (4H, m), 1.11-1.28 (1H, m), 1.41 (6H, s), 2.95 (3H, s), 3.44-3.50 (2H, m), 3.78-3.80 (2H, m), 4.55-4.59 (2H, m), 6.32-6.68 (4H, m), 7.16-7.96 (5H, m), 8.20 (1H, br s), 8.33 (1H, s), 8.65(1H, br s).

Ejemplo C-101



Producción de clorhidrato de N-[2-(4-{[3-cloro-4-(3-isobutoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

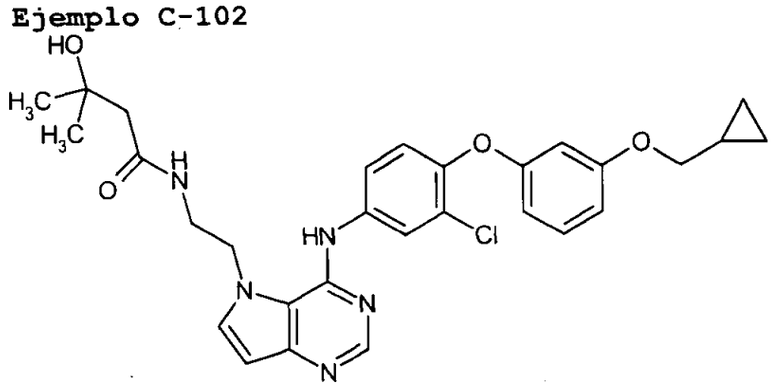
Se disolvió N-[2-(4-{[3-cloro-4-(3-isobutoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida (1.00 g) en acetato de etilo (10 ml), a ello se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (5.0 ml), y el sólido precipitado se recogió por filtración. El sólido se lavó con éter diisopropílico para dar el compuesto del título (1.03 g) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 0.95-0.98 (6H, m), 1.92-2.04 (1H, m), 3.05 (3H, s), 3.40-3.56 (2H, m), 3.72-3.75 (2H, m), 4.07 (2H, s), 4.71-4.75 (2H, m), 6.47-7.32 (6H, m), 7.62-7.97

933.

(3H, m), 8.73 (1H, s), 8.83-8.88 (1H, m), 10.03 (1H, s).

Ejemplo C-102



Producción de N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

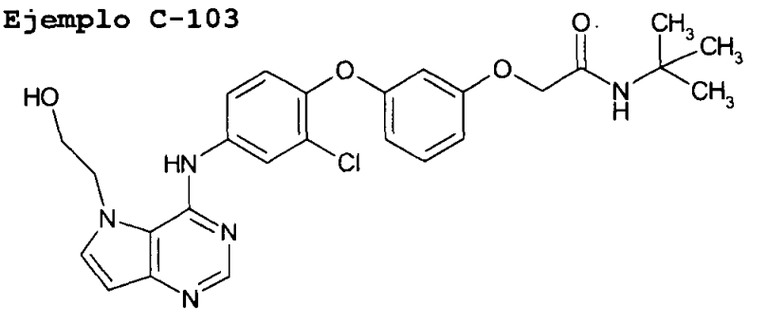
A una solución de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (100 mg), ácido 3-hidroxi-3-metilbutanoico (293 mg) y 1-hidroxibenzotriazol (10 mg) en tetrahidrofurano (15 ml) se añadieron trietilamina (0.3 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (216 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→90:10) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título

934

(66 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 0.29-0.58 (4H, m), 1.11-1.28 (1H, m), 1.16 (6H, s), 2.20 (2H, s), 3.35-3.41 (2H, m), 3.78-3.80 (2H, m), 4.49-4.54 (2H, m), 4.66 (1H, s), 6.43-7.26 (6H, m), 7.63-8.00 (3H, m), 8.25 (1H, br s), 8.32 (1H, s), 8.86(1H, br s).

Ejemplo C-103



Producción de N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenoxi]acetamida

(i) Producción de 2-[3-(4-amino-2-clorofenoxi)fenoxi]-N-(ter-butil)acetamida

A una solución de 3-(2-cloro-4-nitrofenoxi)fenol (1.0 g) en N,N-dimetilformamida (10 ml) se añadieron bromoacetato de etilo (1.26 g) y carbonato de potasio (1.20 g) y la mezcla se agitó a temperatura ambiente durante 18 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se disolvió en tetrahidrofurano (20 ml), a ello se añadió solución acuosa 1

N de hidróxido de sodio (5.0 ml) y la mezcla se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se agregaron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. A una solución del residuo obtenido, 2-metilpropan-2-amina (1.0 ml) y 1-hidroxibenzotriazol (10 mg) en tetrahidrofurano (15 ml) se añadieron trietilamina (1.3 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (1.50 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (23 ml), se añadieron hierro reducido (550 mg) y cloruro de calcio (70 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a

936.

presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→0:1) para dar el compuesto del título (375 mg) en forma de un aceite marrón.

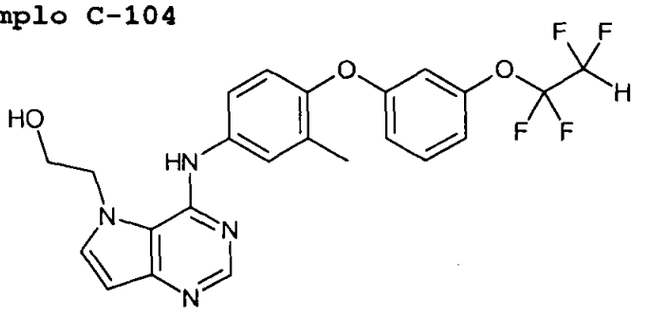
^{1}H-RMN (DMSO-d_6) δ: 1.29 (9H, s), 4.35 (2H, s), 5.35 (2H, s), 6.31-7.34 (2H, m), 6.52-6.58 (2H, m), 6.70-6.72 (1H, m), 6.88-6.93 (1H, m), 7.13-7.20 (1H, m).

(ii) Producción de N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenoxi]acetamida

Al usar 2-[3-(4-amino-2-clorofenoxi)fenoxi]-N-(ter-butil)acetamida (100 mg), benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (87 mg), alcohol isopropílico (5.0 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y metanol (5.0 ml) y de la misma manera que en el Ejemplo C-57, se obtuvo el compuesto del título (73 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.27 (9H, s), 3.86-3.89 (2H, m), 4.37 (2H, s), 4.51-4.55 (2H, m), 6.48-7.66 (9H, m), 7.95-8.97 (1H, m), 8.33 (1H, s), 9.87(1H, br s).

Ejemplo C-104



937.

Producción de 2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-metil-4-nitro-1-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]benceno

Una mezcla de 2-fluoro-5-nitrotolueno (2.10 g) y 3-(1,1,2,2-tetrafluoroetoxi)fenol (3.01 g) se disolvió en N,N-dimetilformamida (13 ml), se añadió carbonato de potasio (3.04 g), y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 100:0→80:20) para dar el compuesto del título (4.05 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.39 (3H, s), 5.91 (1H, tt, J= 2.8 Hz, 53.0 Hz), 6.87 (1H, d, J= 9.0 Hz), 6.89-6.98 (2H, m), 7.02-7.14 (1H, m), 7.41 (1H, t, J= 8.2 Hz), 8.04 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.18 (1H, d, J= 2.6 Hz).

(ii) Producción de 3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina

Al usar 2-metil-4-nitro-1-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]benceno (4.04 g), hierro reducido

938.

(3.45 g), cloruro de calcio (691 mg) y etanol (108 ml)/agua (12 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (3.45 g) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 2.09 (3H, s), 3.59 (2H, br s), 5.86 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.53 (1H, dd, J= 3.0 Hz, 8.7 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.67 (1H, t, J= 2.2 Hz), 6.72-6.77 (1H, m), 6.80 (1H, d, J= 8.7 Hz), 6.81-6.86 (1H, m), 7.19-7.27 (1H, m).

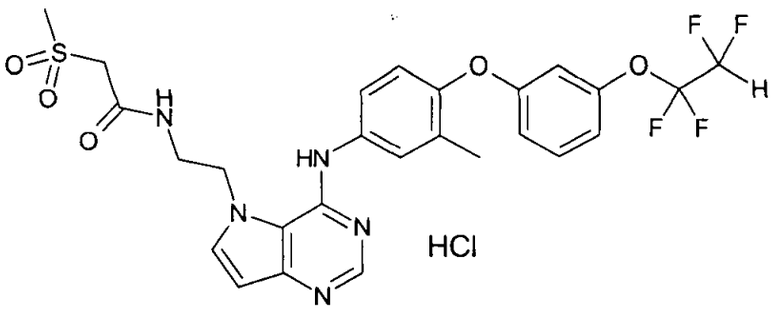
(iii) Producción de 2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (102 mg), 3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina (110 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1.5 ml) y de la misma manera que en el Ejemplo C-72(iii), se obtuvo el compuesto del título (114 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 2.23 (3H, s), 4.14 (2H, t, J= 4.5 Hz), 4.32-4.42 (2H, m), 5.89 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.15 (1H, d, J= 3.4 Hz), 6.75-7.02 (5H, m), 7.20-7.34 (1H, m), 7.40-7.52 (2H, m), 8.24 (1H, s), 9.30 (1H, s).

939

Ejemplo C-105



Producción de clorhidrato de 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida

(i) Producción de {2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Se disolvieron [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (304 mg) y 3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]anilina (331 mg) en alcohol isopropílico (10 ml), y la mezcla se agitó a 70°C durante 20 h. Se añadió una solución acuosa saturada de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 67:33→10:90) para dar el compuesto del título (540

940

mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 2.21 (3H, s), 3.43-3.57 (2H, m), 4.40-4.54 (2H, m), 5.00 (1H, t, J= 5.5 Hz), 5.88 (1H, tt, J= 2.9 Hz, 53.0 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.75-6.80 (1H, m), 6.82-6.93 (2H, m), 6.94-7.02 (1H, m), 7.16 (1H, d, J= 3.0 Hz), 7.27 (1H, t, J= 8.1 Hz), 7.64-7.74 (2H, m), 8.36 (1H, br s), 8.50 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Se disolvió {2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (537 mg) en tetrahidrofurano (2 ml), se añadió ácido clorhídrico 6 N (0.8 ml), y la mezcla se agitó a 50°C durante 15 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en etanol, y la mezcla se volvió a concentrar a presión reducida. El precipitado se recogió por filtración para dar el compuesto del título (460 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 2.19 (3H, s), 3.22-3.48 (2H, m), 4.99 (2H, t, J= 6.1 Hz), 6.72 (1H, d, J= 3.2 Hz), 6.76 (1H, t, J= 2.3 Hz), 6.80 (1H, tt, J= 3.1 Hz, 52 Hz), 6.90-6.96 (1H, m), 7.00-7.07 (1H, m), 7.11 (1H, d, J= 8.7 Hz), 7.47

(1H, dd, J= 2.5 Hz, 8.7 Hz), 7.49 (1H, t, J= 8.3 Hz), 7.54 (1H, d, J= 2.5 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.29 (3H, br s), 8.68 (1H, s), 9.87 (1H, br s).

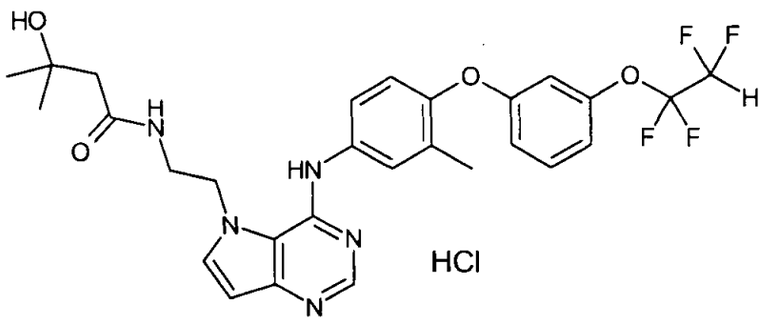
(iii) Producción de clorhidrato de 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (121 mg), ácido metilsulfonilacético (48.8 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (47 mg), trietilamina (0.3 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (64.3 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida. El compuesto se disolvió en acetato de etilo, se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y se cristalizó en acetato de etilo/etanol para dar el compuesto del título (104 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 2.19 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.07 (2H, m), 4.70 (2H, t, J= 6.4 Hz), 6.61-6.99 (1H, m), 6.64 (1H, d, J= 3.2 Hz), 6.76 (1H, t, J=

2.3 Hz), 6.91-6.96 (1H, m), 6.99-7.07 (1H, m), 7.12 (1H, d, J= 8.5 Hz), 7.44-7.61 (3H, m), 7.91 (1H, d, J= 3.2 Hz), 8.68 (1H, s), 8.78 (1H, t, J= 5.7 Hz), 9.85 (1H, s).

Ejemplo C-106



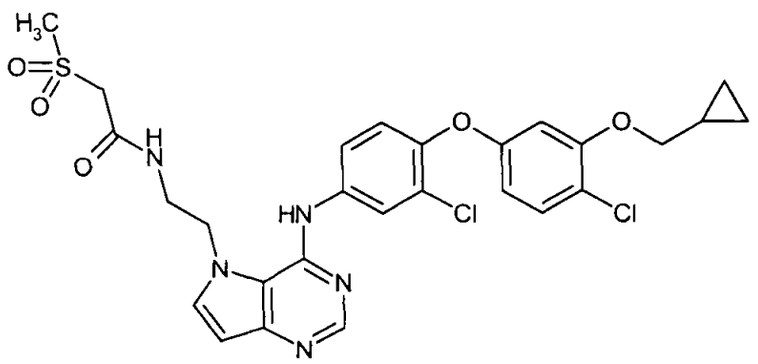
Producción de clorhidrato de 3-hidroxi-3-metil-N-{2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}butanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (120 mg), ácido 3-hidroxi-3-metilbutanoico (40.5 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (47.6 mg), trietilamina (0.3 ml) y clorhidrato de 1-etil-3-(3'-dimetilaminopropil)carbodiimida (66.1 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo 3-hidroxi-3'-metil-N-{2-[4-({3-metil-4-[3-(1,1,2,2-tetrafluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}butanamida. El compuesto se disolvió en acetato de etilo, se trató con solución de cloruro de

hidrógeno 4 N/acetato de etilo, y se cristalizó en éter diisopropílico/acetato de etilo para dar el compuesto del título (108 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.11 (6H, s), 2.18 (3H, s), 2.20 (2H, s), 3.44-3.56 (2H, m), 4.65 (2H, t, J= 6.8 Hz), 6.60-6.99 (1H, m), 6.65 (1H, d, J= 3.0 Hz), 6.75 (1H, t, J= 2.3 Hz), 6.91-6.96 (1H, m), 6.99-7.06 (1H, m), 7.11 (1H, d, J= 8.7 Hz), 7.49 (1H, t, J= 8.3 Hz), 7.54 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.60 (1H, d, J= 2.5 Hz), 7.95 (1H, d, J= 3.0 Hz), 8.37 (1H, t, J= 5.5 Hz), 8.68 (1H, s), 10.16 (1H, s).

Ejemplo C-107



Producción de N-{2-[4-({3-cloro-4-[4-cloro-3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 3-cloro-4-[4-cloro-3-(ciclopropilmetoxi)fenoxi]anilina

A una solución de 3-cloro-4-fluoronitrobenceno (5.00 g), 4-clorobenceno-1.3-diol (4.11 g) en N,N-dimetilformamida (35 ml) se añadió carbonato de potasio (5.50

g) y la mezcla se agitó a temperatura ambiente durante 5 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en N,N-dimetilformamida (15 ml), se añadieron 1-(bromometil)ciclopropano (1.3 ml) y carbonato de potasio (1.50 g) y la mezcla se agitó a temperatura ambiente durante 12 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo dos veces con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 1:0→1:1). El producto crudo obtenido se disolvió en 15% de etanol con contenido de agua (30 ml), se añadieron hierro reducido (550 mg) y cloruro de calcio (70 mg), y la mezcla se agitó a 80°C durante 8 h. El sólido se eliminó por filtración, y el filtrado se concentró a presión reducida. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el

residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 4:1→0:1) para dar el compuesto del título (868 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 0.35-0.68 (4H, m), 0.84-0.90 (1H, m), 3.87 (2H, d, J = 6.7 Hz), 5.36 (2H, s), 6.33-7.34 (1H, m), 6.52-6.58 (2H, m), 6.69-6.71 (1H, m), 6.86-6.92 (1H, m), 7.13-7.21 (1H, m).

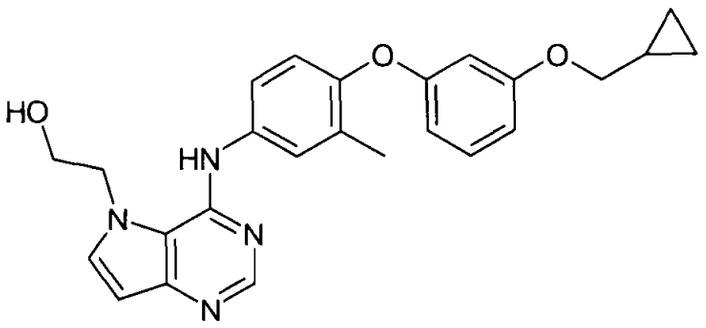
(ii) Producción de N-{2-[4-({3-cloro-4-[4-cloro-3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar 3-cloro-4-[4-cloro-3-(ciclopropilmetoxi)fenoxi]anilina (200 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (183 mg), alcohol isopropílico (9 ml), metanol (15 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (8.0 ml), ácido metilsulfonilacético(170 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (300 mg), 1-hidroxibenzotriazol (50 mg), trietilamina (1.1 ml) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (61 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 0.36-0.42 (2H, m), 0.62-0.68 (2H, m), 0.86-0.90 (1H, m), 3.13 (3H, s), 3.68-3.72 (2H, m), 3.86 (2H, d, J = 6.7 Hz), 3.98 (2H, s), 4.45-4.52 (2H, m), 6.43-

7.28 (6H, m), 7.50 (1H, br s), 7.68-7.72 (1H, m), 7.92 (1H, s), 8.18 (1H, br s), 8.49 (1H, s).

Ejemplo C-108



Producción de 2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 3-(2-metil-4-nitrofenoxi)fenol

Al usar 2-fluoro-5-nitrotolueno (10.0 g), resorcinol (24.8 g), carbonato de potasio (31.3 g) y N,N-dimetilformamida (120 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (7.19 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.39 (3H, s), 5.12 (1H, s), 6.52 (1H, t, J= 2.3 Hz), 6.55-6.61 (1H, m), 6.64-6.70 (1H, m), 6.84 (1H, d, J= 9.0 Hz), 7.24 (1H, t, J= 8.1 Hz), 7.99 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.14 (1H, d, J= 2.8 Hz).

(ii) Producción de 1-[3-(ciclopropilmetoxi)fenoxi]-2-metil-4-nitrobenceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (939 mg), 1-(bromometil)ciclopropano (0.55 ml), carbonato de potasio (963

mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (1.02 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.28-0.42 (2H, m), 0.58-0.71 (2H, m), 1.17-1.36 (1H, m), 2.39 (3H, s), 3.78 (2H, d, J= 7.2 Hz), 6.53-6.63 (2H, m), 6.71-6.78 (1H, m), 6.82 (1H, d, J= 8.8 Hz), 7.27 (1H, t, J= 8.1 Hz), 7.98 (1H, dd, J= 2.8 Hz, 8.8 Hz), 8.14 (1H, d, 2.8 Hz).

(iii) Producción de 4-[3-(ciclopropilmetoxi)fenoxi]-3-metilanilina

Al usar 1-[3-(ciclopropilmetoxi)fenoxi]-2-metil-4-nitrobenceno (1.01 g), hierro reducido (964 mg), cloruro de calcio (196 mg) y etanol (36 ml)/agua (4 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (809 mg) en forma de un aceite de color marrón negruzco.

^{1}H-RMN ($CDCl_3$) δ: 0.26-0.38 (2H, m), 0.55-0.68 (2H, m), 1.13-1.34 (1H, m), 2.09 (3H, s), 3.54 (2H, br s), 3.73 (2H, d, J= 6.9 Hz), 6.37-6.45 (2H, m), 6.47-6.54 (2H, m), 6.57 (1H, d, J= 2.5 Hz), 6.78 (1H, d, J= 8.5 Hz), 7.07-7.16 (1H, m).

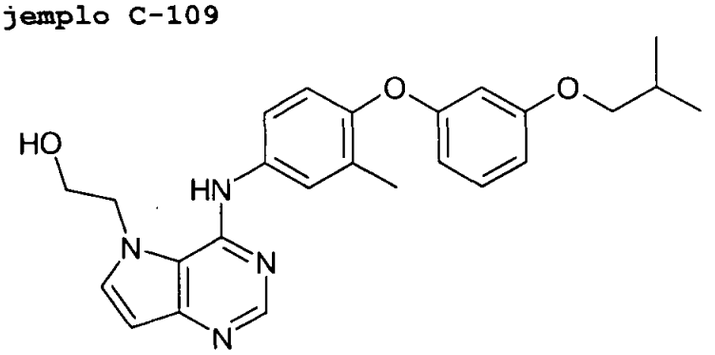
(iv) Producción de 2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-

d]pirimidin-5-il)etilo (99.7 mg), 4-[3-(ciclopropilmetoxi)fenoxi]-3-metilanilina (98.7 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1.5 ml) y de la misma manera que en el Ejemplo C-72(iii), se obtuvo el compuesto del título (106 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 0.29-0.39 (2H, m), 0.58-0.70 (2H, m), 1.17-1.33 (1H, m), 2.24 (3H, s), 3.77 (2H, d, J= 7.0 Hz), 4.08-4.17 (2H, m), 4.37 (2H, t, J= 4.4 Hz), 6.13 (1H, d, J= 3.0 Hz), 6.47-6.62 (3H, m), 6.94 (1H, d, J= 3.0 Hz), 6.97 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J= 8.1 Hz), 7.37-7.48 (2H, m), 8.23 (1H, s), 9.28 (1H, s).

Ejemplo C-109



Producción de 2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etanol

(i) Producción de 1-(3-isobutoxifenoxi)-2-metil-4-nitrobenceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (822 mg), bromuro de isobutilo (0.55 ml), carbonato de potasio (834 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el

Ejemplo C-104(i), se obtuvo el compuesto del título (884 mg) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.02 (6H, d, J= 6.8 Hz), 1.97-2.18 (1H, m), 2.40 (3H, s), 3.70 (2H, d, J= 6.4 Hz), 6.52-6.64 (2H, m), 6.71-6.78 (1H, m), 6.82 (1H, d, J= 9.1 Hz), 7.22-7.33 (1H, m), 7.99 (1H, dd, J= 3.0 Hz, 9.1 Hz), 8.14 (1H, d, J= 3.0 Hz).

(ii) Producción de 4-(3-isobutoxifenoxi)-3-metilanilina

Al usar 1-(3-isobutoxifenoxi)-2-metil-4-nitrobenceno (879 mg), hierro reducido (823 mg), cloruro de calcio (162 mg) y etanol (27 ml)/agua (3 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (756 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 1.00 (6H, d, J= 6.6 Hz), 1.95-2.10 (1H, m), 2.11 (3H, s), 3.55 (2H, br s), 3.66 (2H, d, J= 6.3 Hz), 6.35-6.44 (2H, m), 6.49-6.52 (1H, m), 6.52-6.55 (1H, m), 6.58 (1H, d, J= 3.0 Hz), 6.80 (1H, d, J= 8.5 Hz), 7.12 (1H, t, J= 8.1 Hz).

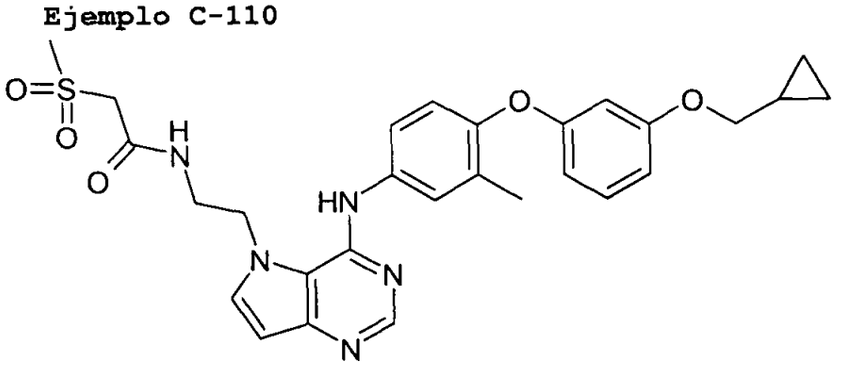
(iii) Producción de 2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (110 mg), 4-(3-isobutoxifenoxi)-3-metilanilina (103 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1.5 ml) y de la misma

manera que en el Ejemplo C-72(iii), se obtuvo el compuesto del título (116 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.02 (6H, d, J= 6.8 Hz), 1.97-2.16 (1H, m), 2.25 (3H,s), 3.70 (2H, d, J= 6.4 Hz), 4.12 (2H, t, J= 4.3 Hz), 4.35 (2H, t, J= 4.3 Hz), 6.10 (1H, d, J= 3.2 Hz), 6.45-6.54 (2H, m), 6.54-6.62 (1H, m), 6.91 (1H, d, J= 3.2 Hz), 6.97 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J=8.3 Hz), 7.37-7.48 (2H, m), 8.21 (1H, s), 9.31 (1H, s).

Ejemplo C-110



Producción de N-{2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de {2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (402 mg), 4-[3-(ciclopropilmetoxi)fenoxi]-3-metilanilina (395 mg) y alcohol isopropílico (15 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (710 mg) en forma

de un polvo de color anaranjado pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.27-0.39 (2H, m), 0.54-0.69 (2H, m), 1.16-1.32 (1H, m), 1.46 (9H, s), 2.22 (3H, s), 3.41-3.58 (2H, m), 3.76 (2H, d, J= 6.8 Hz), 4.39-4.53 (2H, m), 4.99 (1H, d, J= 9.5 Hz), 6.46-6.63 (4H, m), 6.95 (1H, d, J= 9.5 Hz), 7.09-7.20 (2H, m), 7.55-7.73 (2H, m), 8.28 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (707 mg), ácido clorhídrico 6 N (1 ml) y etanol (3 ml) y de la misma manera que en el Ejemplo C-105(ii), se obtuvo el compuesto del título (578 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 0.25-0.36 (2H, m), 0.49-0.62 (2H, m), 1.12-1.27 (1H, m), 2.19 (3H, s), 3.20-3.33 (2H, m), 3.79 (2H, d, J= 6.9 Hz), 5.01 (2H, t, J= 6.1 Hz), 6.40-6.49 (2H, m), 6.62-6.69 (1H, m), 6.71 (1H, d, J= 3.0 Hz), 7.01 (1H, d, J= 8.5 Hz), 7.19-7.29 (1H, m), 7.40 (1H, dd, J= 2.5 Hz, 8.5 Hz), 7.49 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.0 Hz), 8.33 (3H, br s), 8.67 (1H, s), 9.90 (1H, br s).

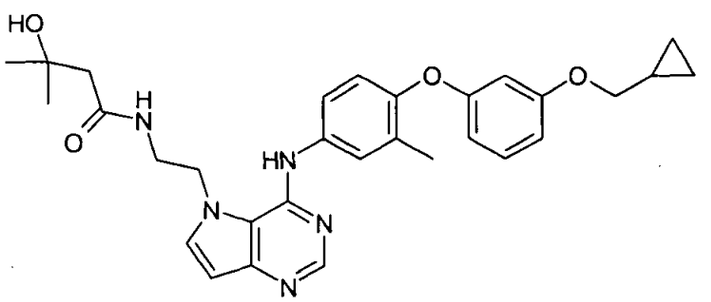
(iii) Producción de N-{2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-

pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (120 mg), ácido metilsulfonilacético (50.5 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (51.5 mg), trietilamina (0.35 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (116 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo el compuesto del título (72.4 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.28-0.39 (2H, m), 0.57-0.70 (2H, m), 1.17-1.34 (1H, m), 2.24 (3H, s), 3.08 (3H, s), 3.62-3.75 (2H, m), 3.77 (2H, d, J= 7.0 Hz), 3.93 (2H, s), 4.38-4.53 (2H, m), 6.45-6.63 (4H, m), 6.95 (1H, d, J= 8.5 Hz), 7.11-7.23 (2H, m), 7.36-7.50 (2H, m), 7.57 (1H, d, J= 2.1 Hz), 7.83 (1H, s), 8.47 (1H, s).

Ejemplo C-111



Producción de N-{2-[4-({4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-

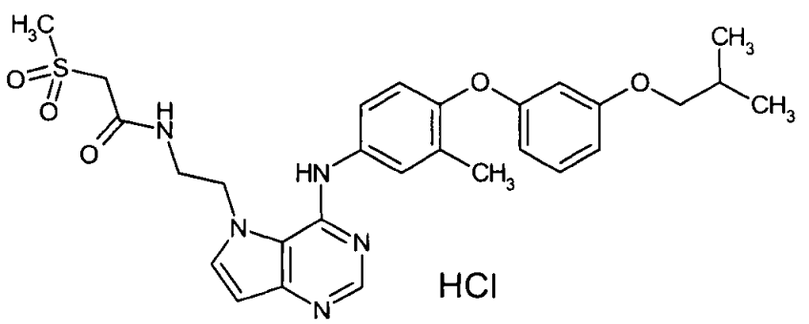
953

metilbutanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(ciclopropilmetoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (121 mg), ácido 3-hidroxi-3-metilbutanoico (46.2 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (59.8 mg), trietilamina (0.35 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (88.0 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo el compuesto del título (60.0 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.29-0.38 (2H, m), 0.58-0.68 (2H, m), 1.17-1.33 (1H, m), 1.30 (6H, s), 2.24 (3H, s), 2.44 (2H, s), 3.56-3.70 (2H, m), 3.77 (2H, d, J= 7.0 Hz), 4.41-4.53 (2H, m), 6.48-6.62 (4H, m), 6.86-6.93 (1H, m), 6.95 (1H, d, J= 8.7 Hz), 7.11-7.22 (2H, m), 7.54 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.62 (1H, d, J= 2.5 Hz), 8.32 (1H, s), 8.47 (1H, s).

Ejemplo C-112



Producción de clorhidrato de N-[2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

(i) Producción de [2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (307 mg), 4-(3-isobutoxifenoxi)-3-metilanilina (304 mg) y alcohol isopropílico (12 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (504 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.01 (6H, d, J= 6.8 Hz), 1.46 (9H, s), 1.97-2.14 (1H, m), 2.23 (3H, s), 3.41-3.58 (2H, m), 3.68 (2H, d, J= 6.4 Hz), 4.39-4.54 (2H, m), 5.01 (1H, t, J= 5.5 Hz), 6.45-6.63 (4H, m), 6.96 (1H, d, J= 8.7 Hz), 7.09-7.21 (2H, m), 7.58-7.71 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-[4-(3-isobutoxifenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar [2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (499 mg), ácido clorhídrico 6 N (1 ml) y etanol (3 ml) y de la misma manera que en el Ejemplo C-105(ii), se obtuvo el compuesto del título (429 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 0.96 (6H, d, J= 6.6 Hz), 1.91-2.08 (1H, m), 2.20 (3H, s), 3.21-3.85 (2H, m), 3.73 (2H, d J=

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6.4 Hz), 5.02 (2H, t, J= 6.1 Hz), 6.40-6.52 (2H, m), 6.64-6.70 (1H, m), 6.72 (1H, d, J= 3.2 Hz), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.5 Hz), 8.05 (1H, d, J= 3.2 Hz), 8.37 (3H, br s), 8.68 (1H, s), 9.94 (1H, br s).

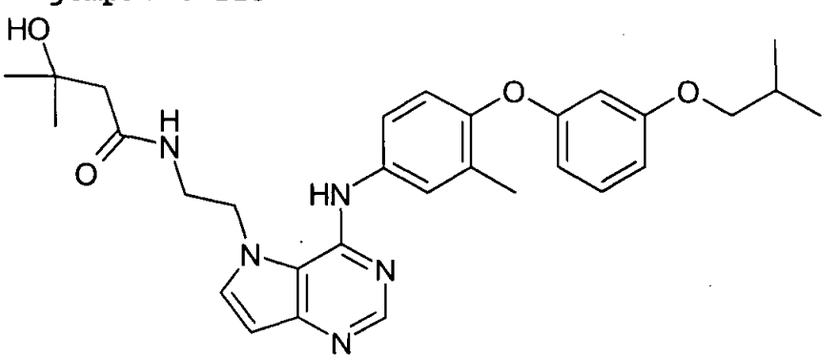
(iii) Producción de clorhidrato de N-[2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-[4-(3-isobutoxifenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (119 mg), ácido metilsulfonilacético (50.3 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (50.1 mg), trietilamina (0.35 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (82.7 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo N-[2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida. El compuesto se disolvió en acetato de etilo y se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y el precipitado se recogió por filtración para dar el compuesto del título (104 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 0.96 (6H, d, J= 6.6 Hz), 1.88-2.09 (1H, m), 2.20 (3H, s), 3.06 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.73 (2H, d, J= 6.6 Hz), 4.06 (2H, s), 4.69 (2H, t, J=

6.0 Hz), 6.39-6.52 (2H, m), 6.64 (1H, d, J= 3.2 Hz), 6.65-6.72 (1H, m), 7.02 (1H, d, J= 8.8 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.45 (1H, dd, J= 2.5 Hz, 8.8 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.2 Hz), 8.67 (1H, s), 8.77 (1H, t, J= 6.0 Hz), 9.82 (1H, s).

Ejemplo C-113



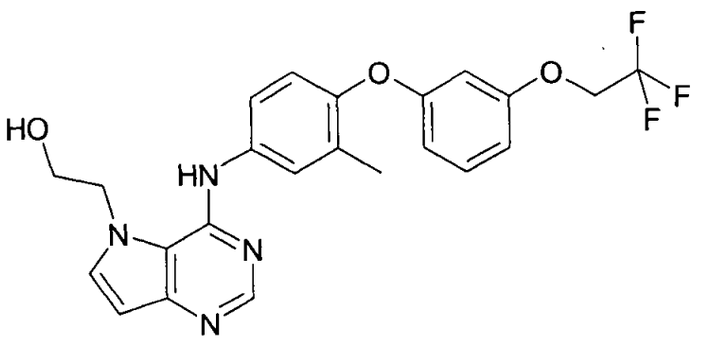
Producción de 3-hidroxi-N-[2-(4-{[4-(3-isobutoxifenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-metilbutanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-[4-(3-isobutoxifenoxi)-3-metilfenil]-5H-pirrolo[3,2-d]pirimidin-4-amina (120 mg), ácido 3-hidroxi-3-metilbutanoico (46.1 mg), tetrahidrofurano (0.6 ml)/N,N-dimetilformamida (0.6 ml), 1-hidroxibenzotriazol (50.2 mg), trietilamina (0.35 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (82.7 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo el compuesto del título (91.0 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 1.01 (6H, d, J= 6.6 Hz), 1.30 (6H,

s), 1.97-2.15 (1H, m), 2.25 (3H, s), 2.44 (2H, s), 3.57-3.67 (2H, m), 3.69 (2H, d, J= 6.6 Hz), 4.41-4.54 (2H, m), 6.44-6.63 (4H, m), 6.84 (1H, t, J= 5.9 Hz), 6.95 (1H, d, J= 8.7 Hz), 7.11-7.21 (2H, m), 7.55 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.63 (1H, d, J= 2.5 Hz), 8.31 (1H, s), 8.48 (1H, s).

Ejemplo C-114



Producción de 2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-metil-4-nitro-1-[3-(2,2,2-trifluoroetoxi)fenoxi]benceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (797 mg), 1.1,1-trifluoro-2-yodoetano (0.5 ml), carbonato de potasio (903 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (780 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.39 (3H, s), 4.35 (2H, q, J= 8.0 Hz), 6.64 (1H, t, J= 2.4 Hz), 6.67-6.74 (1H, m), 6.74-6.81 (1H, m), 6.84 (1H, d, J= 9.0 Hz), 7.34 (1H, t, J= 8.3 Hz), 8.02 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.16 (1H, d, J= 2.8 Hz).

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(ii) Producción de 3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]anilina

Al usar 2-metil-4-nitro-1-[3-(2,2,2-trifluoroetoxi)fenoxi]benceno (774 mg), hierro reducido (685 mg), cloruro de calcio (138 mg) y etanol (22.5 ml)/agua (2.5 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (529 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.08 (3H, s), 3.57 (2H, br s), 4.28 (2H, q, J= 8.0 Hz), 6.43 (1H, t, J= 2.5 Hz), 6.48-6.56 (3H, m), 6.58 (1H, d, J= 2.8 Hz), 6.78 (1H, d, J= 8.5 Hz), 7.17 (1H, t, J= 8.3 Hz).

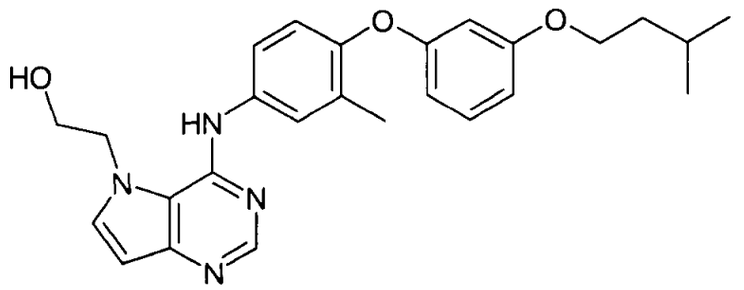
(iii) Producción de 2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (101 mg), 3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]anilina (100 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo C-72(iii), se obtuvo el compuesto del título (63.9 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.23 (3H, s), 4.13 (2H, t, J= 4.4 Hz), 4.25-4.43 (4H, m), 6.13 (1H, d, J= 3.2 Hz), 6.54 (1H, t, J= 2.3 Hz), 6.56-6.68 (2H, m), 6.94 (1H, d, J= 3.2 Hz), 6.98 (1H, d, J= 8.5 Hz), 7.23 (1H, t, J= 8.3 Hz), 7.39-7.49 (2H,

m), 8.23 (1H, s), 9.32 (1H, s).

Ejemplo C-115



Producción de 2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-metil-1-[3-(3-metilbutoxi)fenoxi]-4-nitrobenceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (855 mg), 1-yodo-3-metilbutano (0.8 ml), carbonato de potasio (968 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (983 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (6H, d, J= 6.6 Hz), 1.67 (2H, q, J= 6.6 Hz), 1.74-1.93 (1H, m), 2.40 (3H, s), 3.97 (2H, t, J= 6.6 Hz), 6.55-6.62 (2H, m), 6.71-6.79 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.24-7.33 (1H, m), 8.00 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.6 Hz).

(ii) Producción de 3-metil-4-[3-(3-metilbutoxi)fenoxi]anilina

Al usar 2-metil-1-[3-(3-metilbutoxi)fenoxi]-4-

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nitrobenceno (978 mg), hierro reducido (879 mg), cloruro de calcio (176 mg) y etanol (27 ml)/agua (3 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (835 mg) en forma de un aceite marrón.

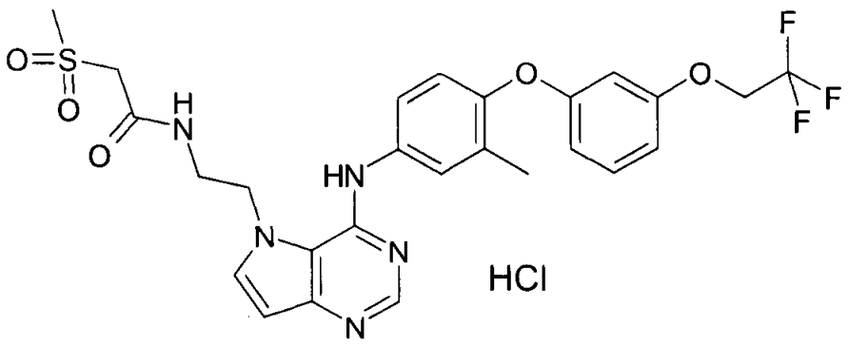
^{1}H-RMN ($CDCl_3$) δ: 0.94 (6H, d, J= 6.7 Hz), 1.64 (2H, q, J= 6.7 Hz), 1.72-1.90 (1H, m), 2.10 (3H, s), 3.55 (2H, br s), 3.93 (2H, t, J= 6.7 Hz), 6.36-6.44 (2H, m), 6.48-6.55 (2H, m), 6.58 (1H, d, J= 2.8 Hz), 6.80 (1H, d, J= 8.3 Hz), 7.06-7.18 (1H, m).

(iii) Producción de 2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (105 mg), 3-metil-4-[3-(3-metilbutoxi)fenoxi]anilina (102 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo C-72(iii), se obtuvo el compuesto del título (91.5 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (6H, d, J= 6.7 Hz), 1.66 (2H, q, J= 6.7 Hz), 1.75-1.92 (1H, m), 2.25 (3H, s), 3.96 (2H, t, J= 6.7 Hz), 4.12 (2H, t, J= 4.4 Hz), 4.31-4.41 (2H, m), 6.11 (1H, d, J= 3.2 Hz), 6.46-6.54 (2H, m), 6.54-6.62 (1H, m), 6.92 (1H, d, J= 3.2 Hz), 6.97 (1H, d, J= 8.3 Hz), 7.12-7.22 (1H, m), 7.36-7.50 (2H, m), 8.22 (1H, s), 9.29 (1H, s).

Ejemplo C-116



Producción de clorhidrato de 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida

(i) Producción de {2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (305 mg), 3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]anilina (326 mg) y alcohol isopropílico (12 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (489 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 2.21 (3H, s), 3.42-3.58 (2H, m), 4.31 (2H, q, J= 8.1 Hz), 4.41-4.55 (2H, m), 5.03 (1H, t, J= 5.0 Hz), 6.53 (1H, t, J= 2.4 Hz), 6.56-6.67 (3H, m), 6.91-7.02 (1H, m), 7.16 (1H, d, J= 3.2 Hz), 7.21 (1H, t, J= 8.2 Hz), 7.56-7.77 (2H, m), 8.38 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (484 mg), ácido clorhídrico 6 N (1 ml) y etanol (3 ml) y de la misma manera que en el Ejemplo C-105(ii), se obtuvo el compuesto del título (423 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 2.20 (3H, s), 3.21-3.33 (2H, m), 4.78 (2H, q, J= 8.9 Hz), 5.01 (2H, t, J= 6.1 Hz), 6.56 (1H, dd, J= 2.0 Hz, 8.0 Hz), 6.64 (1H, t, J= 2.0 Hz), 6.72 (1H, d, J= 3.2 Hz), 6.81 (1H, dd, J= 2.0 Hz, 8.0 Hz), 7.04 (1H, d, J= 8.7 Hz), 7.33 (1H, t, J= 8.0 Hz), 7.43 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.52 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.2 Hz), 8.34 (3H, br s), 8.68 (1H, s), 9.92 (1H, br s).

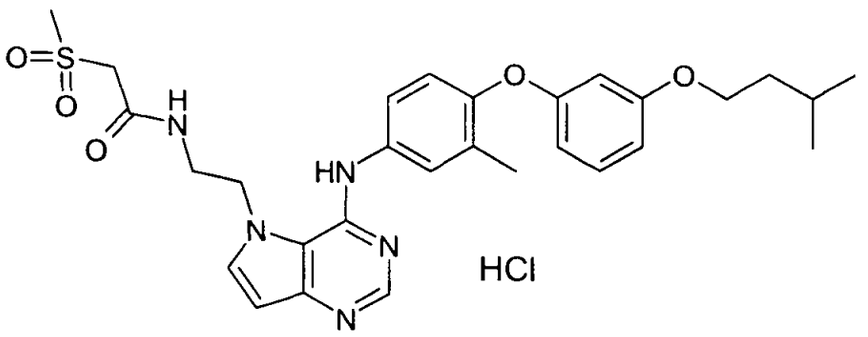
(iii) Producción de clorhidrato de 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (152 mg), ácido metilsulfonilacético (64.5 mg), tetrahidrofurano (0.8

ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (70.6 mg), trietilamina (0.4 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (93.8 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo 2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida. El compuesto se disolvió en acetato de etilo y se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y el precipitado se recogió por filtración para dar el compuesto del título (132 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 2.20 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.07 (2H, s), 4.69 (2H, t, J= 6.5 Hz), 4.77 (2H, q, J= 8.9 Hz), 6.52-6.59 (1H, m), 6.61-6.68 (2H, m), 6.81 (1H, dd, J= 2.3 Hz, 8.1 Hz), 7.04 (1H, d, J= 8.7 Hz), 7.33 (1H, t, J= 8.1 Hz), 7.47 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.54 (1H, d, J= 2.5 Hz), 7.91 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.79 (1H, t, J= 5.5 Hz), 9.85 (1H, s).

Ejemplo C-117



Producción de clorhidrato de N-{2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de {2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (400 mg), 3-metil-4-[3-(3-metilbutoxi)fenoxi]anilina (408 mg) y alcohol isopropílico (15 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (692 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95 (6H, d, J= 6.6 Hz), 1.46 (9H, s), 1.61-1.71 (2H, m), 1.74-1.91 (1H, m), 2.23 (3H, s), 3.42-3.58 (2H, m), 3.95 (2H, t, J= 6.6 Hz), 4.39-4.54 (2H, m), 5.01 (1H, t, J= 6.1 Hz), 6.45-6.62 (4H, m), 6.96 (1H, d, J= 8.9 Hz), 7.10-7.22 (2H, m), 7.57-7.74 (2H, m), 8.33 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (685 mg), ácido clorhídrico 6 N (1 ml) y etanol (3 ml) y de la misma manera que en el

Ejemplo C-105(ii), se obtuvo el compuesto del título (602 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 0.92 (6H, d, J= 6.6 Hz), 1.59 (2H, q, J= 6.6 Hz), 1.67-1.86 (1H, m), 2.20 (3H, s), 3.20-3.33 (2H, m), 3.97 (2H, t, J= 6.6 Hz), 5.01 (2H, t, J= 6.2 Hz), 6.40-6.52 (2H, m), 6.68 (1H, dd, J= 2.0 Hz, 8.3 Hz), 6.72 (1H, d, J= 3.0 Hz), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.3 Hz), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.0 Hz), 8.05 (1H, d, J= 3.0 Hz), 8.35 (3H, br s), 8.67 (1H, s), 9.91 (1H, br s).

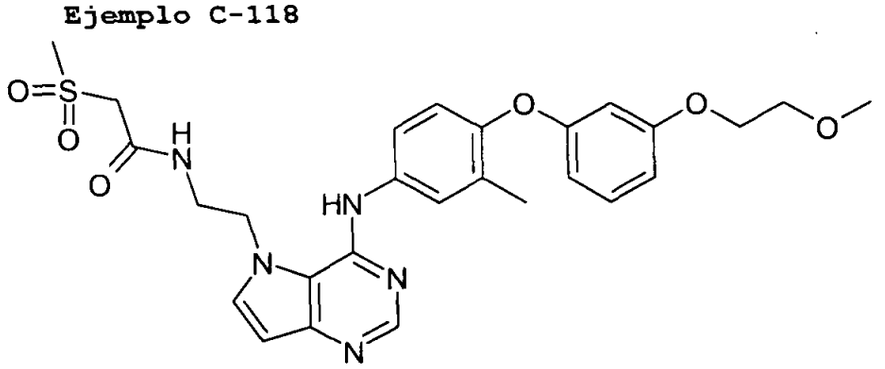
(iii) Producción de clorhidrato de N-{2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (150 mg), ácido metilsulfonilacético (60.9 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (68.1 mg), trietilamina (0.4 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)-carbodiimida (92.2 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo N-{2-[4-({3-metil-4-[3-(3-metilbutoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida. El compuesto se disolvió en acetato de etilo y se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y el precipitado se recogió

por filtración para dar el compuesto del título (116 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 0.92 (6H, d, J= 6.6 Hz), 1.59 (2H, q, J= 6.6 Hz), 1.67-1.84 (1H, m), 2.20 (3H, s), 3.05 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.97 (2H, t, J= 6.6 Hz), 4.06 (2H, s), 4.69 (2H, t, J= 6.0 Hz), 6.40-6.52 (2H, m), 6.64 (1H, d, J= 3.2 Hz), 6.66-6.72 (1H, m), 7.02 (1H, d, J= 8.7 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.45 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.2 Hz), 8.67 (1H, s), 8.78 (1H, t, J= 6.0 Hz), 9.83 (1H, s).

Ejemplo C-118



Producción de N-{2-[4-({4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 1-[3-(2-metoxietoxi)fenoxi]-2-metil-4-nitrobenceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (806 mg), 1-bromo-2-metoxietano (0.5 ml), carbonato de potasio (910 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (855 mg)

en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.39 (3H, s), 3.45 (3H, s), 3.69-3.80 (2H, m), 4.06-4.15 (2H, m), 6.57-6.65 (2H, m), 6.75-6.80 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.24-7.33 (1H, m), 7.99 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.8 Hz).

(ii) Producción de 4-[3-(2-metoxietoxi)fenoxi]-3-metilanilina

Al usar 1-[3-(2-metoxietoxi)fenoxi]-2-metil-4-nitrobenceno (850 mg), hierro reducido (825 mg), cloruro de calcio (167 mg) y etanol (27 ml)/agua (3 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (707 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 2.09 (3H, s), 3.43 (3H, s), 3.56 (2H, br s), 3.67-3.76 (2H, m), 4.02-4.09 (2H, m), 6.35-6.63 (5H, m), 6.79 (1H, d, J= 8.3 Hz), 7.13 (1H, t, J= 8.3 Hz).

(iii) Producción de {2-[4-({4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (358 mg), 4-[3-(2-metoxietoxi)fenoxi]-3-metilanilina (364 mg) y alcohol isopropílico (15 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (563 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 2.22 (3H, s), 3.44

968.

(3H, s), 3.45-3.56 (2H, m), 3.69-3.77 (2H, m), 4.04-4.10 (2H, m), 4.40-4.52 (2H, m), 5.01 (1H, t, J= 5.7 Hz), 6.49-6.65 (4H, m), 6.91-6.99 (1H, m), 7.12-7.23 (2H, m), 7.53-7.73 (2H, m), 8.31 (1H, br s), 8.49 (1H, s).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (558 mg), ácido clorhídrico 6 N (1 ml) y etanol (4 ml) y de la misma manera que en el Ejemplo C-105(ii), se obtuvo el compuesto del título (471 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 2.19 (3H, s), 3.21-3.38 (2H, m), 3.29 (3H, s), 3.58-3.69 (2H, m), 4.00-4.13 (2H, m), 5.00 (2H, t, J= 6.0 Hz), 6.44-6.54 (2H, m), 6.65-6.71 (1H, m), 6.72 (1H, d, J= 3.2 Hz), 7.03 (1H, d, J= 8.7 Hz), 7.20-7.33 (1H, m), 7.41 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.50 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.2 Hz), 8.32 (3H, br s), 8.68 (1H, s), 9.88 (1H, br s).

(v) Producción de N-{2-[4-({4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(2-metoxietoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-

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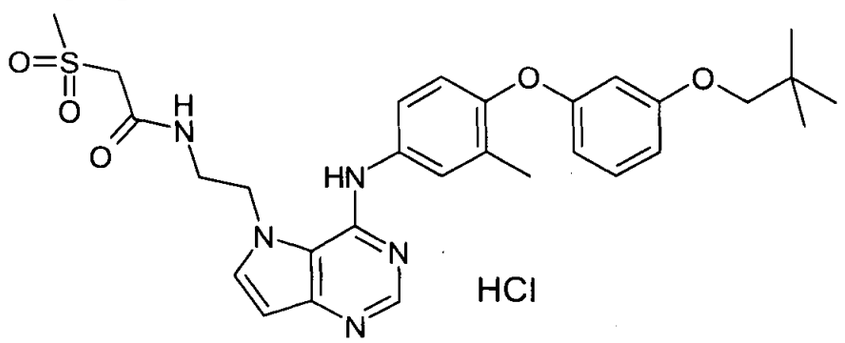
d]pirimidin-4-amina (151 mg), ácido metilsulfonilacético (67.3 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (94.2 mg), trietilamina (0.4 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (122 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo el compuesto del título (98.4 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.23 (3H, s), 3.08 (3H, s), 3.44 (3H, s), 3.63-3.78 (4H, m), 3.93 (2H, s), 4.04-4.13 (2H, m), 4.38-4.54 (2H, m), 6.51 (1H, t, J= 2.4 Hz), 6.53-6.66 (3H, m), 6.94 (1H, d, J= 8.7 Hz), 7.13-7.23 (2H, m), 7.44 (1H, dd, J= 2.0 Hz, 8.7 Hz), 7.51 (1H, t, J= 5.7 Hz), 7.56 (1H, d, J= 2.0 Hz), 7.83 (1H, s), 8.46 (1H, s).

Ejemplo C-119



Producción de clorhidrato de N-{2-[4-({4-[3-(2.2-dimetilpropoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 1-[3-(2.2-dimetilpropoxi)fenoxi]-2-metil-4-nitrobenceno

Al usar 3-(2-metil-4-nitrofenoxi)fenol (803 mg), 1-

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yodo-2,2-dimetilpropano (0.75 ml), carbonato de potasio (911 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo C-104(i), se obtuvo el compuesto del título (826 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.03 (9H, s), 2.40 (3H, s), 3.57 (2H, s), 6.55-6.62 (2H, m), 6.73-6.79 (1H, m), 6.82 (1H, d, J= 9.0 Hz), 7.28 (1H, t, J= 8.5 Hz), 8.00 (1H, dd, J= 2.5 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.5 Hz).

(ii) Producción de 4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilanilina

Al usar 1-[3-(2,2-dimetilpropoxi)fenoxi]-2-metil-4-nitrobenceno (821 mg), hierro reducido (876 mg), cloruro de calcio (147 mg) y etanol (27 ml)/agua (3 ml) y de la misma manera que en el Ejemplo C-72(ii), se obtuvo el compuesto del título (745 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 1.01 (9H, s), 2.11 (3H, s), 3.53 (2H, s), 3.54 (2H, br s), 6.35-6.41 (1H, m), 6.43 (1H, t, J= 2.4 Hz), 6.48-6.56 (2H, m), 6.59 (1H, d, J= 2.8 Hz), 6.80 (1H, d, J= 8.0 Hz), 7.12 (1H, t, J= 8.0 Hz).

(iii) Producción de {2-[4-({4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (351 mg), 4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilanilina (357 mg) y alcohol

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isopropílico (15 ml) y de la misma manera que en el Ejemplo C-105(i), se obtuvo el compuesto del título (592 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.02 (9H, s), 1.46 (9H, s), 2.24 (3H, s), 3.42-3.55 (2H, m), 3.56 (2H, s), 4.39-4.55 (2H, m), 5.02 (1H, t, J= 5.8 Hz), 6.44-6.65 (4H, m), 6.96 (1H, d, J= 8.5 Hz), 7.09-7.22 (2H, m), 7.56-7.72 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (586 mg), ácido clorhídrico 6 N (1 ml) y etanol (4 ml) y de la misma manera que en el Ejemplo C-105(ii), se obtuvo el compuesto del título (369 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 0.98 (9H, s), 2.20 (3H, s), 3.18-3.36 (2H, m), 3.62 (2H, s), 4.99 (2H, t, J= 6.2 Hz), 6.40-6.55 (2H, m), 6.63-6.77 (2H, m), 7.02 (1H, d, J= 8.5 Hz), 7.26 (1H, t, J= 8.2 Hz), 7.41 (1H, dd, J= 2.3 Hz, 8.5 Hz), 7.50 (1H, d, J= 2.3 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.29 (3H, br s), 8.67 (1H, s), 9.86 (1H, br s).

(v) Producción de clorhidrato de N-{2-[4-({4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}amino)-5H-

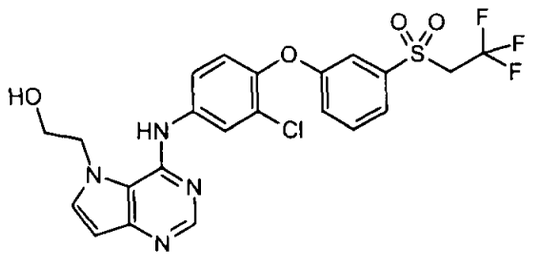
pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (152 mg), ácido metilsulfonilacético (63.0 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (86.5 mg), trietilamina (0.4 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (125 mg) y de la misma manera que en el Ejemplo C-72(i), se obtuvo N-{2-[4-({4-[3-(2,2-dimetilpropoxi)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida. El compuesto se disolvió en acetato de etilo y se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y el precipitado se recogió por filtración para dar el compuesto del título (126 mg) en forma de cristales amarillos.

^{1}H-RMN (DMSO-d_6) δ: 0.98 (9H, s), 2.20 (3H, s), 3.05 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 3.61 (2H, s), 4.07 (2H, s), 4.70 (2H, t, J= 6.0 Hz), 6.40-6.53 (2H, m), 6.64 (1H, d, J= 3.0 Hz), 6.69 (1H, dd, J= 1.7 Hz, 8.0 Hz), 7.02 (1H, d, J= 8.5 Hz), 7.26 (1H, t, J= 8.0 Hz), 7.45 (1H, dd, J= 2.0 Hz, 8.5 Hz), 7.53 (1H, d, J= 2.0 Hz), 7.91 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.80 (1H, t, J= 6.0 Hz), 9.86 (1H, s).

973.

Ejemplo C-120



Producción de 2-{4-[(3-cloro-4-{3-[(2,2,2-trifluoroetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

(i) Producción de 2-cloro-4-nitro-1-{3-[(2,2,2-trifluoroetil)tio]fenoxi}benceno

A una solución de 3-mercaptofenol (2.0 g) y trietilamina (2.70 ml) en N,N-dimetilformamida (20 ml) se añadió 2,2,2-trifluoro-1-yodoetano (1.72 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 4 h, se añadieron 3-cloro-4-fluoronitrobenceno (2.77 g) y carbonato de potasio (2.18 g). La mezcla de reacción se agitó a temperatura ambiente durante 20 h, se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 19:1→3:1) para dar el compuesto del título (4.27 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_6$) δ: 3.48 (2H, q, J = 9.6 Hz), 6.91 (1H, d, J = 9.0 Hz), 6.98-7.02 (1H, m), 7.19-7.21 (1H, m), 7.34-7.44 (2H, m), 8.09 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.40 (1H, d, J = 2.7 Hz).

(ii) Producción de 2-cloro-4-nitro-1-{3-[(2,2,2-trifluoroetil)sulfonil]fenoxi}benceno

A una solución de 2-cloro-4-nitro-1-{3-[(2,2,2-trifluoroetil)tio]fenoxi}benceno (2.0 g) en acetato de etilo (20 ml) se añadió ácido 3-cloroperbenzoico al 70% (2.80 g) a 0°C. La mezcla de reacción se agitó a 0°C durante 2 h y a temperatura ambiente durante 4 días, se añadió solución acuosa de tiosulfato de sodio a la mezcla de reacción, y la mezcla se agitó durante 1 h. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó sucesivamente con bicarbonato de sodio acuoso y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 9:1→2:3) para dar el compuesto del título (2.34 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.94 (2H, q, J = 8.7 Hz), 7.01 (1H, d, J = 9.0 Hz), 7.38-7.43 (1H, m), 7.60-7.62 (1H, m), 7.66-7.71 (1H, m), 7.81-7.85 (1H, m), 8.15 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.43 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-{3-[(2,2,2-

trifluoroetil)sulfonil]fenoxi}anilina

Una mezcla de 2-cloro-4-nitro-1-{3-[(2,2,2-trifluoroetil)sulfonil]fenoxi}benceno (2.34 g), hierro reducido (1.54 g) y cloruro de calcio (0.31 g) en 15% de etanol con contenido de agua (70 ml) se calentó a reflujo durante 10 h. El material insoluble se filtró, y el filtrado se concentró a presión reducida. Se agregó bicarbonato de sodio acuoso al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 3:1→3:7) para dar el compuesto del título (892 mg) en forma de un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ: 3.77 (2H, br s), 3.87 (2H, q, J = 9.0 Hz), 6.60 (1H, dd, J = 2.7, 8.7 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.85 (1H, d, J = 8.7 Hz), 7.20-7.25 (1H, m), 7.35-7.37 (1H, m), 7.51 (1H, t, J = 8.1 Hz), 7.61 (1H, d, J = 8.1 Hz).

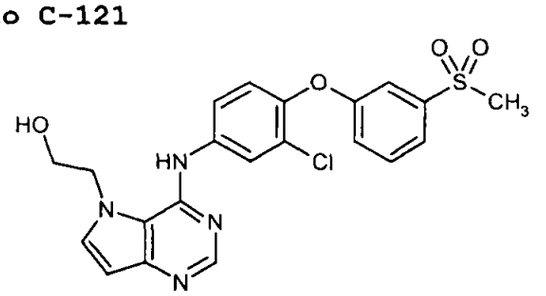
(iv) Producción de 2-{4-[(3-cloro-4-{3-[(2,2,2-trifluoroetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

Una solución de 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina (100 mg) y 3-cloro-4-{3-[(2,2,2-trifluoroetil)sulfonil]fenoxi}anilina (117 mg) en alcohol

isopropílico (3.0 ml) se agitó a 80°C durante 4 días. Después de concentrar a presión reducida, metanol (5.0 ml) y ácido clorhídrico 6 N (1.0 ml) se añadieron al residuo. La mezcla se agitó a temperatura ambiente durante 4 h, y se añadió bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, acetato de etilo→acetato de etilo:metanol = 9:1) para dar el compuesto del título (99 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.90 (2H, q, J = 9.0 Hz), 4.16-4.25 (2H, m), 4.43-4.50 (2H, m), 4.91-5.02 (1H, m), 6.32 (1H, d, J = 3.0 Hz), 7.08 (1H, d, J = 3.0 Hz), 7.11 (1H, d, J = 8.7 Hz), 7.27-7.33 (1H, m), 7.42-7.47 (1H, m), 7.52-7.58 (2H, m), 7.64-7.67 (1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.35 (1H, s), 9.45 (1H, s).

Ejemplo C-121



Producción de 2-[4-({3-cloro-4-[3-(metilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-cloro-1-[3-(metiltio)fenoxi]-4-nitrobenceno

A una solución de 3-mercaptofenol (3.0 g) y trietilamina (3.64 ml) en N,N-dimetilformamida (30 ml) se añadió yoduro de metilo (1.48 ml) a 0°C. La mezcla de reacción se agitó a 0°C durante 1 h y a temperatura ambiente durante 30 min, se añadieron 3-cloro-4-fluoronitrobenceno (4.18 g) y carbonato de potasio (3.29 g) a la mezcla de reacción. La mezcla de reacción se agitó a temperatura ambiente durante 14 h, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 19:1→3:1) para dar el compuesto del título (2.84 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.49 (3H, s), 6.80-6.84 (1H, m), 6.91 (1H, d, J = 9.3 Hz), 6.96-6.97 (1H, m), 7.11-7.15 (1H, m), 7.32-7.37 (1H, m), 8.07 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.39 (1H, d, J = 2.7 Hz).

(ii) Producción de 2-cloro-1-[3-(metilsulfonil)fenoxi]-4-nitrobenceno

A una solución de 2-cloro-1-[3-(metiltio)fenoxi]-4-nitrobenceno (2.84 g) en acetato de etilo (50 ml) se añadió

ácido 3-cloroperbenzoico al 70% (5.21 g) a 0°C. La mezcla de reacción se agitó a 0°C durante 1 h, se añadió solución acuosa de tiosulfato de sodio a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla se extrajo con acetato de etilo, la capa orgánica se lavó sucesivamente con bicarbonato de sodio acuoso y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 4:1→2:3) para dar el compuesto del título (2.79 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.09 (3H, s), 7.02 (1H, d, J = 8.7 Hz), 7.32-7.36 (1H, m), 7.61-7.67 (2H, m), 7.79-7.83 (1H, m), 8.13 (1H, dd, J = 2.4 Hz, 8.7 Hz), 8.42 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(metilsulfonil)fenoxi]anilina

Al usar 2-cloro-1-[3-(metilsulfonil)fenoxi]-4-nitrobenceno (2.90 g), hierro reducido (2.50 g), cloruro de calcio (0.50 g) y 15% de etanol con contenido de agua (90 ml) y de la misma manera que en el Ejemplo C-120(iii), se obtuvo el compuesto del título (2.29 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.03 (3H, s), 3.74 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.4 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.4 Hz), 7.13-7.17 (1H, m), 7.36-7.38 (1H,

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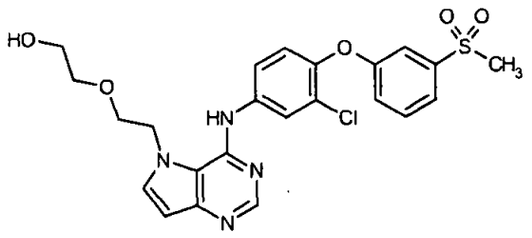
m), 7.44-7.50 (1H, m), 7.56-7.60 (1H, m).

(iv) Producción de 2-[4-({3-cloro-4-[3-(metilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Una solución de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg) y 3-cloro-4-[3-(metilsulfonil)fenoxi]anilina (98.3 mg) en alcohol isopropílico (2.0 ml) se agitó a 80°C durante 3 días. La mezcla de reacción se enfrió hasta temperatura ambiente, se añadió solución acuosa 1 N de hidróxido de sodio (1.0 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, acetato de etilo→acetato de etilo:metanol = 9:1) para dar el compuesto del título (116 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 3.06 (3H, s), 4.18 (2H, t, J = 4.7 Hz), 4.44 (2H, t, J = 4.7 Hz), 6.27 (1H, d, J = 3.0 Hz), 7.05 (1H, d, J = 3.0 Hz), 7.11 (1H, d, J = 9.0 Hz), 7.22-7.28 (1H, m), 7.43-7.45 (1H, m), 7.50-7.55 (2H, m), 7.61-7.64 (1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.31 (1H, s), 9.50 (1H, s).

Ejemplo C-122



Producción de 2-{2-[4-({3-cloro-4-[3-(metilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (100 mg), 3-cloro-4-[3-(metilsulfonil)fenoxi]anilina (86.1 mg), alcohol isopropílico (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo el compuesto del título (117 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.78-1.85 (1H, m), 3.05 (3H, s), 3.78-3.84 (4H, m), 4.03 (2H, t, J = 4.4 Hz), 4.59 (2H, t, J = 4.4 Hz), 6.64 (1H, d, J = 3.3 Hz), 7.09 (1H, d, J = 9.0 Hz), 7.22-7.27 (2H, m), 7.39-7.41 (1H, m), 7.48-7.53 (1H, m), 7.61 (1H, s), 7.63 (1H, dd, J = 2.7 Hz, 9.0 Hz), 7.94 (1H, d, J = 2.7 Hz), 8.53 (1H, s), 8.85 (1H, s).

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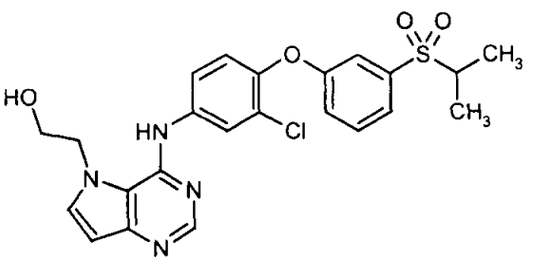
Ejemplo C-123



Producción de 2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-cloro-1-[3-(isopropiltio)fenoxi]-4-nitrobenceno

A una solución de 3-mercaptofenol (1.5 g) y ter-butóxido de sodio (1.37 g) en N,N-dimetilformamida (25 ml) se añadió 2-bromopropano (1.23 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 16 h, se agregaron ter-butóxido de sodio (1.37 g) y 3-cloro-4-fluoronitrobenceno (1.88 g) a la mezcla de reacción, y la mezcla se agitó durante 4 h. También se adicionó 3-cloro-4-fluoronitrobenceno (0.17 g) a la mezcla de reacción y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 19:1→4:1) para dar el

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compuesto del título (3.36 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (6H, d, J = 6.9 Hz), 3.42 (1H, quinteto, J = 6.9 Hz), 6.88-6.92 (2H, m), 7.07-7.08 (1H, m), 7.21-7.27 (1H, m), 7.32-7.37 (1H, m), 8.06 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.38 (1H, d, J = 2.7 Hz).

(ii) Producción de 2-cloro-1-[3-(isopropilsulfonil)fenoxi]-4-nitrobenceno

Al usar 2-cloro-1-[3-(isopropiltio)fenoxi]-4-nitrobenceno (3.36 g), ácido 3-cloroperbenzoico al 70% (5.63 g) y acetato de etilo (50 ml) y de la misma manera que en el Ejemplo C-121(ii), se obtuvo el compuesto del título (3.36 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (6H, d, J = 6.9 Hz), 3.22 (1H, quinteto, J = 6.9 Hz), 6.99 (1H, d, J = 9.0 Hz), 7.33-7.37 (1H, m), 7.54-7.55 (1H, m), 7.61-7.66 (1H, m), 7.74-7.77 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(isopropilsulfonil)fenoxi]anilina

Al usar 2-cloro-1-[3-(isopropilsulfonil)fenoxi]-4-nitrobenceno (3.30 g), hierro reducido (2.59 g), cloruro de calcio (0.52 g) y 15% de etanol con contenido de agua (100 ml) y de la misma manera que en el Ejemplo C-120(iii), se obtuvo el compuesto del título (3.00 g) en forma de un aceite amarillo.

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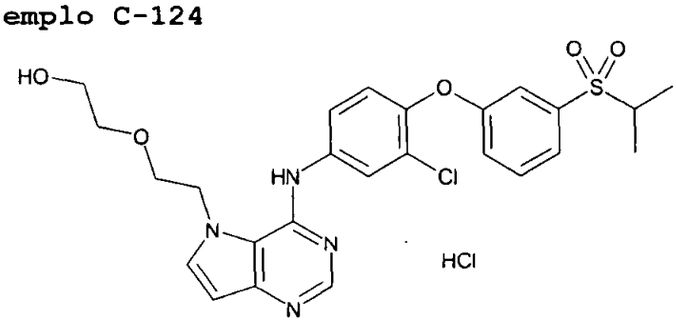
^{1}H-RMN ($CDCl_3$) δ: 1.28 (6H, d, J = 6.9 Hz), 3.16 (1H, quinteto, J = 6.9 Hz), 3.73 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.14-7.19 (1H, m), 7.28-7.30 (1H, m), 7.44-7.54 (2H, m).

(iv) Producción de 2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg), 3-cloro-4-[3-(isopropilsulfonil)fenoxi]anilina (140 mg), alcohol isopropílico (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo el compuesto del título (127 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.30 (6H, d, J = 6.9 Hz), 3.19 (1H, quinteto, J = 6.9 Hz), 4.16 (2H, t, J = 4.5 Hz), 4.43 (2H, t, J = 4.5 Hz), 5.30-5.71 (1H, m), 6.26 (1H, d, J = 3.0 Hz), 7.05 (1H, d, J = 3.0 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.23-7.30 (1H, m), 7.35-7.37 (1H, m), 7.48-7.61 (3H, m), 7.84 (1H, d, J = 2.4 Hz), 8.31 (1H, s), 9.53 (1H, s).

Ejemplo C-124



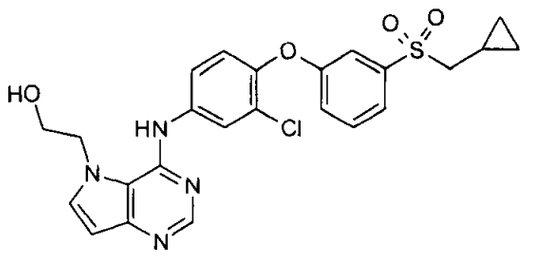
Producción de clorhidrato de 2-{2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (100 mg), 3-cloro-4-[3-(isopropilsulfonil)fenoxi]anilina (113 mg), alcohol isopropílico (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo un aceite de color amarillo pálido. A una solución del aceite obtenido en etanol (5.0 ml) se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (0.50 ml) a temperatura ambiente. La mezcla se concentró a presión reducida, y los cristales resultantes se recogieron por filtración. Los cristales se lavaron con acetato de etilo para dar el compuesto del título (130 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz), 3.38-3.54 (5H, m), 3.82-3.89 (2H, m), 4.75-4.83 (2H, m), 6.69 (1H, d, J = 3.0 Hz), 7.23-7.25 (1H, m), 7.39-7.44 (2H, m), 7.61-7.75 (3H, m), 7.99-8.03 (2H, m), 8.73 (1H, s), 9.84 (1H, br

s).

Ejemplo C-125



Producción de 2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

(i) Producción de 2-cloro-1-{3-[(ciclopropilmetil)tio]fenoxi}-4-nitrobenceno

A una solución de 3-mercaptofenol (1.5 g) y ter-butóxido de sodio (1.26 g) en N,N-dimetilformamida (15 ml) se añadió 1-(bromometil)ciclopropano (1.27 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 16 h, ter-butóxido de sodio (1.27 g) y 3-cloro-4-fluoronitrobenceno (1.88 g) se añadieron a la mezcla de reacción, y la mezcla se agitó durante 3 días. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 19:1→4:1) para dar el compuesto del título (2.93 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.25-0.30 (2H, m), 0.58-0.64 (2H, m), 0.99-1.13 (1H, m), 2.89 (2H, d, J = 7.2 Hz), 6.84-6.89 (1H, m), 6.90 (1H, d, J = 9.0 Hz), 7.05 (1H, t, J = 2.1 Hz), 7.20-7.24 (2H, m), 7.31-7.36 (1H, m), 8.06 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.39 (1H, d, J = 2.7 Hz).

(ii) Producción de 2-cloro-1-{3-[(ciclopropilmetil)sulfonil]fenoxi}-4-nitrobenceno

Al usar 2-cloro-1-{3-[(ciclopropilmetil)tio]fenoxi}-4-nitrobenceno (2.93 g), ácido 3-cloroperbenzoico al 70% (4.73 g) y acetato de etilo (60 ml) y de la misma manera que en el Ejemplo C-121(ii), se obtuvo el compuesto del título (2.90 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 0.14-0.20 (2H, m), 0.57-0.63 (2H, m), 0.95-1.09 (1H, m), 3.05 (2H, d, J = 7.2 Hz), 7.00 (1H, d, J = 9.0 Hz), 7.33-7.36 (1H, m), 7.59-7.66 (2H, m), 7.78-7.82 (1H, m), 8.13 (1H, dd, J= 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}anilina

Al usar 2-cloro-1-{3-[(ciclopropilmetil)sulfonil]fenoxi}-4-nitrobenceno (2.84 g), hierro reducido (2.57 g), cloruro de calcio (0.51 g) y 15% de etanol con contenido de agua (85 ml) y de la misma manera que en el Ejemplo C-120(iii), se obtuvo el compuesto del título

(2.60 g) en forma de un aceite de color amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.10-0.16 (2H, m), 0.52-0.58 (2H, m), 0.90-1.06 (1H, m), 2.99 (2H, d, J = 7.5 Hz), 3.74 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.15-7.19 (1H, m), 7.34-7.35 (1H, m), 7.44-7.49 (1H, m), 7.55-7.59 (1H, m).

(iv) Producción de 2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg), 3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}anilina (123 mg), alcohol isopropílico (2.0 ml), 1-metil-2-pirrolidona (2.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.0 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo el compuesto del título (126 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 0.11-0.19 (2H, m), 0.53-0.63 (2H, m), 0.94-1.05 (1H, m), 3.01 (2H, d, J = 7.2 Hz), 4.13-4.21 (2H, m), 4.39-4.47 (2H, m), 5.11-5.31 (1H, m), 6.29 (1H, d, J = 3.3 Hz), 7.06 (1H, d, J = 3.3 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.24-7.30 (1H, m), 7.40-7.42 (1H, m), 7.48-7.54 (2H, m), 7.60-7.63 (1H, m), 7.83 (1H, d, J = 2.4 Hz), 8.32 (1H, s), 9.48 (1H, s).

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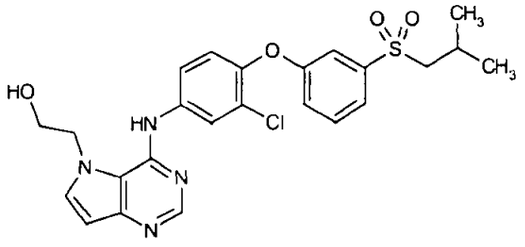
Ejemplo C-126



Producción de 2-[4-({3-cloro-4-[3-(isobutilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 2-cloro-1-[3-(isobutiltio)fenoxi]-4-nitrobenceno

A una solución de 3-mercaptofenol (1.5 g) y ter-butóxido de sodio (1.26 g) en N,N-dimetilformamida (15 ml) se añadió 1-bromo-2-metilpropano (1.42 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 días, se añadieron ter-butóxido de sodio (1.26 g) y 3-cloro-4-fluoronitrobenceno (2.08 g) a la mezcla de reacción y la mezcla se agitó durante 6 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 19:1→3:1) para dar el compuesto del título (3.63 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (6H, d, J = 6.6 Hz), 1.83-

1.96 (1H, m), 2.82 (2H, d, J = 6.3 Hz), 6.81-6.84 (1H, m), 6.89 (1H, d, J = 9.0 Hz), 6.99-7.01 (1H, m), 7.15-7.19 (1H, m), 7.29-7.34 (1H, m), 8.05 (1H, dd, J = 2.4 Hz, 9.0 Hz), 8.37 (1H, d, J = 2.4 Hz).

(ii) Producción de 2-cloro-1-[3-(isobutilsulfonil)fenoxi]-4-nitrobenceno

Al usar 2-cloro-1-[3-(isobutiltio)fenoxi]-4-nitrobenceno (3.63 g), ácido 3-cloroperbenzoico al 70% (5.80 g) y acetato de etilo (50 ml) y de la misma manera que en el Ejemplo C-121(ii), se obtuvo el compuesto del título (3.88 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.08 (6H, d, J = 6.6 Hz), 2.20-2.23 (1H, m), 3.00 (2H, d, J = 6.6 Hz), 7.00 (1H, d, J = 9.0 Hz), 7.31-7.35 (1H, m), 7.58 (1H, t, J = 2.1 Hz), 7.60-7.66 (1H, m), 7.76-7.80 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.41 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(isobutilsulfonil)fenoxi]anilina

Al usar 2-cloro-1-[3-(isobutilsulfonil)fenoxi]-4-nitrobenceno (3.88 g), hierro reducido (2.93 g), cloruro de calcio (0.58 g) y 15% de etanol con contenido de agua (120 ml) y de la misma manera que en el Ejemplo C-120(iii), se obtuvo el compuesto del título (3.40 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (6H, d, J = 6.6 Hz), 2.13-

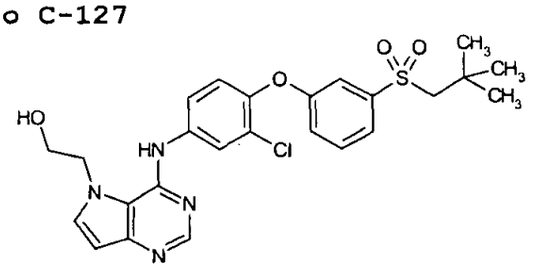
2.28 (1H, m), 2.96 (2H, d, J = 6.6 Hz), 3.74 (2H, br s), 6.60 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.93 (1H, d, J = 8.7 Hz), 7.13-7.18 (1H, m), 7.34 (1H, t, J = 2.1 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.54-7.57 (1H, m).

(iv) Producción de 2-[4-({3-cloro-4-[3-(isobutilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg), 3-cloro-4-[3-(isobutilsulfonil)fenoxi]anilina (123 mg), alcohol isopropílico (5.0 ml) y solución acuosa 1 N de hidróxido de sodio (2.0 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo el compuesto del título (112 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.06 (6H, d, J =6.9 Hz), 2.18-2.29 (1H, m), 2.98 (2H,d, J = 6.6 Hz), 4.12-4.21 (2H, m), 4.39-4.48 (2H, m), 5.45-5.60 (1H, m), 6.25 (1H, d, J = 3.0 Hz), 7.04 (1H, d, J = 3.0 Hz), 7.09 (1H, d, J = 8.7 Hz), 7.23-7.27 (1H, m), 7.39-7.41 (1H, m), 7.48-7.53 (2H, m), 7.57-7.61 (1H, m), 7.83 (1H, d, J = 2.4 Hz), 8.30 (1H, s), 9.50 (1H, s).

Ejemplo C-127



Producción de 2-{4-[(3-cloro-4-{3-[(2,2-dimetilpropil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

(i) Producción de 2-cloro-1-{3-[(2,2-dimetilpropil)tio]fenoxi}-4-nitrobenceno

A una solución de 3-mercaptofenol (1.5 g) y ter-butóxido de sodio (1.26 g) en N,N-dimetilformamida (15 ml) se añadió 1-bromo-2,2-dimetilpropano (1.64 ml) a temperatura ambiente. Tras agitar a 70°C durante 24 h, la mezcla se enfrió hasta temperatura ambiente, se agregaron ter-butóxido de sodio (1.26 g) y 3-cloro-4-fluoronitrobenceno (2.08 g), y la mezcla se agitó a temperatura ambiente durante 3 días. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 19:1→7:3) para dar el compuesto del título (2.80 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.05 (9H, s), 2.89 (2H, s), 6.80-6.84 (1H, m), 6.88 (1H, d, J = 9.0 Hz), 7.02-7.04 (1H, m), 7.18-7.22 (1H, m), 7.28-7.33 (1H, m), 8.05 (1H, dd, J = 3.0 Hz, 9.0 Hz), 8.37 (1H, d, J = 3.0 Hz).

(ii) Producción de 2-cloro-1-{3-[(2,2-

dimetilpropil)sulfonil]fenoxi}-4-nitrobenceno

Al usar 2-cloro-1-{3-[(2,2-dimetilpropil)tio]fenoxi}-4-nitrobenceno (2.80 g), ácido 3-cloroperbenzoico al 70% (4.32 g) y acetato de etilo (56 ml) y de la misma manera que en el Ejemplo C-121(ii), se obtuvo el compuesto del título (3.04 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.20 (9H, s), 3.05 (2H, s), 7.00 (1H, d, J = 9.0 Hz), 7.30-7.34 (1H, m), 7.59-7.66 (2H, m), 7.77-7.81 (1H, m), 8.13 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.42 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-{3-[(2,2-dimetilpropil)sulfonil]fenoxi}anilina

Al usar 2-cloro-1-{3-[(2,2-dimetilpropil)sulfonil]fenoxi}-4-nitrobenceno (3.0 g), hierro reducido (2.18 g), cloruro de calcio (0.43 g) y 15% de etanol con contenido de agua (90 ml) y de la misma manera que en el Ejemplo C-120(iii), se obtuvo el compuesto del título (2.34 g) en forma de un amorfo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.17 (9H, s), 3.01 (2H, s), 3.73 (2H, br s), 6.59 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.92 (1H, d, J = 9.0 Hz), 7.08-7.14 (1H, m), 7.35-7.36 (1H, m), 7.42-7.47 (1H, m), 7.53-7.57 (1H, m).

(iv) Producción de 2-{4-[(3-cloro-4-{3-[(2,2-dimetilpropil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-

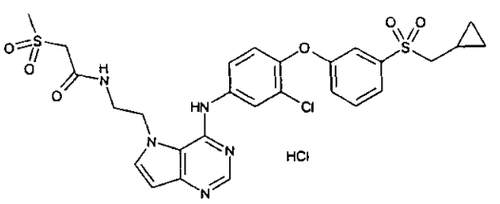
993

d]pirimidin-5-il}etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (100 mg), 3-cloro-4-{3-[(2,2-dimetilpropil)sulfonil]fenoxi}anilina (140 mg), alcohol isopropílico (3.0 ml) y solución acuosa 1 N de hidróxido de sodio (1.5 ml) y de la misma manera que en el Ejemplo C-121(iv), se obtuvo el compuesto del título (131 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.19 (9H, s), 3.04 (2H, s), 4.11-4.20 (2H, m), 4.35-5.46 (2H, m), 5.81-5.96 (1H, m), 6.20 (1H, d, J = 3.3 Hz), 7.02 (1H, d, J = 3.3 Hz), 7.08 (1H, d, J = 8.7 Hz), 7.20-7.27 (1H, m), 7.41-7.43 (1H, m), 7.46-7.52 (2H, m), 7.56-7.63 (1H, m), 7.83 (1H, d, J = 2.7 Hz), 8.27 (1H, s), 9.55 (1H, s).

Ejemplo C-128



Producción de clorhidrato de N-(2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de (2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-

d]pirimidin-5-il)etil]carbamato de ter-butilo (1.00 g) y 3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}anilina (1.14 g) en alcohol isopropílico (10 ml) se agitó a 80°C durante 14 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna (eluyente, hexano:acetato de etilo = 1:1→acetato de etilo→acetato de etilo:metanol = 9:1) para dar el compuesto del título (1.86 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.10-0.20 (2H, m), 0.54-0.61 (2H, m), 0.92-1.06 (1H, m), 1.50 (9H, s), 3.01 (2H, d, J = 6.9 Hz), 3.43-3.53 (2H, m), 4.43-4.52 (2H, m), 5.02-5.10 (1H, m), 6.61 (1H, d, J = 3.0 Hz), 7.09 (1H, d, J = 9.0 Hz), 7.19 (1H, d, J = 3.0 Hz), 7.21-7.28 (1H, m), 7.46-7.52 (2H, m), 7.60-7.63 (1H, m), 7.91 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.06 (1H, d, J = 2.7 Hz), 8.51 (1H, s), 8.62 (1H, br s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de (2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-

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pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo (1.86 g), ácido clorhídrico 6 N (5.0 ml) y etanol (20 ml) se agitó a 60°C durante 3 días. Después de concentrar a presión reducida, etanol se añadió al residuo. La mezcla se concentró a presión reducida, y los cristales resultantes se recogieron por filtración y se lavó con éter diisopropílico para dar el compuesto del título (1.66 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 0.09-0.14 (2H, m), 0.41-0.48 (2H, m), 0.76-0.88 (1H, m), 3.22-3.38 (4H, m), 4.94-5.05 (2H, m), 6.74 (1H, d, J = 2.7 Hz), 7.30-7.45 (3H, m), 7.61-7.74 (3H, m), 7.92-7.97 (1H, m), 8.00-8.08 (1H, m), 8.23-8.32 (3H, m), 8.72 (1H, s), 9.99 (1H, br s).

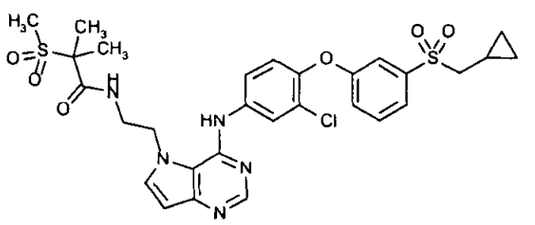
(iii) Producción de clorhidrato de N-(2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (100 mg), ácido metilsulfonilacético (48.4 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (101 mg), monohidrato de 1-hidroxibenzotriazol (80 mg) y trietilamina (0.073 ml) en N,N-dimetilformamida (5.0 ml) se agitó a temperatura ambiente durante 20 h. Se añadió agua a la mezcla de reacción y la

mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar un amorfo de color amarillo pálido. A una solución del amorfo de color amarillo pálido obtenido en etanol (5.0 ml) se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (0.5 ml) a temperatura ambiente. Tras agitar a temperatura ambiente durante 1 h, los cristales resultantes se recogieron por filtración y se lavó con acetato de etilo para dar el compuesto del título (81 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 0.06-0.13 (2H, m), 0.40-0.47 (2H, m), 0.75-0.90 (1H, m), 3.06 (3H, s), 3.30 (2H, d, J = 6.9 Hz), 3.49-3.60 (2H, m), 4.06 (2H, s), 4.64-4.73 (2H, m), 6.66 (1H, d, J = 2.7 Hz), 7.30-7.44 (3H, m), 7.65-7.74 (3H, m), 7.91-7.99 (2H, m), 8.68-8.79 (2H, m), 8.86 (1H, br s).

Ejemplo C-129



Producción de N-(2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-metil-2-(metilsulfonil)propanamida

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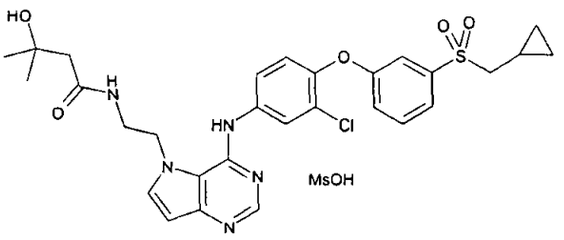
Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (120 mg), ácido 2-metil-2-(metilsulfonil)propanoico (52 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (90 mg), monohidrato de 1-hidroxibenzotriazol (72 mg) y trietilamina (0.088 ml) en N,N-dimetilformamida (5.0 ml) se agitó a temperatura ambiente durante 2 días. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) para dar el compuesto del título (120 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.11-0.18 (2H, m), 0.54-0.61 (2H, m), 0.92-1.07 (1H, m), 1.70 (6H, s), 2.93 (3H, s), 3.01 (2H, d, J = 7.2 Hz), 3.64-3.74 (2H, m), 4.43-4.52 (2H, m), 6.64 (1H, d, J = 3.3 Hz), 6.99 (1H, d, J = 9.0 Hz), 7.21 (1H, d, J = 3.3 Hz), 7.22-7.32 (2H, m), 7.42-7.44 (1H, m), 7.51 (1H, t, J = 8.1 Hz), 7.60-7.64 (1H, m), 7.89 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.07 (1H, d, J = 2.7 Hz), 8.37 (1H, s), 8.53 (1H, s).

998

Ejemplo C-130



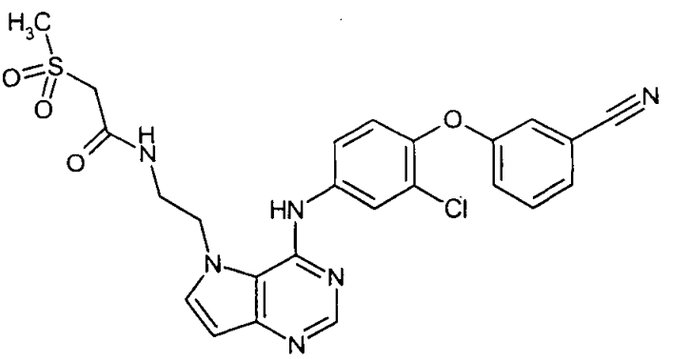
Producción de metansulfonato de N-(2-{4-[(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-(3-cloro-4-{3-[(ciclopropilmetil)sulfonil]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (120 mg), ácido 3-hidroxi-3-metilbutanoico (49.7 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (121 mg), monohidrato de 1-hidroxibenzotriazol (97 mg) y trietilamina (0.090 ml) en N,N-dimetilformamida (5.0 ml) se agitó a temperatura ambiente durante 20 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 4:1) para dar una forma amorfa incolora. A una solución de la forma amorfa de color amarillo pálido obtenida en acetato de etilo (5.0 ml) se

añadió ácido metansulfónico (12.4 µl) a temperatura ambiente. Tras agitar a temperatura ambiente durante 1 h, los cristales resultantes se recogieron por filtración y se lavó con acetato de etilo para dar el compuesto del título (116 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 0.08-0.14 (2H, m), 0.41-0.47 (2H, m), 0.75-0.88 (1H, m), 1.12 (6H, s), 2.20 (2H, s), 2.30 (3H, s), 3.29 (2H, d, J = 7.2 Hz), 3.43-3.56 (2H, m), 4.62 (2H, t, J = 7.5 Hz), 6.66 (1H, d, J=3.0 Hz), 7.31-7.45 (3H, m), 7.64-7.76 (3H, m), 7.93-8.01 (2H, m), 8.34 (1H, t, J = 5.4 Hz), 8.72 (1H, s), 10.14 (1H, br s).

Ejemplo C-131



Producción de N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

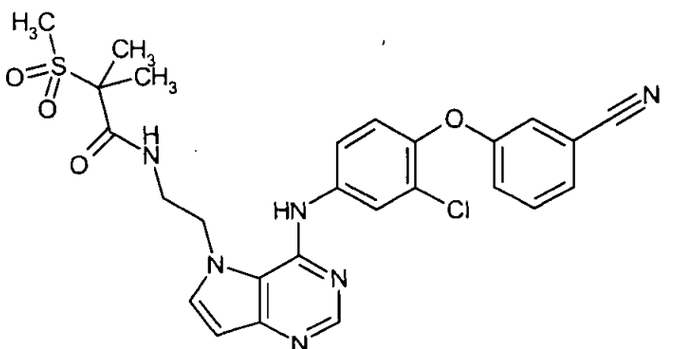
Al usar 3-(4-amino-2-clorofenoxi)benzonitrilo (115 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (125 mg), alcohol isopropílico (2.0 ml), metanol (2 ml), solución de cloruro de

L000

hidrógeno 4 N/acetato de etilo (3.0 ml), ácido metilsulfonilacético (170 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (360 mg), 1-hidroxibenzotriazol (15 mg), trietilamina (0.86 ml) y N,N-dimetilformamida (15 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (169 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 3.10 (3H, s), 3.44-3.49 (2H, m), 4.05 (2H, s), 4.55-4.60 (2H, m), 6.51-6.52 (1H, m), 7.24-8.01 (8H, m), 8.38 (1H, s), 8.66-8.69 (1H, m), 8.81 (1H, s).

Ejemplo C-132



Producción de N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida

Al usar 3-(4-amino-2-clorofenoxi)benzonitrilo (115 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (125 mg), alcohol isopropílico (2.0 ml), metanol (2 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml), ácido 2-metil-2-(metilsulfonil)propanoico (210 mg), clorhidrato de 1-etil-3-

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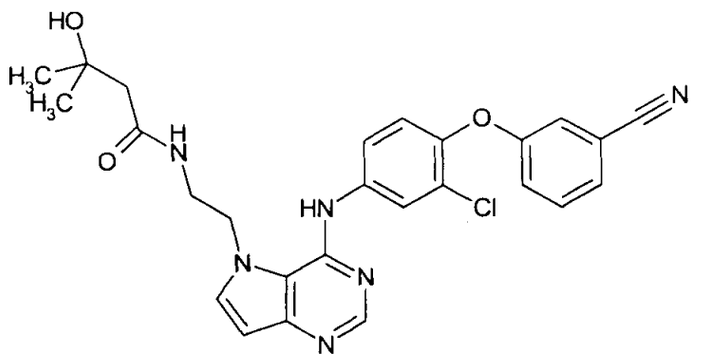
(3-dimetilaminopropil)carbodiimida (370 mg), 1-hidroxibenzotriazol (40 mg), trietilamina (1.0 ml) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (173 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.41 (6H, s), 2.95 (3H, s), 3.42-3.49 (2H, m), 4.58-4.62 (2H, m), 6.50-6.51 (1H, m), 7.24-8.00 (8H, m), 8.20 (1H, br s), 8.40 (1H, s), 8.88 (1H, s).

Ejemplo C-133



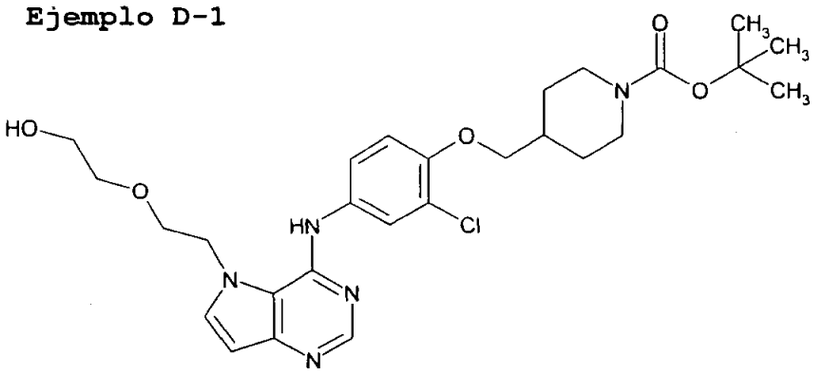
Producción de N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

Al usar 3-(4-amino-2-clorofenoxi)benzonitrilo (115 mg), [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (125 mg), alcohol isopropílico (2.0 ml), metanol (2 ml), solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml), ácido 3-hidroxi-3-metilbutanoico (190 mg), clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (320 mg), 1-hidroxibenzotriazol (15 mg), trietilamina (0.5 ml) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo C-53(ii), se obtuvo el compuesto del título (115 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.13 (6H, s), 2.20 (2H, s), 3.42-3.49 (2H, m), 4.50-4.55 (2H, m), 4.66 (1H, s), 6.50-6.51 (1H, m), 7.24-8.06 (8H, m), 8.24 (1H, br s), 8.35 (1H, s), 8.92 (1H, s).

Ejemplo D-1



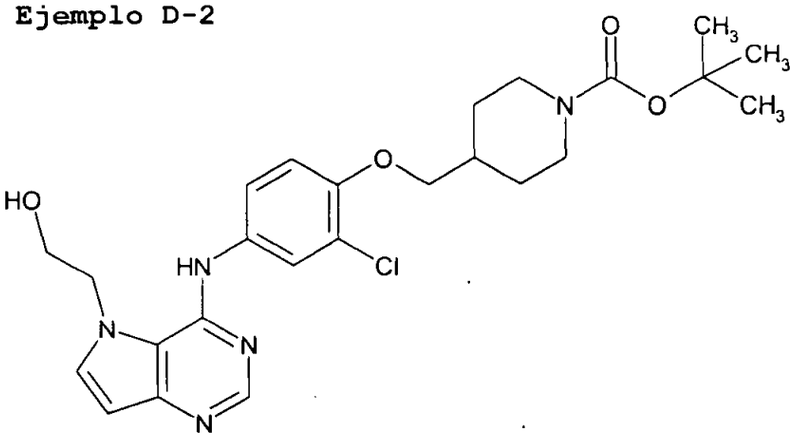
Producción de 4-{[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]metil}piperidin-1-carboxilato de ter-butilo

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (156 mg), 4-[(4-amino-2-clorofenoxi)metil]piperidin-1-carboxilato de ter-butilo (200 mg) y alcohol isopropílico (15 ml) se agitó a 80°C durante la noche. Después de concentrar a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado a la mezcla de reacción y la mezcla se extrajo con

acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20). Las fracciones objeto se concentraron a presión reducida. El producto crudo se disolvió en metanol (5.0 ml), tetrahidrofurano (4.0 ml) y solución acuosa 1 N de hidróxido de sodio (3.0 ml) se añadieron y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo/hexano para dar el compuesto del título (74 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.13-1.27 (2H, m), 1.40 (9H, s), 1.76-1.80 (2H, m), 1.86-2.03 (1H, m), 2.65-2.86 (2H, m), 3.47 (4H, s), 3.78-4.01 (6H, m), 4.60-4.68 (3H, m), 6.47 (1H, d, J= 3.1 Hz), 7.12 (1H, d, J= 9.1 Hz), 7.50 (1H, dd, J= 9.1, 2.7 Hz), 7.63 (1H, d, J= 3.1 Hz), 7.78 (1H, d, J= 2.7 Hz), 8.26 (1H, s), 8.68 (1H, br s).

Ejemplo D-2



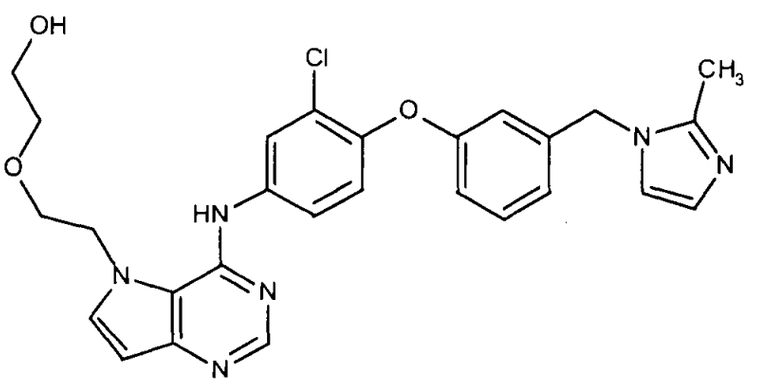
Producción de 4-[(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)metil]piperidin-1-carboxilato de ter-butilo

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (200 mg), 4-[(4-amino-2-clorofenoxi)metil]piperidin-1-carboxilato de ter-butilo (293 mg) y alcohol isopropílico (5.0 ml) se agitó a 80°C durante la noche. Después de concentrar a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→80:20). Las fracciones objeto se concentraron a presión reducida. El producto crudo se disolvió en metanol (5.0 ml), tetrahidrofurano (4.0 ml) y solución acuosa 1 N de hidróxido de sodio (4.0 ml) se

añadieron a la mezcla y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo/hexano para dar el compuesto del título (147 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.13-1.27 (2H, m), 1.40 (9H, s), 1.76-1.80 (2H, m), 1.86-2.03 (1H, m), 2.65-2.86 (2H, m), 3.83-4.01 (6H, m), 4.50 (2H, t, J= 4.1 Hz), 6.18-6.21 (1H, m), 6.46 (1H, d, J= 3.1 Hz), 7.13 (1H, d, J= 9.1 Hz), 7.46 (1H, dd, J= 9.1, 2.7 Hz), 7.60 (1H, d, J= 3.1 Hz), 7.75 (1H, d, J= 2.7 Hz), 8.26 (1H, s), 9.53 (1H, br s).

Ejemplo E-1



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Producción de 2-(2-{4-[(3-cloro-4-{3-[(2-metil-1H-imidazol-1-il)metil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol

(i) Producción de [3-(2-cloro-4-nitrofenoxi)fenil]metanol

A una solución de 3-(hidroximetil)fenol (6.21 g) y 3-cloro-4-fluoronitrobenceno (9.24 g) en N,N-dimetilformamida (50 ml) se añadió carbonato de potasio (10.37 g) a temperatura ambiente y la mezcla se agitó durante 4 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida, y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60) para dar el compuesto del título (5.55 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.78 (1H, t, J = 5.7 Hz), 4.74 (2H, d, J = 5.7 Hz), 6.90 (1H, d, J = 9.0 Hz), 6.95-7.05 (1H, m), 7.12 (1H, s), 7.25-7.30 (1H, m), 7.43 (1H, t, J =8.0 Hz), 8.05-8.10 (1H, m), 8.35-8.40 (1H, m).

(ii) Producción de 1-[3-(2-cloro-4-nitrofenoxi)bencil]-2-metil-1H-imidazol

A una solución de [3-(2-cloro-4-nitrofenoxi)fenil]metanol (1.12 g) en tetrahidrofurano (30

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ml) se añadieron trietilamina (0.67 ml) y cloruro de metansulfonilo (0.33 ml) bajo enfriamiento con hielo, y la mezcla se agitó a 0°C durante 1 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. Se agregaron 2-metilimidazol (328 mg), carbonato de potasio (829 mg) y N,N-dimetilformamida (10 ml) al residuo obtenido, y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo) para dar el compuesto del título (0.96 g) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.35 (3H, s), 5.08 (2H, s), 6.75-6.9 (3H, m), 6.90-7.05 (3H, m), 7.41 (1H, t, J = 7.8 Hz), 8.06 (1H, dd, J = 2.7 Hz, 9.0 Hz), 8.38 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-{3-[(2-metil-1H-imidazol-1-il)metil]fenoxi}anilina

A una solución de 1-[3-(2-cloro-4-nitrofenoxi)bencil]-2-metil-1H-imidazol (0.96 g) en metanol (10 ml) se añadió platino-carbón activado al 5% (192 mg) bajo

una atmósfera de nitrógeno. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 19 h, y se filtró el platino-carbón activado al 5%. El filtrado se concentró a presión reducida y el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0) para dar el compuesto del título (494 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.32 (3H, s), 3.69 (2H, br s), 4.99 (2H, s), 6.56 (1H, dd, J = 2.7 Hz, 9.0 Hz), 6.60-6.70 (2H, m), 6.70-6.85 (3H, m), 6.87 (1H, d, J = 9.0 Hz), 6.93 (1H, d, J = 1.2 Hz), 7.22 (1H, t, J = 7.6 Hz).

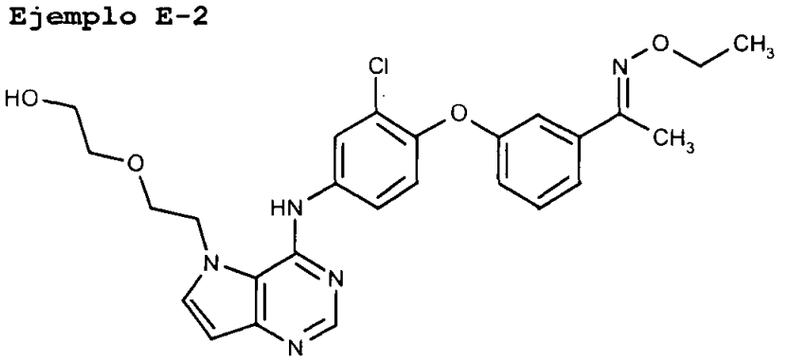
(iv) Producción de 2-(2-{4-[(3-cloro-4-{3-[(2-metil-1H-imidazol-1-il)metil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (207 mg), 3-cloro-4-{3-[(2-metil-1H-imidazol-1-il)metil]fenoxi}anilina (154 mg), 1-metil-2-pirrolidona (5.0 ml) y clorhidrato de piridina (139 mg) se agitó a 120°C durante 22 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato

de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (2.3 ml) y tetrahidrofurano (4 ml) y la mezcla se agitó a temperatura ambiente durante 21 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (119 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.21 (3H, s), 3.70-3.85 (4H, m), 4.02 (2H, t, J = 4.2 Hz), 4.57 (2H, t, J = 4.2 Hz), 5.01 (2H, s), 5.99 (1H, s), 6.63 (1H, d, J = 3.3 Hz), 6.75-6.85 (1H, m), 6.83 (1H, d, J = 8.1 Hz), 6.92 (1H, d, J = 9.0 Hz), 6.95-7.05 (1H, m), 7.21 (1H, d, J = 3.0 Hz), 7.25-7.30 (1H, m), 7.32 (1H, t, J = 8.0 Hz), 7.65 (1H, dd, J = 2.4 Hz, 9.0 Hz), 8.02 (1H, d, J = 2.4 Hz), 8.54 (1H, s), 8.98 (1H, s).

Ejemplo E-2



Producción de O-etiloxima de (1E)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}etanona

(i) Producción de O-etiloxima de (1E)-1-[3-(4-amino-2-clorofenoxi)fenil]etanona

A una solución de 1-[3-(4-amino-2-clorofenoxi)fenil]etanona (1.31 g) en etanol (50 ml) se añadieron clorhidrato de O-etilhidroxilamina (2.44 g) y acetato de sodio (2.05 g) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (1.54 g) en forma de un aceite anaranjado.

^{1}H-RMN ($CDCl_3$) δ: 1.31 (3H, t, J= 7.0 Hz), 2.19 (3H, s), 3.66 (2H, br s), 4.22 (2H, q, J= 7.0 Hz), 6.56 (1H, dd, J= 2.8 Hz, 8.7 Hz), 6.77-6.83 (2H, m), 6.89 (1H, d, J= 8.7 Hz), 7.21-7.28 (2H, m), 7.29-7.35 (1H, m).

(ii) Producción de O-etiloxima de (1E)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-

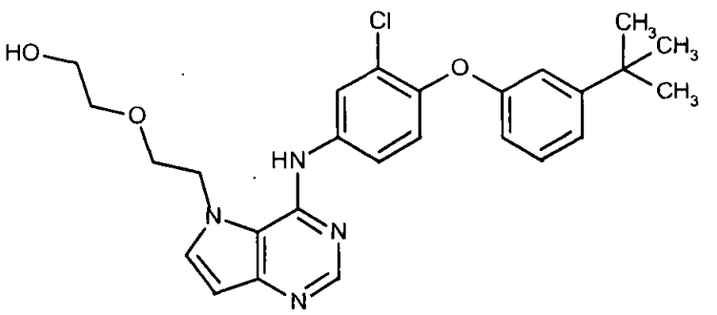
d]pirimidin-4-il}amino)fenoxi]fenil}etanona

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (173 mg), O-etiloxima de (1E)-1-[3-(4-amino-2-clorofenoxi)fenil]etanona (153 mg) y alcohol isopropílico (3 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml), y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (134 mg) en forma de un

polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (3H, t, J= 7.1 Hz), 1.88-2.04 (1H, m), 2.21 (3H, s), 3.70-3.82 (4H, m), 3.99-4.05 (2H, m), 4.24 (2H, q, J= 7.1 Hz), 4.53-4.59 (2H, m), 6.61 (1H, d, J= 3.0 Hz), 6.86-6.92 (1H, m), 7.01 (1H, d, J= 8.9 Hz), 7.20 (1H, d, J= 3.0 Hz), 7.27-7.40 (3H, m), 7.56 (1H, dd, J= 2.7 Hz, 8.9 Hz), 7.87 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.75 (1H, br s).

Ejemplo E-3



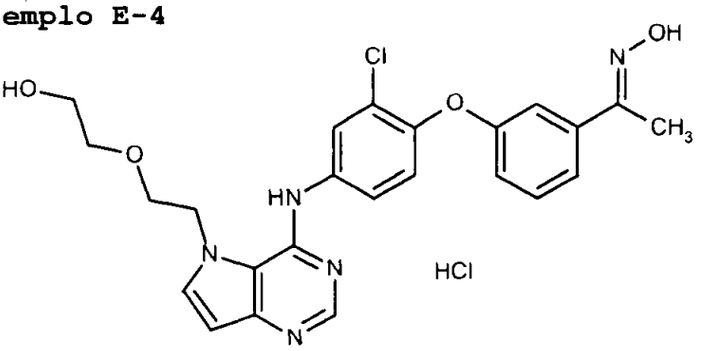
Producción de 2-[2-(4-{[4-(3-ter-butilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (173 mg), 4-(3-ter-butilfenoxi)-3-cloroanilina (138 mg), alcohol isopropílico (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-2(ii), se obtuvo el compuesto del título (189 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (9H, s), 1.95-2.30 (1H, m),

3.70-3.82 (4H, m), 3.99-4.05 (2H, m), 4.52-4.59 (2H, m), 6.60 (1H, d, J= 3.0 Hz), 6.68-6.74 (1H, m), 6.99 (1H, d, J= 8.9 Hz), 7.08-7.15 (2H, m), 7.14-7.28 (2H, m), 7.54 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.86 (1H, d, J= 2.5 Hz), 8.49 (1H, s), 8.73 (1H, br s).

Ejemplo E-4



Producción de clorhidrato de oxima de (1E)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}etanona

(i) Producción de benzoato de 2-[2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (1.04 g), 1-[3-(4-amino-2-clorofenoxi)fenil]etanona (785 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se

evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (1.59 g) en forma de un sólido amarillo.

^{1}H-RMN ($CDCl_3$) δ: 2.59 (3H, s), 3.93-3.99 (2H, m), 4.05-4.12 (2H, m), 4.46-4.52 (2H, m), 4.55-4.62 (2H, m), 6.63 (1H, d, J= 3.2 Hz), 6.82 (1H, d, J= 8.8 Hz), 7.07-7.12 (1H, m), 7.22 (1H, d, J= 3.2 Hz), 7.29-7.54 (6H, m), 7.63-7.69 (1H, m), 7.75-7.82 (2H, m), 7.89 (1H, d, J= 2.7 Hz), 8.50 (1H, s), 8.77 (1H, br s).

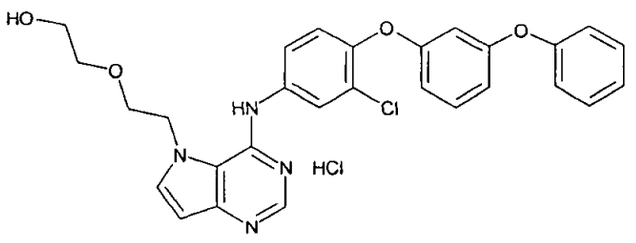
(ii) Producción de clorhidrato de oxima de (1E)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}etanona

A una solución de benzoato de 2-[2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (171 mg) en etanol (5 ml) se añadieron hidroxilamina clorhidrato (104 mg) y acetato de sodio (123 mg) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, y metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (0.6 ml) se añadieron al residuo obtenido.

La mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol, y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en etanol-acetato de etilo para dar el compuesto del título (75 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 2.14 (3H, s), 3.40-3.54 (4H, m), 3.81-3.89 (2H, m), 4.76-4.85 (2H, m), 6.69 (1H, d, J= 3.0 Hz), 7.00-7.06 (1H, m), 7.22 (1H, m), 7.27 (1H, d, J= 8.7 Hz), 7.37-7.48 (2H, m), 7.62 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.96 (1H, d, J= 2.5 Hz), 8.01 (1H, m), 8.73 (1H, s), 9.80-9.90 (1H, m), 11.31 (1H, s).

Ejemplo E-5



Producción de clorhidrato de 2-[2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

(i) Producción de 2-cloro-4-nitro-1-(3-fenoxifenoxi)benceno

Se disolvieron 2-cloro-1-fluoro-4-nitrobenceno (0.943 g) y 3-fenoxifenol (1 g) en N,N-dimetilformamida (5.4 ml), y se agregó carbonato de potasio (1.07 g). La mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml), y se lavó con agua (70 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano/acetato de etilo = 100/0→70/30) para dar el compuesto del título (1.75 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 6.73 (1H, t, J= 2 Hz), 6.78 (1H, m), 6.89 (1H, m), 6.95 (2H, d, J= 9 Hz), 7.05 (2H, m), 7.16 (1H, m), 7.37 (3H, m), 8.07 (1H, dd, J= 3 Hz, 9 Hz), 8.37 (1H, d, J= 3 Hz).

(ii) Producción de 3-cloro-4-(3-fenoxifenoxi)anilina

Se suspendió 2-cloro-4-nitro-1-(3-fenoxifenoxi)benceno (1.7 g) en etanol (49 ml)/agua (5.45 ml), se agregó cloruro de calcio (306 mg) y la mezcla se disolvió con calentamiento agitando a 90°C durante 10 min. Se

añadió hierro reducido (1.85 g) y la mezcla se agitó con calentamiento a 90°C durante 16 h. Tras enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de celite, y el filtrado se concentró a presión reducida. El sólido residual se diluyó con acetato de etilo (200 ml), y se lavó con salmuera saturada (100 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se purificó por cromatografía en gel de sílice (hexano/acetato de etilo = 80/20→60/40) para dar el compuesto del título (1.58 g) en forma de un aceite.

^{1}H-RMN ($CDCl_3$) δ: 3.67 (2H, br s), 6.50-6.70 (4H, m), 6.76 (1H, d, J= 3 Hz), 6.92 (1H, d, J= 9 Hz), 7.01 (2H, m), 7.10 (1H, m), 7.20 (1H, m), 7.33 (2H, m).

(iii) Producción de clorhidrato de 2-[2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

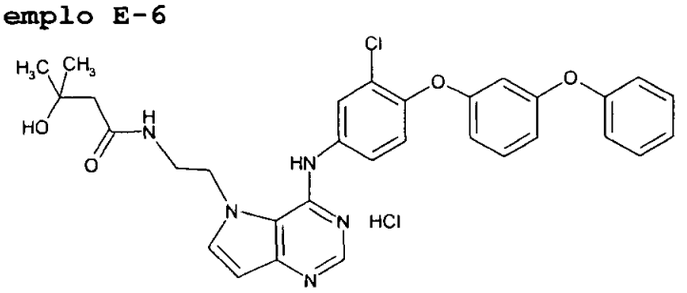
Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (150 mg), 3-cloro-4-(3-fenoxifenoxi)anilina (201 mg) y 1-metil-2-pirrolidona (0.863 ml) se agitó con calentamiento a 140°C durante 3 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml), y se lavó con bicarbonato de sodio acuoso (30 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro, y se concentró a presión reducida. El residuo se purificó por

1018.

cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→0:100) y las fracciones objeto se concentraron a presión reducida. El residuo obtenido se disolvió en metanol (1.89 ml), se añadió solución acuosa 1 N de hidróxido de sodio (0.433 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se adicionó ácido clorhídrico 1 N (0.433 ml), y la mezcla se diluyó con acetato de etilo (80 ml), y se lavó con salmuera saturada (30 ml). La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→85:15). La fracción con el compuesto del título se concentró a presión reducida, y el residuo se disolvió en acetato de etilo (4 ml). Se añadió ácido clorhídrico 4 N (0.125 ml) a la mezcla, y la mezcla se cristalizó en éter isopropílico/acetato de etilo para dar el compuesto del título (129 mg).

^{1}H-RMN (DMSO-d_6) δ: 3.46 (4H, d, J= 2 Hz), 3.84 (2H, br s), 4.85 (2H, br s), 6.60 (1H, s), 7.07 (2H, d, J= 8 Hz), 7.18 (2H, t, J= 8 Hz), 7.29 (1H, d, J= 8 Hz), 7.30-7.50 (3H, m), 7.64 (1H, d, J= 9 Hz), 7.96 (1H, d, J= 1 Hz), 8.04 (1H, d, J= 3 Hz), 8.74 (1H, s), 10.02 (1H, br s).

Ejemplo E-6



Producción de clorhidrato de N-[2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

(i) Producción de [2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (0.5 g) y 3-cloro-4-(3-fenoxifenoxi)anilina (786 mg) en alcohol isopropílico (5 ml) se agitó a 80°C durante 12 h. Se agregó bicarbonato de sodio acuoso (30 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (80 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 7:3→acetato de etilo) para dar el compuesto del título (713 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 3.48 (2H, m), 4.46

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(2H, m), 5.12 (1H, t, J= 5 Hz), 6.59 (1H, d, J= 3 Hz), 6.69 (3H, m), 7.00-7.40 (8H, m), 7.85 (1H, dd, J= 3 Hz, 9 Hz), 7.98 (1H, d, J= 3 Hz), 8.50 (1H, s), 8.58 (1H, br s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-fenoxifenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (683 mg), ácido clorhídrico 2 N (8.46 ml) y tetrahidrofurano (16.9 ml) se agitó a 60°C durante 20 h. El solvente se evaporó a presión reducida, se añadió etanol, y la mezcla luego se concentró. El polvo precipitado se recogió por filtración. El polvo se lavó con éter isopropílico para dar el compuesto del título (622 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.30 (2H, m), 5.08 (2H, m), 6.60 (1H, t, J= 2 Hz), 6.73 (3H, m), 7.06 (2H, m), 7.18 (1H, m), 7.29 (1H, d, J= 9 Hz), 7.41 (3H, m), 7.64 (1H, dd, J= 3 Hz, 9 Hz), 7.90 (1H, d, J= 3 Hz), 8.10 (1H, d, J= 3 Hz), 8.42 (3H, br s), 8.73 (1H, s).

(iii) Producción de clorhidrato de N-[2-(4-{[3-cloro-4-(3-fenoxifenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[3-cloro-4-(3-fenoxifenoxi)fenil]-5H-pirrolo[3,2-d]pirimidin-

4-amina (195 mg), ácido 3-hidroxi-3-metilbutanoico (0.058 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15). La fracción con el compuesto del título se concentró a presión reducida, y el residuo se disolvió en acetato de etilo (4 ml). Se añadió ácido clorhídrico 4 N (0.169 ml), y la mezcla se cristalizó en acetato de etilo para dar el compuesto del título (176 mg).

^{1}H-RMN (DMSO-d_6) δ: 1.10 (6H, s), 2.19 (2H, s), 3.48 (2H, q, J= 6 Hz), 4.66 (2H, t, J= 6 Hz), 6.60 (1H, t, J= 3 Hz), 6.67 (1H, d, J=3 Hz), 6.72 (2H, dt, J= 3 Hz, 9 Hz), 7.06 (2H, d, J= 8 Hz), 7.17 (1H, t, J= 7 Hz), 7.29 (1H, d, J= 9 Hz), 7.40 (3H, m), 7.67 (1H, dd, J= 3 Hz, 9 Hz), 7.92 (1H, d, J= 3 Hz), 7.98 (1H, d, J= 3 Hz), 8.40 (1H, m), 8.71 (1H, s).

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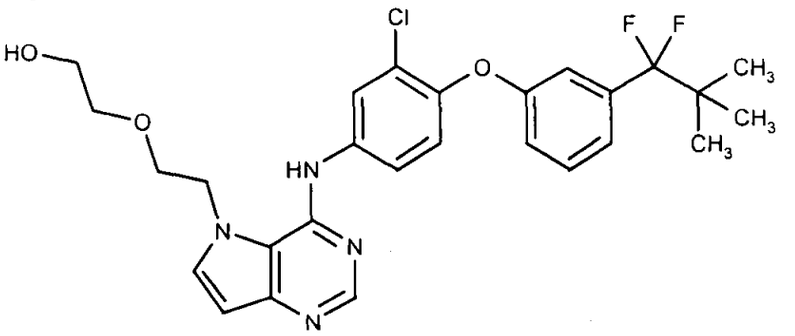
Ejemplo E-7



Producción de 2-{2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2,2-dimetilpropan-1-ona

Una mezcla de 2-cloro-1-fluoro-4-nitrobenceno (2.63 g), 1-(3-hidroxifenil)-2,2-dimetilpropan-1-ona (2.55 g), carbonato de potasio (2.97 g) y N,N-dimetilformamida (20 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida, se añadió agua y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 2:98→15:85). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (5.17 g) en forma de un aceite de cloro verde amarillento pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.35 (9H, s), 6.92 (1H, d, J= 9.1

Hz), 7.18 (1H, ddd, J= 1.1 Hz, 2.6 Hz, 8.1 Hz), 7.37 (1H, m), 7.45-7.52 (1H, m), 7.56-7.60 (1H, m), 8.08 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.7 Hz).

(ii) Producción de 2-cloro-1-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]-4-nitrobenceno

Una solución de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2,2-dimetilpropan-1-ona (3.34 g) y trifluoruro de dietilaminoazufre (6.85 g) en diclorometano (100 ml) se agitó con calentamiento a reflujo durante la noche. Se agregaron hielo y solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con diclorometano. La capa de diclorometano se lavó con salmuera saturada, y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 2:98→15:85). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (3.63 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.05 (9H, s), 6.87 (1H, d, J= 9.1 Hz), 7.11-7.18 (2H, m), 7.31-7.37 (1H, m), 7.44-7.52 (1H, m), 8.07 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]anilina

Una mezcla de 2-cloro-1-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]-4-nitrobenceno (712 mg), hierro

reducido (372 mg), cloruro de calcio (123 mg) y 10% de etanol con contenido de agua (20 ml) se agitó con calentamiento a reflujo durante 7 h. Por separado, se agitaron una mezcla de 2-cloro-1-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]-4-nitrobenceno (3.00 g), hierro reducido (1.57 g), cloruro de calcio (520 mg) y 10% de etanol con contenido de agua (100 ml) con calentamiento a reflujo durante la noche. Se combinaron y el sólido se eliminó por filtración. El filtrado se concentró y se añadió agua al residuo obtenido, y la mezcla se extrajo con acetato de etilo. La capa de acetato de etilo se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 15:85→30:70). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (2.40 g) en forma de un sólido de color marrón pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.02 (9H, s), 3.68 (2H, br s), 6.57 (1H, dd, J= 2.7 Hz, 8.8 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.87-6.95 (3H, m), 7.05-7.11 (1H, m), 7.28-7.33 (1H, m).

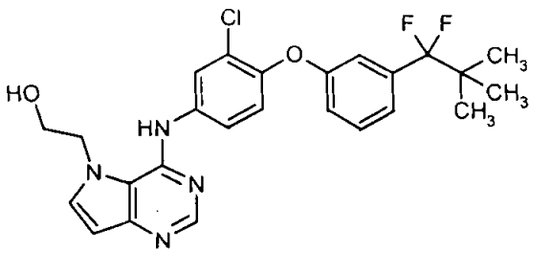
(iv) Producción de 2-{2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (173 mg), 3-cloro-4-[3-(1,1-

difluoro-2,2-dimetilpropil)fenoxi]anilina (163 mg), alcohol isopropílico (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-2(ii), se obtuvo el compuesto del título (198 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (9H, s), 2.05 (1H, br s), 3.70-3.84 (4H, m), 4.02 (2H, t, J= 4.3 Hz), 4.56 (2H, t, J= 4.3 Hz), 6.61 (1H, d, J= 3.2 Hz), 6.94-7.08 (3H, m), 7.13 (1H, d, J= 7.7 Hz), 7.20 (1H, d, J= 3.2 Hz), 7.32 (1H, t, J= 8.0 Hz), 7.58 (1H, dd, J= 2.6 Hz, 8.9 Hz), 7.89 (1H, d, J= 2.6 Hz), 8.51 (1H, s), 8.78 (1H, br s).

Ejemplo E-8



Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (151 mg), 3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]anilina (163 mg) y alcohol isopropílico (3 ml) se agitó a 80°C durante 9 h. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de

etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0). Las fracciones objeto se concentraron a presión reducida. Al residuo se añadieron metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (191 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.05 (9H, s), 4.11-4.18 (2H, m), 4.33-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.50 (1H, br s), 6.95 (1H, d, J = 3.3 Hz), 6.97-7.08 (3H, m), 7.14 (1H, d, J = 7.7 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.82 (1H, d, J = 2.5 Hz), 8.21 (1H, s), 9.56 (1H, br s).

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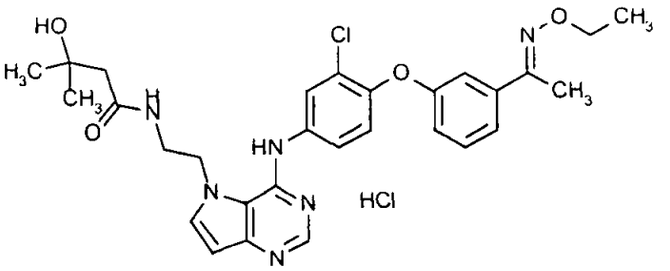
Ejemplo E-9



Producción de clorhidrato de N-(2-{4-[(3-cloro-4-{3-[(1E)-N-etoxiacetoimidoil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

(i) Producción de [2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (890 mg), 1-[3-(4-amino-2-clorofenoxi)fenil]etanona (785 mg) y alcohol isopropílico (10 ml) se agitó a 80°C durante la noche. Se añadió una solución acuosa de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0). Las fracciones objeto se concentraron a presión reducida y el residuo se cristalizó en acetona-éter dietílico para dar el compuesto del título (1.14

g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 2.59 (3H, m), 3.44-3.55 (2H, m), 4.44-4.53 (2H, m), 5.08 (1H, t, J = 5.6 Hz), 6.61 (1H, d, J = 3.3 Hz), 7.05 (1H, d, J = 8.9 Hz), 7.15-7.21 (2H, m), 7.41 (1H, t, J = 8.0 Hz), 7.56 (1H, m), 7.66 (1H, d, J = 7.7 Hz), 7.89 (1H, dd, J = 2.7 Hz, 8.9 Hz), 8.03 (1H, d, J = 2.7 Hz), 8.52 (1H, s), 8.60 (1H, br s).

(ii) Producción de N-[2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

A [2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (1.10 g) se añadieron etanol (2 ml) y solución de cloruro de hidrógeno 4 N/acetato de etilo (5 ml) y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró a presión reducida. A una solución del residuo obtenido en N,N-dimetilformamida (20 ml) se añadieron ácido 3-hidroxi-3-metilbutanoico (374 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (607 mg), monohidrato de 1-hidroxibenzotriazol (485 mg) y trietilamina (0.882 ml) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y

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el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0→metanol:acetato de etilo = 20:80) y cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→10:90). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (596 mg) en forma de un polvo amorfo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.32 (6H, s), 2.48 (2H, s), 2.59 (3H, s), 3.58-3.68 (2H, m), 4.44-4.54 (2H, m), 6.59 (1H, d, J = 3.3 Hz), 7.05 (1H, d, J = 8.8 Hz), 7.09-7.22 (3H, m), 7.42 (1H, t, J = 7.8 Hz), 7.57 (1H, m), 7.64-7.69 (1H, m), 7.74 (1H, dd, J = 2.6 Hz, 8.8 Hz), 8.07 (1H, d, J = 2.6 Hz), 8.50 (1H, s), 8.66 (1H, br s).

(iii) Producción de clorhidrato de N-(2-{4-[(3-cloro-4-{3-[(1E)-N-etoxiacetoimidoil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

A una solución de N-[2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida (157 mg) en etanol (5 ml) se añadieron clorhidrato de O-etilhidroxilamina (88 mg) y acetato de sodio (74 mg) y la mezcla se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La

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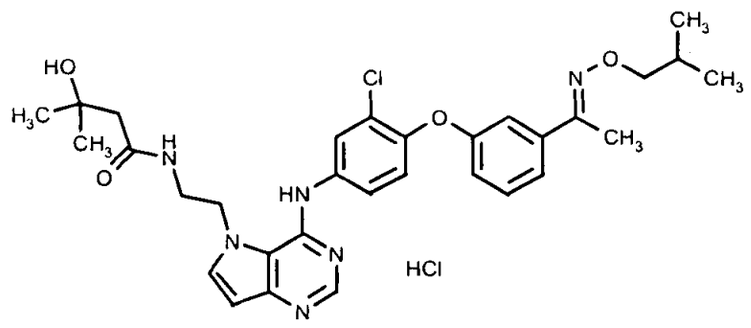
capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→15:85). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol, y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en acetato de etilo-éter dietílico para dar el compuesto del título (91 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.11 (6H, s), 1.25 (3H, t, J = 7.1 Hz), 2.18 (3H, s), 2.20 (2H, s), 3.43-3.55 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 4.66 (2H, t, J = 6.7 Hz), 6.67 (1H, d, J = 3.2 Hz), 6.95-7.02 (1H, m), 7.22 (1H, d, J = 8.9 Hz), 7.33 (1H, m), 7.40-7.49 (2H, m), 7.67 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 7.98 (1H, d, J = 3.2 Hz), 8.40 (1H, t, J = 5.6 Hz), 8.72 (1H, s), 10.28 (1H, br s).

Ejemplo E-10



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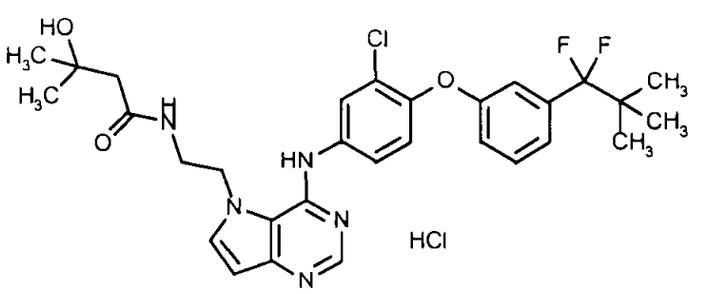
Producción de clorhidrato de N-(2-{4-[(3-cloro-4-{3-[(1E)-N-isobutoxiacetoimidoil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-3-hidroxi-3-metilbutanamida

Al usar N-[2-(4-{[4-(3-acetilfenoxi)-3-clorofenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida (157 mg), etanol (5 ml), clorhidrato de O-isobutilhidroxilamina (113 mg), acetato de sodio (74 mg) y solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml) y de la misma manera que en el Ejemplo E-9(iii), se obtuvo el compuesto del título (87 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.92 (6H, d, J = 6.9 Hz), 1.11 (6H, s), 1.90-2.05 (1H, m), 2.20 (5H, s), 3.44-3.54 (2H, m), 3.91 (2H, d, J = 6.6 Hz), 4.66 (2H, t, J = 6.7 Hz), 6.67 (1H, d, J = 3.0 Hz), 6.94-7.02 (1H, m), 7.22 (1H, d, J = 8.9 Hz), 7.32 (1H, m), 7.40-7.48 (2H, m), 7.67 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 7.99 (1H, d, J = 3.0 Hz), 8.40 (1H, t, J = 5.5 Hz), 8.72 (1H, s), 10.29 (1H, br s).

Ejemplo E-11



Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

(i) Producción de {2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (594 mg), 3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]anilina (652 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo E-9(i), se obtuvo el compuesto del título (1.15 g) en forma de un polvo amorfo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (9H, s), 1.49 (9H, s), 3.42-3.54 (2H, m), 4.41-4.52 (2H, m), 5.20 (1H, t, J = 5.4 Hz), 6.58 (1H, d, J = 3.3 Hz), 6.96-7.08 (3H, m), 7.12 (1H, d, J = 7.7 Hz), 7.17 (1H, d, J = 3.3 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.84 (1H, dd, J = 2.5 Hz, 8.8 Hz), 8.01 (1H, d, J = 2.5 Hz), 8.50 (1H, s), 8.61 (1H, br s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

A {2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-

5-il]etil}carbamato de ter-butilo (1.15 g) se añadió metanol (10 ml) y se concentró ácido clorhídrico (2 ml), y la mezcla se agitó a temperatura ambiente durante la noche y a 60°C durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadieron alcohol isopropílico y metanol, y la mezcla se volvió a concentrar a presión reducida. Se añadieron alcohol isopropílico y éter diisopropílico al residuo, y los cristales se recogieron por filtración para dar el compuesto del título (1.09 g) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.99 (9H, s), 3.24-3.36 (2H, m), 5.01 (2H, t, J = 6.1 Hz), 6.73 (1H, d, J = 3.1 Hz), 6.93 (1H, m), 7.11 (1H, dd, J = 2.4 Hz, 8.0 Hz), 7.19 (1H, d, J = 8.1 Hz), 7.27 (1H, d, J = 8.9 Hz), 7.51 (1H, t, J = 8.0 Hz), 7.62 (1H, dd, J = 2.4 Hz, 8.9 Hz), 7.90 (1H, d, J = 2.4 Hz), 8.05 (1H, d, J = 3.1 Hz), 8.23-8.33 (3H, m), 8.71 (1H, s), 10.06 (1H, br s).

(iii) Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (168 mg), ácido 3-hidroxi-3-metilbutanoico (53 mg), clorhidrato de 1-etil-3-(3-

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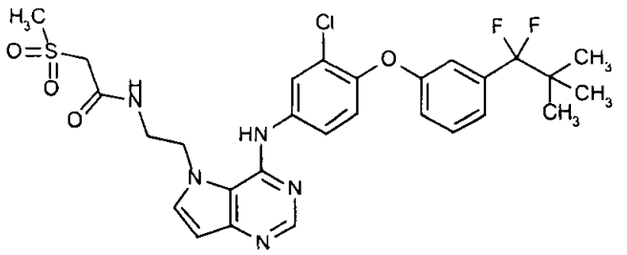
dimetilaminopropil)carbodiimida (86 mg), monohidrato de 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se disolvió en acetato de etilo-etanol, y se añadió solución de cloruro de hidrógeno 1 N/acetato de etilo (0.3 ml). El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en acetato de etilo para dar el compuesto del título (134 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.99 (9H, s), 1.11 (6H, s), 2.20 (2H, s), 3.44-3.54 (2H, m), 4.66 (2H, t, J = 7.0 Hz), 6.67 (1H, d, J = 3.2 Hz), 6.92 (1H, m), 7.13 (1H, dd, J = 2.3 Hz, 8.1 Hz), 7.20 (1H, d, J = 7.7 Hz), 7.29 (1H, d, J = 8.9 Hz), 7.52 (1H, t, J = 8.0 Hz), 7.70 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.96 (1H, d, J = 2.5 Hz), 7.99 (1H, d, J = 3.2 Hz), 8.41 (1H, t, J = 5.1 Hz), 8.73 (1H, s), 10.28 (1H, br s).

Ejemplo E-12

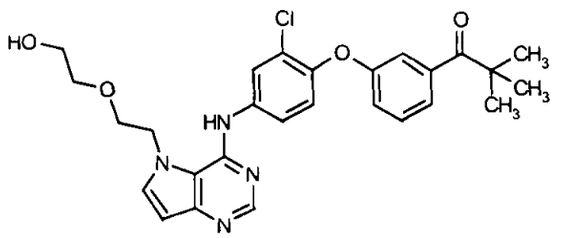


Producción de N-{2-[4-({3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-{3-cloro-4-[3-(1,1-difluoro-2,2-dimetilpropil)fenoxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina (168 mg), ácido metilsulfonilacético (62 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (86 mg), monohidrato de 1-hidroxibenzotriazol (69 mg), trietilamina (0.100 ml) y N,N-dimetilformamida (3 ml) se agitó a temperatura ambiente durante la noche. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, metanol:acetato de etilo = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (153 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (9H, s), 3.14 (3H, s), 3.65-3.75 (2H, m), 3.98 (2H, s), 4.44-4.53 (2H, m), 6.59 (1H, d, J = 3.0 Hz), 6.98-7.04 (2H, m), 7.07 (1H, m), 7.15 (1H, d, J = 7.7 Hz), 7.21 (1H, d, J = 3.0 Hz), 7.34 (1H, d, J = 8.0 Hz), 7.62 (1H, t, J = 5.5 Hz), 7.72 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.94 (1H, d, J = 2.5 Hz), 8.18 (1H, br s), 8.50 (1H, s).

Ejemplo E-13



Producción de 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona

(i) Producción de 1-[3-(4-amino-2-clorofenoxi)fenil]-2,2-dimetilpropan-1-ona

Una mezcla de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2,2-dimetilpropan-1-ona (1.03 g), hierro reducido (575 mg), cloruro de calcio (190 mg) y 10% de etanol con contenido de agua (30 ml) se agitó con calentamiento a reflujo durante la noche. La mezcla de reacción se filtró para eliminar el sólido, y el filtrado se concentró. Se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión

reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (708 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 1.31 (9H, s), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.5 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.91 (1H, d, J = 8.5 Hz), 6.94-7.00 (1H, m), 7.16 (1H, m), 7.26-7.35 (2H, m).

(ii) Producción de 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona

Al usar benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (734 mg), 1-[3-(4-amino-2-clorofenoxi)fenil]-2,2-dimetilpropan-1-ona (645 mg), alcohol isopropílico (10 ml), metanol (25 ml), tetrahidrofurano (5 ml) y solución acuosa 1 N de hidróxido de sodio (5 ml) y de la misma manera que en el Ejemplo E-2(ii), se obtuvo el compuesto del título (858 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.33 (9H, s), 3.70-3.82 (4H, m), 4.02 (2H, t, J = 4.4 Hz), 4.55 (2H, t, J = 4.4 Hz), 6.58 (1H, d, J = 3.3 Hz), 7.00-7.06 (2H, m), 7.19 (1H, d, J = 3.3 Hz), 7.22 (1H, m), 7.28-7.39 (2H, m), 7.57 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.89 (1H, d, J = 2.6 Hz), 8.48 (1H, s), 8.81 (1H, br s).

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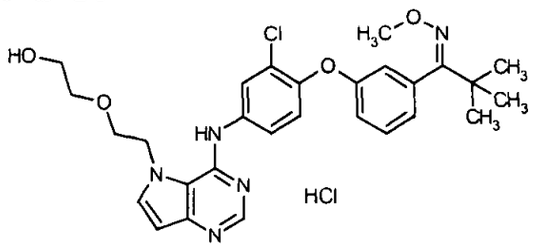
Ejemplo E-14

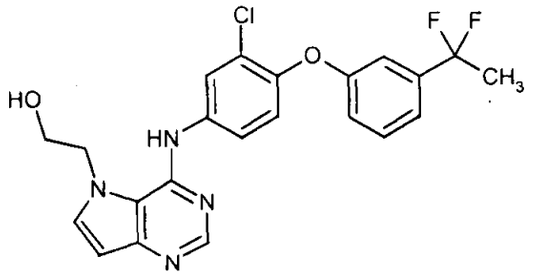


Producción de clorhidrato de O-metiloxima de (1Z)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona

Al usar 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona (204 mg), etanol (5 ml), clorhidrato de O-metilhidroxilamina (100 mg), acetato de sodio (98 mg) y solución de cloruro de hidrógeno 1 N/acetato de etilo (0.4 ml) y de la misma manera que en el Ejemplo E-9(iii), se obtuvo el compuesto del título (201 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.10 (9H, s), 3.41-3.51 (4H, m), 3.65 (3H, s), 3.84 (2H, t, J = 4.4 Hz), 4.78-4.85 (2H, m), 6.62 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 6.82 (1H, d, J = 7.7 Hz), 6.94 (1H, dd, J = 2.5 Hz, 8.0 Hz), 7.22 (1H, d, J = 8.9 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.61 (1H, dd, J = 2.5 Hz, 8.9 Hz), 7.95 (1H, d, J = 2.5 Hz), 8.02 (1H, d, J = 3.0 Hz), 8.73 (1H, s), 9.92 (1H, br s).

Ejemplo E-15



Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoroetil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]etanona

Al usar 2-cloro-1-fluoro-4-nitrobenceno (3.51 g), 3'-hidroxiacetofenone (2.72 g), carbonato de potasio (4.15 g) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo E-7(i), se obtuvo el compuesto del título (5.60 g) en forma de un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.62 (3H, s), 6.92 (1H, d, J = 9.1 Hz), 7.28-7.33 (1H, m), 7.56 (1H, t, J = 8.0 Hz), 7.65 (1H, m), 7.82-7.88 (1H, m), 8.09 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.41 (1H, d, J = 2.6 Hz).

(ii) Producción de 2-cloro-1-[3-(1,1-difluoroetil)fenoxi]-4-nitrobenceno

Una solución de 1-[3-(2-cloro-4-nitrofenoxi)fenil]etanona (2.92 g), trifluoruro de dietilaminoazufre (8.06 g) en 1,2-dimetoxietano (10 ml) se agitó a 50°C durante 5 días. La mezcla de reacción se vertió

en hielo, y a ello se añadió solución acuosa 8 N de hidróxido de sodio (20 ml). Se agregó acetato de etilo, y la capa orgánica se separó, se lavó con salmuera saturada, y se secó sobre sulfato de sodio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 0:100→20:80). Las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (2.75 g) en forma de un sólido anaranjado.

^{1}H-RMN ($CDCl_3$) δ: 1.93 (3H, t, J = 18.1 Hz), 6.92 (1H, d, J = 9.1 Hz), 7.11-7.17 (1H, m), 7.25 (1H, m), 7.38-7.44 (1H, m), 7.51 (1H, t, J = 7.8 Hz), 8.08 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(1,1-difluoroetil)fenoxi]anilina

Al usar 2-cloro-1-[3-(1,1-difluoroetil)fenoxi]-4-nitrobenceno (2.51 g), hierro reducido (1.99 g), cloruro de calcio (493 mg) y 10% de etanol con contenido de agua (100 ml) y de la misma manera que en el Ejemplo E-13(i), se obtuvo el compuesto del título (1.81 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.89 (3H, t, J = 18.1 Hz), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.86-6.92 (1H, m), 6.91 (1H, d, J = 8.6 Hz), 7.04 (1H, m), 7.13-7.18 (1H, m), 7.32 (1H, t, J = 8.0 Hz).

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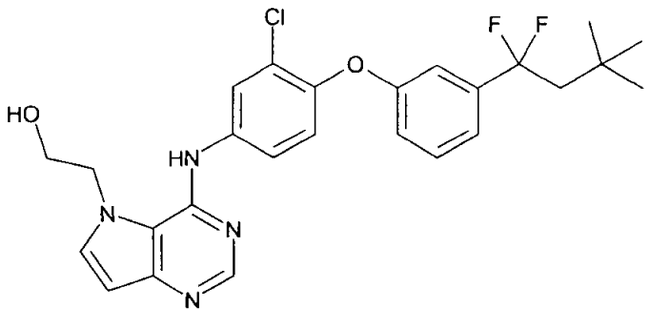
(iv) Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoroetil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (151 mg), 3-cloro-4-[3-(1,1-difluoroetil)fenoxi]anilina (142 mg), alcohol isopropílico (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-8, se obtuvo el compuesto del título (149 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.92 (3H, t, J = 18.1 Hz), 4.10-4.18 (2H, m), 4.32-4.39 (2H, m), 6.06 (1H, d, J = 3.2 Hz), 6.72 (1H, br s), 6.93 (1H, d, J = 3.2 Hz), 6.97-7.02 (1H, m), 7.05 (1H, d, J = 8.8 Hz), 7.13 (1H, m), 7.20 (1H, d, J = 8.0 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.47 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.81 (1H, d, J = 2.5 Hz), 8.18 (1H, s), 9.61 (1H, br s).

Ejemplo E-16



Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoro-3,3-dimetilbutil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-3,3-dimetilbutan-1-ona

Al usar 2-cloro-1-fluoro-4-nitrobenceno (1.76 g), 1-(3-hidroxifenil)-3,3-dimetilbutan-1-ona (1.92 g), carbonato de potasio (2.07 g) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo E-7(i), se obtuvo el compuesto del título (3.24 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.07 (9H, s), 2.85 (2H, s), 6.90 (1H, d, J = 9.1 Hz), 7.25-7.30 (1H, m), 7.54 (1H, t, J = 8.0 Hz), 7.63 (1H, m), 7.80-7.86 (1H, m), 8.08 (1H, dd, J = 2.7 Hz, 9.1 Hz), 8.41 (1H, d, J = 2.7 Hz).

(ii) Producción de 2-cloro-1-[3-(1,1-difluoro-3,3-dimetilbutil)fenoxi]-4-nitrobenceno

Al usar 1-[3-(2-cloro-4-nitrofenoxi)fenil]-3,3-dimetilbutan-1-ona (1.90 g), trifluoruro de dietilaminoazufre (5.0 ml) y 1,2-dimetoxietano (10 ml) y de la misma manera que en el Ejemplo E-15(ii), se obtuvo el compuesto del título (52 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.02 (9H, s), 2.07 (2H, t, J = 19.1 Hz), 6.88 (1H, d, J = 9.3 Hz), 7.09-7.15 (1H, m), 7.21 (1H, m), 7.38 (1H, d, J = 7.7 Hz), 7.49 (1H, t, J = 7.8 Hz), 8.08 (1H, dd, J = 2.7 Hz, 9.3 Hz), 8.40 (1H, d, J = 2.7 Hz).

(iii) Producción de 3-cloro-4-[3-(1,1-difluoro-3,3-dimetilbutil)fenoxi]anilina

Al usar 2-cloro-1-[3-(1,1-difluoro-3,3-

dimetilbutil)fenoxi]-4-nitrobenceno (130 mg), hierro reducido (99 mg), cloruro de calcio (25 mg) y 10% de etanol con contenido de agua (10 ml) y de la misma manera que en el Ejemplo E-13(i), se obtuvo el compuesto del título (100 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.99 (9H, s), 2.04 (2H, t, J = 18.9 Hz), 3.69 (2H, br s), 6.58 (1H, dd, J = 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J = 2.7 Hz), 6.85-6.90 (1H, m), 6.90 (1H, d, J = 8.6 Hz), 7.00 (1H, m), 7.12 (1H, d, J = 7.7 Hz), 7.30 (1H, t, J = 8.1 Hz).

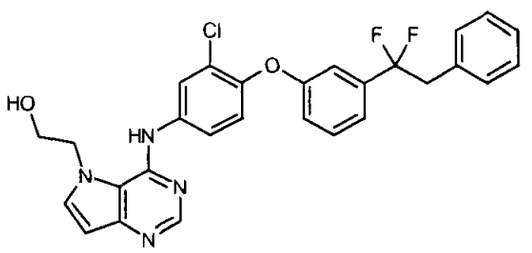
(iv) Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoro-3,3-dimetilbutil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (121 mg), 3-cloro-4-[3-(1,1-difluoro-3,3-dimetilbutil)fenoxi]anilina (100 mg), alcohol isopropílico (5 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-8, se obtuvo el compuesto del título (67 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.01 (9H, s), 2.07 (2H, t, J = 19.0 Hz), 4.11-4.18 (2H, m), 4.33-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.49 (1H, br s), 6.94 (1H, d, J = 3.3 Hz), 6.95-7.01 (1H, m), 7.04 (1H, d, J = 8.7 Hz), 7.10 (1H, m), 7.17 (1H, d, J = 7.7 Hz), 7.35 (1H, t, J = 8.0 Hz), 7.47 (1H, dd,

J = 2.6 Hz, 8.7 Hz), 7.81 (1H, d, J = 2.6 Hz), 8.20 (1H, s), 9.55 (1H, br s).

Ejemplo E-17



Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoro-2-feniletil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2-feniletanona

Al usar 2-cloro-1-fluoro-4-nitrobenceno (702 mg), 1-(3-hidroxifenil)-2-feniletanona (849 mg), carbonato de potasio (829 mg) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo E-7(i), se obtuvo el compuesto del título (725 mg) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 4.26 (2H, s), 6.86 (1H, d, J = 9.1 Hz), 7.20-7.36 (6H, m), 7.53 (1H, t, J = 8.0 Hz), 7.65 (1H, m), 7.86-7.92 (1H, m), 8.05 (1H, dd, J = 2.6 Hz, 9.1 Hz), 8.39 (1H, d, J = 2.6 Hz).

(ii) Producción de 2-cloro-1-[3-(1,1-difluoro-2-feniletil)fenoxi]-4-nitrobenceno

Al usar 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2-

feniletanona (478 mg), trifluoruro de dietilaminoazufre (2.0 ml) y 1,2-dimetoxietano (5 ml) y de la misma manera que en el Ejemplo E-15(ii), se obtuvo el compuesto del título (372 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 3.41 (2H, t, J = 15.4 Hz), 6.59 (1H, d, J = 9.1 Hz), 6.91 (1H, m), 7.01-7.13 (3H, m), 7.20-7.29 (4H, m), 7.44 (1H, t, J = 8.0 Hz), 7.99 (1H, dd, J = 2.5 Hz, 9.1 Hz), 8.35 (1H, d, J = 2.5 Hz).

(iii) Producción de 3-cloro-4-[3-(1,1-difluoro-2-feniletil)fenoxi]anilina

Al usar 2-cloro-1-[3-(1,1-difluoro-2-feniletil)fenoxi]-4-nitrobenceno (372 mg), hierro reducido (186 mg), cloruro de calcio (62 mg) y 10% de etanol con contenido de agua (10 ml) y de la misma manera que en el Ejemplo E-13(i), se obtuvo el compuesto del título (200 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 3.36 (2H, t, J = 15.9 Hz), 3.67 (2H, br s), 6.54 (1H, dd, J = 2.7 Hz, 8.8 Hz), 6.77 (1H, d, J = 2.7 Hz), 6.78-6.84 (2H, m), 6.85-6.91 (1H, m), 6.98 (1H, d, J = 8.0 Hz), 7.05-7.12 (2H, m), 7.20-7.30 (4H, m).

(iv) Producción de 2-[4-({3-cloro-4-[3-(1,1-difluoro-2-feniletil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (169 mg), 3-cloro-4-[3-(1,1-difluoro-

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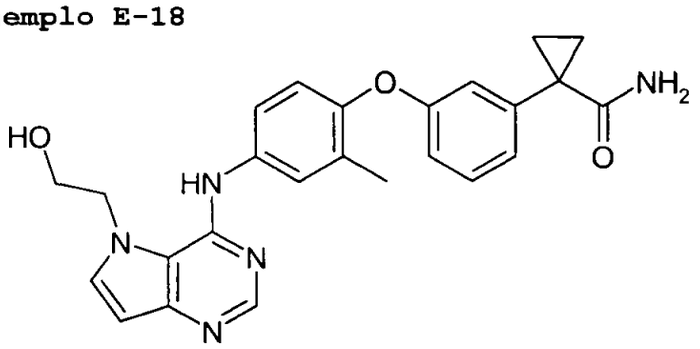
2-feniletil)fenoxi]anilina (200 mg), alcohol isopropílico (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-8, se obtuvo el compuesto del título (171 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 3.39 (2H, t, J = 15.8 Hz), 4.10-4.19 (2H, m), 4.32-4.40 (2H, m), 6.09 (1H, d, J = 3.3 Hz), 6.53 (1H, br s), 6.90-7.14 (7H, m), 7.20-7.38 (4H, m), 7.45 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.5 Hz), 8.21 (1H, s), 9.57 (1H, br s).

Ejemplo E-18



Producción de 1-[3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarboxamida

(i) Producción de 1-(3-metoxifenil)ciclopropancarbonitrilo

Se suspendió hidruro de sodio al 60% (2.72 g) en N,N-dimetilformamida (80 ml) y la mezcla se enfrió hasta 0°C. Una solución de (3-metoxifenil)acetonitrilo (4.00 g) en N,N-dimetilformamida (20 ml) se añadió gota a gota a la

mezcla y la mezcla se agitó a 0°C durante 1 h. Se agregó 1,2-dibromoetano (3.5 ml) gota a gota a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 17 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con éter dietílico. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 100:0→80:20) para dar el compuesto del título (2.76 g) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.36-1.44 (2H, m), 1.67-1.75 (2H, m), 3.81 (3H, s), 6.77-6.89 (3H, m), 7.21-7.29 (1H, m).

(ii) Producción de 1-(3-metoxifenil)ciclopropancarboxamida y ácido 1-(3-metoxifenil)ciclopropancarboxílico

Se disolvió 1-(3-metoxifenil)ciclopropancarbonitrilo (2.75 g) en un solvente mixto de etanol (100 ml)/agua (50 ml), se añadió hidróxido de potasio (8.94 g), y la mezcla se agitó con calentamiento a reflujo durante 5 h. La mezcla de reacción se concentró a presión reducida, el residuo se ajustó hasta pH 1-2 con ácido clorhídrico 6 N, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se

concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 50:50→0:100) para dar 1-(3-metoxifenil)ciclopropancarboxamida (762 mg) y ácido 1-(3-metoxifenil)ciclopropancarboxílico (1.78 g), cada uno en forma de cristales de color anaranjado pálido.

1-(3-metoxifenil)ciclopropancarboxamida

^{1}H-RMN (DMSO-d_6) δ: 0.91-0.98 (2H, m), 1.26-1.34 (2H, m), 3.75 (3H, s), 6.11 (1H, br s), 6.79-6.96 (3H, m), 7.02 (1H, br s), 7.25 (1H, t, J= 8.0 Hz).

ácido 1-(3-metoxifenil)ciclopropancarboxílico

^{1}H-RMN (DMSO-d_6) δ: 1.02-1.20 (2H, m), 1.33-1.50 (2H, m), 3.73 (3H, s), 6.71-7.00 (3H, m), 7.20 (1H, t, J= 7.8 Hz), 12.27 (1H, br s).

(iii) Producción de 1-(3-hidroxifenil)ciclopropancarboxamida

Se disolvió 1-(3-metoxifenil)ciclopropancarboxamida (756 mg) en benzotrifluoruro (20 ml), a ello se añadió solución de tribromuro de boro 1 N/diclorometano (10 ml) a 0°C, y la mezcla se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se enfrió con hielo, se añadió solución acuosa saturada de carbonato ácido de sodio, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se

separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 67:33→0:100) para dar el compuesto del título (350 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 0.85-0.95 (2H, m), 1.22-1.32 (2H, m), 6.04 (1H, br s), 6.59-6.71 (1H, m), 6.71-6.82 (2H, m), 7.02 (1H, br s), 7.12 (1H, t, J= 7.8 Hz), 9.40 (1H, s).

(iv) Producción de 1-[3-(2-metil-4-nitrofenoxi)fenil]ciclopropancarboxamida

Una mezcla de 1-(3-hidroxifenil)ciclopropancarboxamida (345 mg) y 2-fluoro-5-nitrotolueno (347 mg) se disolvió en N,N-dimetilformamida (5 ml), se agregó carbonato de potasio (588 mg), y la mezcla se agitó a temperatura ambiente durante 19 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 67:33→10:90) para dar el compuesto del título (561 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.11 (2H, q, J=3.9 Hz), 1.58-1.70 (2H, m), 2.41 (3H, s), 5.35 (1H, br s), 5.56 (1H, br s), 6.80 (1H, d, J= 9.0 Hz), 6.93-7.00 (1H, m), 7.13 (1H, t, J= 2.1 Hz), 7.27-7.33 (1H, m), 7.41 (1H, t, J= 7.8 Hz), 8.02 (1H, dd, J= 2.0 Hz, 9.0 Hz), 8.18 (1H, d, J= 2.0 Hz).

(v) Producción de 1-[3-(4-amino-2-metilfenoxi)fenil]ciclopropancarboxamida

Se suspendió 1-[3-(2-metil-4-nitrofenoxi)fenil]ciclopropancarboxamida (556 mg) en un solvente mixto de etanol (18 ml)/agua (2 ml), se añadieron hierro reducido (615 mg) y cloruro de calcio (105 mg), y la mezcla se agitó con calentamiento a reflujo durante 4 h. La mezcla de reacción se filtró a través de celite, y el filtrado se concentró a presión reducida. El residuo se disolvió en acetato de etilo, y la solución se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 50:50→0:100) para dar el compuesto del título (433 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 1.03-1.11 (2H, m), 1.54-1.63 (2H, m), 2.09 (3H, s), 3.59 (2H, br s), 5.38 (2H, br s), 6.49-6.56 (1H, m), 6.60 (1H, d, J= 2.8 Hz), 6.72-6.82 (2H, m), 6.89-6.94 (1H, m), 7.01-7.07 (1H, m), 7.23 (1H, t, J= 8.4 Hz).

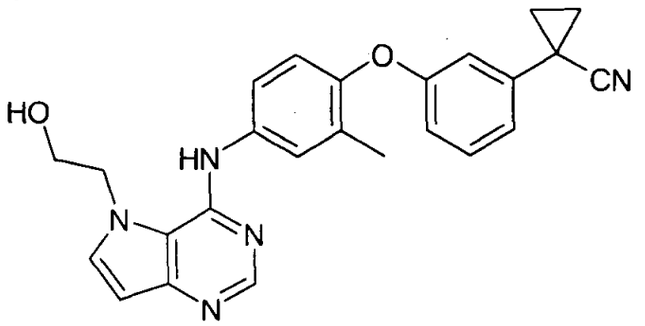
(vi) Producción de 1-[3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarboxamida

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (113 mg) y 1-[3-(4-amino-

2-metilfenoxi)fenil]ciclopropancarboxamida (108 mg) se disolvió en alcohol isopropílico (3 ml), y la mezcla se agitó a 70°C durante 21 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se agregó solución acuosa 1 N de hidróxido de sodio (1 ml) y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 20:80→0:100→acetato de etilo:metanol = 90:10) y se cristalizó en acetato de etilo para dar el compuesto del título (110 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ:,0.90-0.98 (2H, m), 1.25-1.33 (2H, m), 2.16 (3H, s), 3.87 (2H, t, J= 4.5 Hz), 4.52 (2H, t, J= 4.5 Hz), 6.25 (2H, br s), 6.48 (1H, d, J= 3.0 Hz), 6.74-6.82 (1H, m), 6.82-6.87 (1H, m), 6.96-7.09 (3H, m), 7.30 (1H, t, J= 7.9 Hz), 7.47-7.56 (2H, m), 7.62 (1H, d, J= 3.0 Hz), 8.27 (1H, s), 9.61 (1H, br s).

Ejemplo E-19



Producción de 1-[3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarbonitrilo

(i) Producción de 1-(3-hidroxifenil)ciclopropancarbonitrilo

Al usar 1-(3-metoxifenil)ciclopropancarbonitrilo (1.28 g), tolueno (75 ml) y solución de tribromuro de boro 1 N/diclorometano (25 ml) y de la misma manera que en el Ejemplo E-18(iii), se obtuvo el compuesto del título (1.11 g) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 1.37-1.46 (2H, m), 1.69-1.77 (2H, m), 5.16 (1H, s), 6.70-6.81 (2H, m), 6.83 (1H, t, J= 2.1 Hz), 7.21 (1H, t, J= 7.8 Hz).

(ii) Producción de 1-[3-(2-metil-4-nitrofenoxi)fenil]ciclopropancarbonitrilo

Al usar 2-fluoro-5-nitrotolueno (409 mg), 1-(3-hidroxifenil)ciclopropancarbonitrilo (450 mg), carbonato de potasio (731 mg) y N,N-dimetilformamida (8 ml) y de la misma manera que en el Ejemplo E-18(iv), se obtuvo el compuesto del

título (776 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.38-1.47 (2H, m), 1.72-1.82 (2H, m), 2.40 (3H, s), 6.78 (1H, d, J= 9.0 Hz), 6.88-6.95 (1H, m), 7.01 (1H, t, J= 2.1 Hz), 7.10-7.17 (1H, m), 7.38 (1H, t, J= 8.0 Hz), 8.01 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.12-8.22 (1H, m).

(iii) Producción de 1-[3-(4-amino-2-metilfenoxi)fenil]ciclopropancarbonitrilo

Al usar 1-[3-(2-metil-4-nitrofenoxi)fenil]ciclopropancarbonitrilo (771 mg), hierro reducido (847 mg), cloruro de calcio (151 mg) y etanol (27 ml)/agua (3 ml) y de la misma manera que en el Ejemplo E-18(v), se obtuvo el compuesto del título (665 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.36-1.39 (2H, m), 1.67-1.71 (2H, m), 2.09 (3H, s), 3.57 (2H, br s), 6.52 (1H, dd, J= 2.7 Hz, 8.7 Hz), 6.59 (1H, d, J=2.7 Hz), 6.67-6.70 (1H, m), 6.75-6.79 (2H, m), 6.93-6.96 (1H, m), 7.21 (1H, t, J= 8.1 Hz).

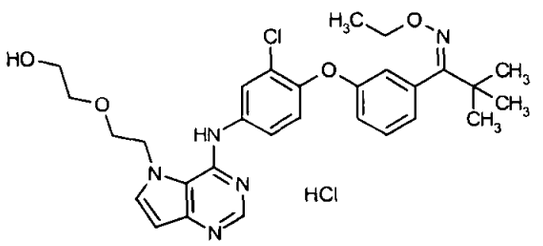
(iv) Producción de 1-[3-(4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarbonitrilo

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (127 mg), 1-[3-(4-amino-2-metilfenoxi)fenil]ciclopropancarbonitrilo (130 mg), alcohol isopropílico (3 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-18(vi),

se obtuvo el compuesto del título (115 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.38-1.45 (2H, m), 1.69-1.76 (2H, m), 2.24 (3H, s), 4.08-4.18 (2H, m), 4.31-4.43 (2H, m), 6.12 (1H, d, J= 3.3 Hz), 6.35 (1H, br s), 6.80 (1H, dd, J= 1.9 Hz, 8.0 Hz), 6.88-7.03 (4H, m), 7.25 (1H, t, J= 8.0 Hz), 7.38-7.51 (2H, m), 8.22 (1H, s), 9.31 (1H, m).

Ejemplo E-20



Producción de clorhidrato de O-etiloxima de (1Z)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona

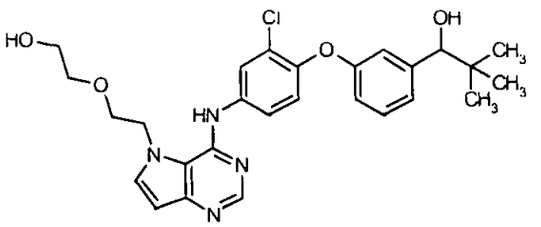
Al usar 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona (255 mg), etanol (5 ml), clorhidrato de O-etilhidroxilamina (146 mg), acetato de sodio (123 mg) y solución de cloruro de hidrógeno 1 N/acetato de etilo (0.5 ml) y de la misma manera que en el Ejemplo E-9(iii), se obtuvo el compuesto del título (144 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.07 (3H, t, J = 7.0 Hz), 1.10 (9H, s), 3.40-3.50 (4H, m), 3.84 (2H, t, J = 4.5 Hz), 3.92

LOSS

(2H, q, J = 7.0 Hz), 4.82 (2H, t, J = 4.5 Hz), 6.61 (1H, m), 6.69 (1H, d, J = 3.0 Hz), 6.82 (1H, d, J = 7.4 Hz), 6.93-6.99 (1H, m), 7.19 (1H, d, J = 8.8 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.61 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.95 (1H, d, J = 2.5 Hz), 8.01 (1H, d, J = 3.0 Hz), 8.71 (1H, s), 9.92 (1H, br s).

Ejemplo E-21



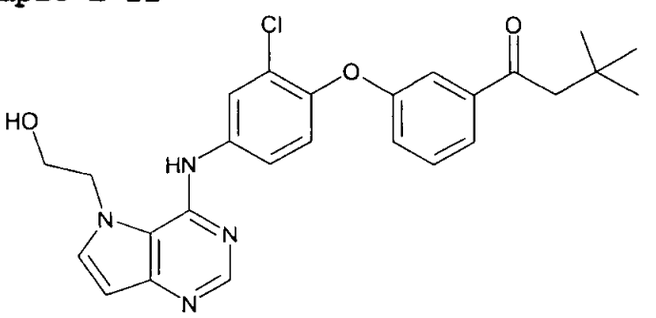
Producción de 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ol

A una solución de 1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona (255 mg) en metanol (5 ml) se añadió borohidruro de sodio (38 mg) y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el residuo obtenido se cristalizó en acetato de etilo-éter diisopropílico para dar el compuesto del título (206 mg) en forma de un polvo blanco.

L056

^{1}H-RMN ($CDCl_3$) δ: 0.92 (9H, s), 2.02 (1H, br s), 2.12 (1H, br s), 3.69-3.80 (4H, m), 4.01 (2H, t, J = 4.4 Hz), 4.36 (1H, s), 4.55 (2H, t, J = 4.4 Hz), 6.59 (1H, d, J = 3.0 Hz), 6.82-6.88 (1H, m), 6.92 (1H, m), 6.96-7.04 (2H, m), 7.19 (1H, d, J = 3.0 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.54 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.85 (1H, d, J = 2.5 Hz), 8.47 (1H, s), 8.73 (1H, br s).

Ejemplo E-22



Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona

(i) Producción de 1-[3-(4-amino-2-clorofenoxi)fenil]-3,3-dimetilbutan-1-ona

A una solución de 1-[3-(2-cloro-4-nitrofenoxi)fenil]-3,3-dimetilbutan-1-ona (1.04 g) en acetato de etilo (20 ml) se añadió platino-carbón activado al 5% (50 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 3 h. El catalizador se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, acetato

de etilo:hexano = 15:85→35:65) y las fracciones objeto se concentraron a presión reducida para dar el compuesto del título (964 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 1.04 (9H, s), 2.80 (2H, s), 3.69 (2H, br s), 6.57 (1H, dd, J = 2.7 Hz, 8.7 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 8.7 Hz), 7.05 (1H, ddd, J = 0.9 Hz, 2.6 Hz, 8.1 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.41 (1H, m), 7.55-7.59 (1H, m).

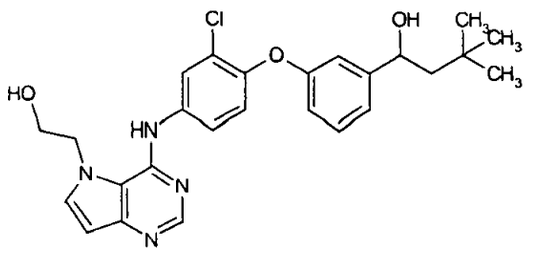
(ii) Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (754 mg), 1-[3-(4-amino-2-clorofenoxi)fenil]-3,3-dimetilbutan-1-ona (795 mg), alcohol isopropílico (5 ml), metanol (10 ml), tetrahidrofurano (2 ml) y solución acuosa 1 N de hidróxido de sodio (2.5 ml) y de la misma manera que en el Ejemplo E-8, se obtuvo el compuesto del título (878 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.06 (9H, s), 2.84 (2H, s), 4.13 (2H, t, J = 4.4 Hz), 4.37 (2H, t, J = 4.4 Hz), 6.09 (1H, d, J = 3.2 Hz), 6.58 (1H, br s), 6.95 (1H, d, J = 3.2 Hz), 7.04 (1H, d, J = 8.8 Hz), 7.13-7.18 (1H, m), 7.39 (1H, t, J = 8.0 Hz), 7.46 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.50 (1H, m), 7.62 (1H, d, J = 7.7 Hz), 7.81 (1H, d, J = 2.6 Hz), 8.19 (1H, s), 9.59 (1H, br s).

1058

Ejemplo E-23

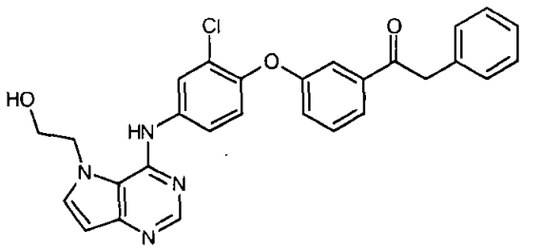


Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ol

Al usar 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona (239 mg), metanol (5 ml) y borohidruro de sodio (38 mg) y de la misma manera que en el Ejemplo E-21, se obtuvo el compuesto del título (234 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.00 (9H, s), 1.61 (1H, dd, J = 3.4 Hz, 14.5 Hz), 1.74 (1H, dd, J = 8.3 Hz, 14.5 Hz), 1.91 (1H, br s), 4.13 (2H, t, J = 4.5 Hz), 4.36 (2H, t, J = 4.5 Hz), 4.82 (1H, dd, J = 3.4 Hz, 8.3 Hz), 6.09 (1H, d, J = 3.0 Hz), 6.52 (1H, br s), 6.85 (1H, dd, J = 2.5 Hz, 8.0 Hz), 6.95 (1H, d, J = 3.0 Hz), 7.00-7.08 (3H, m), 7.28 (1H, t, J = 7.8 Hz), 7.45 (1H, dd, J = 2.6 Hz, 8.8 Hz), 7.80 (1H, d, J = 2.6 Hz), 8.19 (1H, s), 9.56 (1H, br s).

Ejemplo E-24



Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2-feniletanona

(i) Producción de 1-[3-(4-amino-2-clorofenoxi)fenil]-2-feniletanona

Al usar 1-[3-(2-cloro-4-nitrofenoxi)fenil]-2-feniletanona (240 mg), acetato de etilo (10 ml) y platino-carbón activado al 5% (12 mg) y de la misma manera que en el Ejemplo E-22(i), se obtuvo el compuesto del título (192 mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 3.70 (2H, br s), 4.21 (2H, s), 6.57 (1H, dd, J = 2.7 Hz, 8.8 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.89 (1H, d, J = 8.8 Hz), 7.06-7.11 (1H, m), 7.19-7.40 (6H, m), 7.46 (1H, m), 7.64-7.69 (1H, m).

(ii) Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2-feniletanona

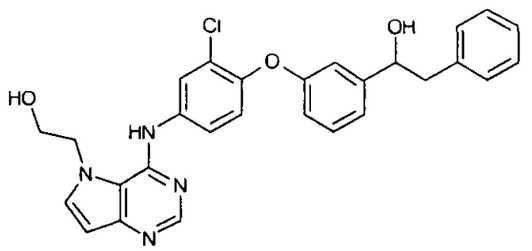
Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (166 mg), 1-[3-(4-amino-2-clorofenoxi)fenil]-2-feniletanona (186 mg), alcohol

L060

isopropílico (3 ml), metanol (5 ml), tetrahidrofurano (1 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-8, se obtuvo el compuesto del título (123 mg) en forma de un polvo de color marrón pálido.

^{1}H-RMN ($CDCl_3$) δ: 4.14 (2H, t, J = 4.5 Hz), 4.25 (2H, s), 4.38 (2H, t, J = 4.5 Hz), 6.15 (1H, d, J = 3.2 Hz), 6.19 (1H, br s), 6.97 (1H, d, J = 3.2 Hz), 7.05 (1H, d, J = 8.7 Hz), 7.17-7.37 (6H, m), 7.42 (1H, t, J = 8.0 Hz), 7.49 (1H, dd, J = 2.7 Hz, 8.7 Hz), 7.54 (1H, m), 7.72 (1H, d, J = 7.7 Hz), 7.82 (1H, d, J = 2.7 Hz), 8.24 (1H, s), 9.55 (1H, br s).

Ejemplo E-25



Producción de 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2-feniletanol

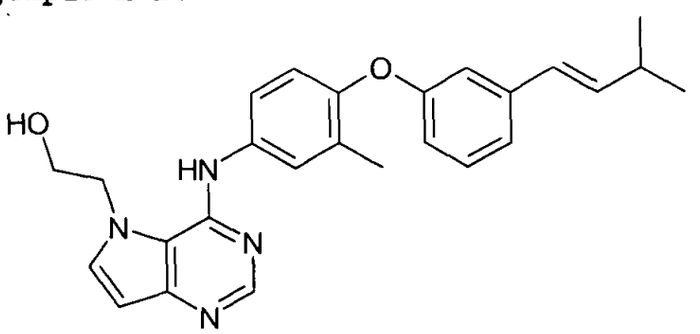
Al usar 1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-2-feniletanona (60 mg), metanol (2 ml) y borohidruro de sodio (10 mg) y de la misma manera que en el Ejemplo E-21, se obtuvo el compuesto del título (24 mg) en forma de un polvo

L66L

blanco.

^{1}H-RMN ($CDCl_3$) δ: 2.08 (1H, br s), 2.98 (1H, dd, J = 8.2 Hz, 13.7 Hz), 3.05 (1H, dd, J = 4.9 Hz, 13.7 Hz), 4.14 (2H, t, J = 4.6 Hz), 4.38 (2H, t, J = 4.6 Hz), 4.89 (1H, dd, J = 4.9 Hz, 8.2 Hz), 6.07 (1H, br s), 6.15 (1H, d, J = 3.3 Hz), 6.87-6.93 (1H, m), 6.96-7.02 (3H, m), 7.08 (1H, d, J = 7.7 Hz), 7.17-7.35 (6H, m), 7.45 (1H, dd, J = 2.5 Hz, 8.8 Hz), 7.79 (1H, d, J = 2.5 Hz), 8.24 (1H, s), 9.48 (1H, br s).

Ejemplo E-26



Producción de 2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

(i) Producción de 3-(2-metil-4-nitrofenoxi)benzaldehído

Al usar 2-fluoro-5-nitrotolueno (3.00 g), 3-hidroxibenzaldehido (2.59 g), carbonato de potasio (4.58 g) y N,N-dimetilformamida (30 ml) y de la misma manera que en el Ejemplo E-18(iv), se obtuvo el compuesto del título (4.14 g) en forma de un sólido de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 2.40 (3H, s), 6.85 (1H, d, J= 9

L062

Hz), 7.28-7.36 (1H, m), 7.46-7.54 (1H, m), 7.60 (1H, t, J= 7.8 Hz), 7.68-7.76 (1H, m), 8.04 (1H, dd, J= 2.8 Hz, 9.0 Hz), 8.19 (1H, d, J= 2.8 Hz), 10.00 (1H, s).

(ii) Producción de 2-metil-1-{3-[3-metilbut-1-en-1-il]fenoxi}-4-nitrobenceno

Se suspendió bromuro de isobutiltrifenilfosfonio (1.86 g) en tetrahidrofurano (20 ml) y la suspensión se enfrió hasta 0°C. Gota a gota se añadió solución 1.6 M de n-butil-litio/hexano (3.5 ml), y la mezcla se agitó a 0°C durante 1 h. Una solución de 3-(2-metil-4-nitrofenoxi)benzaldehído (1.00 g) en tetrahidrofurano (10 ml) se añadió gota a gota a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 2 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con éter dietílico. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 100:0→90:10) para dar el compuesto del título (1.09 g, E/Z= aproximadamente 1/5) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.03 (5H, d, J= 6.5 Hz), 1.09 (1H, d, J= 6.5 Hz), 2.41 (3H, s), 2.40-2.51 (0.17H, m), 2.77-2.92 (0.83H, m), 5.51 (0.83H, dd, J= 10.3 Hz, 11.6 Hz), 6.15-6.38 (1.17H, m), 6.72-6.96 (2.83H, m), 7.03 (0.17H, t, J= 7.7 Hz),

L063

7.11 (0.83H, d, J= 7.7 Hz), 7.20 (0.17H, d, J= 7.7 Hz), 7.28-7.41 (1H, m), 7.94-8.06 (1H, m), 8.11-8.21 (1H, m).

(iii) Producción de 3-metil-4-{3-[3-metilbut-1-en-1-il]fenoxi}anilina

Al usar 2-metil-1-{3-[3-metilbut-1-en-1-il]fenoxi}-4-nitrobenceno (1.08 g), hierro reducido (1.01 g), cloruro de calcio (205 mg) y etanol (36 ml)/agua (4 ml) y de la misma manera que en el Ejemplo E-18(v), se obtuvo el compuesto del título (821 mg, E/Z= aproximadamente 1/5) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.00 (5H, d, J= 6.6 Hz), 1.07 (1H, d, J= 6.6 Hz), 2.12 (3H, s), 2.36-2.52 (0.17H, m), 2.74-2.96 (0.83H, m), 3.55 (2H, br s), 5.43 (0.83H, dd, J= 10.2 Hz, 11.6 Hz), 6.08-6.33 (1.17H, m), 6.47-6.92 (5.83H, m), 6.95-7.01 (0.17H, m), 7.16 (0.17H, t, J= 8.0 Hz), 7.19 (0.83H, t, J= 8.0 Hz).

(iv) Producción de 3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}anilina

Se disolvió 3-metil-4-{3-[3-metilbut-1-en-1-il]fenoxi}anilina (815 mg) en tetrahidrofurano (15 ml), se añadieron disulfuro de difenilo (133 mg) y 2.2'-azobis(butironitrilo) (103 mg), y la mezcla se agitó con calentamiento a reflujo durante 3 días. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se

L064

secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 90:10→50:50) para dar el compuesto del título (181 mg) en forma de un aceite anaranjado.

^{1}H-RMN ($CDCl_3$) δ: 1.06 (6H, d, J= 6.9 Hz), 2.11 (3H, s), 2.35-2.53 (1H, m), 3.55 (2H, br s), 6.13 (1H, dd, J= 6.3 Hz, 16.0 Hz), 6.25 (1H, d, J= 16.0 Hz), 6.51 (1H, dd, J= 3.0 Hz, 8.4 Hz), 6.59 (1H, d, J= 3.0 Hz), 6.65 (1H, dd, J= 2.6 Hz, 8.0 Hz), 6.78 (1H, d, J= 8.4 Hz), 6.81-6.86 (1H, m), 6.97 (1H, d, J= 8.0 Hz), 7.15 (1H, t, J= 8.0 Hz).

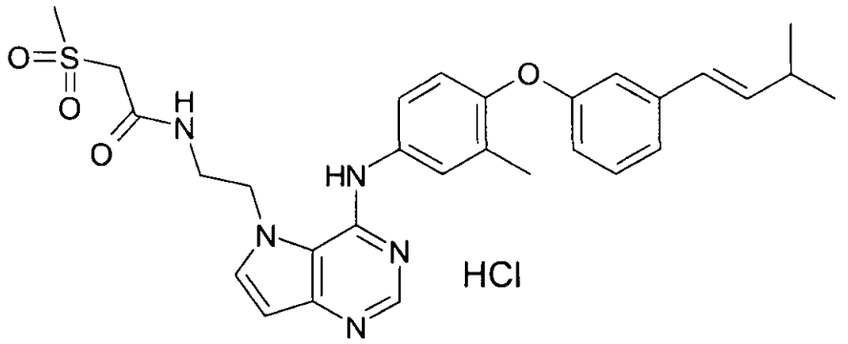
(v) Producción de 2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (69.6 mg), 3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}anilina (65.0 mg), alcohol isopropílico (2 ml) y solución acuosa 1 N de hidróxido de sodio (1 ml) y de la misma manera que en el Ejemplo E-18(vi), se obtuvo el compuesto del título (47.7 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.09 (6H, d, J= 6.8 Hz), 2.26 (3H, s), 2.36-2.56 (1H, m), 4.13 (2H, t, J= 4.5 Hz), 4.31-4.42 (2H, m), 6.12 (1H, d, J= 3.2 Hz), 6.19 (1H, dd, J= 6.6 Hz, 16.2 Hz), 6.30 (1H, d, J= 16.2 Hz), 6.72-6.81 (1H, m), 6.90-

6.99 (3H, m), 7.04 (1H, d, J= 8.0 Hz), 7.21 (1H, t, J= 8.0 Hz), 7.37-7.48 (2H, m), 8.23 (1H, s), 9.28 (1H, s).

Ejemplo E-27



Producción de clorhidrato de N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de (2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (120 mg) y 3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}anilina (109 mg) se disolvió en alcohol isopropílico (5 ml), y se agitó a 70°C durante 22 h. Se añadió una solución acuosa saturada de carbonato ácido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de

L066

etilo = 67:33→10:90) para dar el compuesto del título (186 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.08 (6H, d, J= 6.6 Hz), 1.46 (9H, s), 2.24 (3H, s), 2.35-2.55 (1H, m), 3.42-3.58 (2H, m), 4.40-4.52 (2H, m), 4.95-5.08 (1H, m), 6.18 (1H, dd, J= 6.6 Hz, 16.2 Hz), 6.29 (1H, d, J= 16.2 Hz), 6.58 (1H, d, J= 3.0 Hz), 6.73-6.81 (1H, m), 6.90-6.98 (2H, m), 7.03 (1H, d, J= 8.0 Hz), 7.16 (1H, d, J= 3.0 Hz), 7.20 (1H, t, J= 8.0 Hz), 7.58-7.70 (2H, m), 8.32 (1H, br s), 8.49 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina

Se disolvió (2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo (180 mg) en etanol (1 ml), a ello se añadió ácido clorhídrico 6 N (0.3 ml), y la mezcla se agitó a 50°C durante 12 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en etanol, y la mezcla se volvió a concentrar a presión reducida. El precipitado se recogió por filtración para dar el compuesto del título (158 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.05 (6H, d, J= 6.8 Hz), 2.22 (3H, s), 2.37-2.54 (1H, m), 3.18-3.32 (2H, m), 5.00 (2H, t, J= 6.1 Hz), 6.22-6.41 (2H, m), 6.67-6.79 (2H, m), 6.92-7.04

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(2H, m), 7.16 (1H, d, J= 7.9 Hz), 7.31 (1H, t, J= 7.9 Hz), 7.39 (1H, dd, J= 2.0 Hz, 8.6 Hz), 7.49 (1H, d, J= 2.0 Hz), 8.03 (1H, d, J= 3.2 Hz), 8.31 (3H br s), 8.67 (1H, s), 9.87 (1H, br s).

(iii) Producción de clorhidrato de N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (74.8 mg) y ácido metilsulfonilacético (31.1 mg) se disolvió en tetrahidrofurano (0.4 ml)/N,N-dimetilformamida (0.4 ml), sucesivamente se añadieron 1-hidroxibenzotriazol (32.5 mg), trietilamina (0.2 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (45.0 mg), y la mezcla se agitó a temperatura ambiente durante 24 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 20:80→0:100→acetato de etilo:metanol = 90:10) para dar N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida. El compuesto se disolvió en

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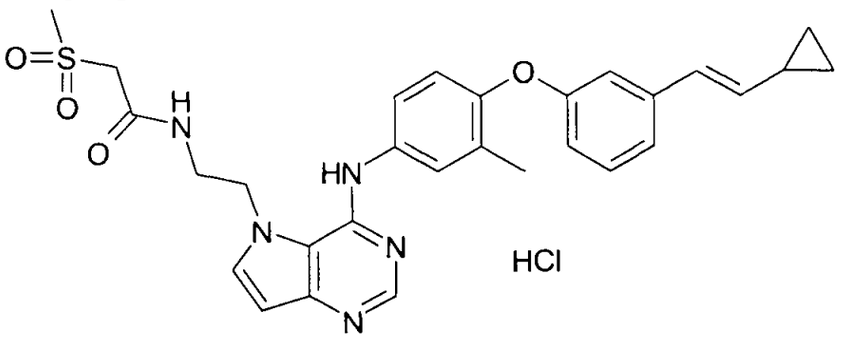
acetato de etilo y se trató con solución de cloruro de hidrógeno 4 N/acetato de etilo, y el precipitado se recogió por filtración para dar el compuesto del título (32.5 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 1.05 (6H, d, J= 6.8 Hz), 2.22 (3H, s), 2.36-2.55 (1H, m), 3.06 (3H, s), 3.47-3.62 (2H, m), 4.06 (2H, s), 4.69 (2H, t, J= 6.4 Hz), 6.20-6.42 (2H, m), 6.64 (1H, d, J= 3.0 Hz), 6.69-6.78 (1H, m), 6.93-7.03 (2H, m), 7.16 (1H, d, J= 8.0 Hz), 7.31 (1H, t, J= 8.0 Hz), 7.44 (1H, dd, J= 2.5 Hz, 8.6 Hz), 7.53 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.67 (1H, s), 8.79 (1H, t, J= 5.6 Hz), 9.85 (1H, s).

Ejemplo E-28



Producción de clorhidrato de N-(2-{4-[(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

(i) Producción de 1-{3-[2-ciclopropilvinil]fenoxi}-2-metil-4-nitrobenceno

Al usar bromuro de (ciclopropilmetil)trifenilfosfonio (1.86 g), tetrahidrofurano

(30 ml), solución 1.6 M de n-butil-litio/hexano (3.5 ml) y 3-(2-metil-4-nitrofenoxi)benzaldehído (1.00 g) y de la misma manera que en el Ejemplo E-26(ii), se obtuvo el compuesto del título (1.15 g, E/Z = aproximadamente 1/2) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 0.43-0.56 (2H, m), 0.76-0.89 (2H, m), 1.50-1.63 (0.33H, m), 1.75-1.91 (0.67H, m), 2.40 (1H, s), 2.41 (2H, s), 5.10 (0.67H, dd, J= 10 Hz, 11.5 Hz), 5.72 (0.33H, dd, J= 8.9 Hz, 15.7 Hz), 6.30 (0.67H, d, J= 11.5 Hz), 6.43 (0.33H, d, J= 15.7 Hz), 6.76 (0.33H, d, J= 9.0 Hz), 6.80 (0.67H, d, J= 9.0 Hz), 6.79-6.84 (0.33H, m), 6.84-6.90 (0.67H, m), 6.96 (0.33H, t, J= 1.9 Hz), 7.09 (0.67H, t, J= 1.9 Hz), 7.13 (0.33H, d, J= 8.0 Hz), 7.27 (0.67H, d, J= 8.0 Hz), 7.30 (0.33H, t, J= 8.0 Hz), 7.36 (0.67H, t, J= 8.0 Hz), 7.93-8.02 (1H, m), 8.09 (1H, m).

(ii) Producción de 1-{3-[(E)-2-ciclopropilvinil]fenoxi}-2-metil-4-nitrobenceno

Al usar 1-{3-[2-ciclopropilvinil]fenoxi}-2-metil-4-nitrobenceno (1.14 g), tetrahidrofurano (25 ml), disulfuro de difenilo (172 mg) y 2.2'-azobis(butironitrilo) (134 mg) y de la misma manera que en el Ejemplo E-26(iv), se obtuvo el compuesto del título (734 mg) en forma de un aceite anaranjado.

^{1}H-RMN ($CDCl_3$) δ: 0.47-0.55 (2H, m), 0.79-0.89 (2H, m), 1.50-1.63 (1H, m), 2.41 (3H, s), 5.73 (1H, dd, J= 9.0 Hz,

15.7 Hz), 6.44 (1H, d, J= 15.7 Hz), 6.77 (1H, d, J= 9.0 Hz), 6.80-6.85 (1H, m), 6.97 (1H, t, J= 2.0 Hz), 7.14 (1H, d, J= 7.7 Hz), 7.30 (1H, t, J= 7.7 Hz), 7.98 (1H, dd, J= 2.2 Hz, 9.0 Hz), 8.15 (1H, d, J= 2.2 Hz).

(iii) Producción de 4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilanilina

Al usar 1-{3-[(E)-2-ciclopropilvinil]fenoxi}-2-metil-4-nitrobenceno (729 mg), hierro reducido (712 mg), cloruro de calcio (156 mg) y etanol (18 ml)/agua (2 ml) y de la misma manera que en el Ejemplo E-18(v), se obtuvo el compuesto del título (352 mg) en forma de un aceite marrón.

^{1}H-RMN ($CDCl_3$) δ: 0.44-0.53 (2H, m), 0.75-0.85 (2H, m), 1.44-1.63 (1H, m), 2.10 (3H, s), 3.54 (2H, br s), 5.67 (1H, dd, J= 9.0 Hz, 15.7 Hz), 6.39 (1H, d, J= 15.7 Hz), 6.51 (1H, dd, J= 2.7 Hz, 8.7 Hz), 6.59 (1H, d, J= 2.7 Hz), 6.61-6.67 (1H, m), 6.75-6.82 (2H, m), 6.92 (1H, d, J= 7.8 Hz), 7.14 (1H, t, J= 7.8 Hz).

(iv) Producción de (2-{4-[(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (352 mg), 4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilanilina (347 mg) y alcohol isopropílico (15 ml) y de la misma manera que en el Ejemplo E-27(i), se obtuvo el compuesto del título (540 mg) en forma

de un sólido blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.47-0.55 (2H, m), 0.75-0.87 (2H, m), 1.46 (9H, s), 1.50-1.61 (1H, m), 2.23 (3H, s), 3.43-3.56 (2H, m), 4.39-4.54 (2H, m), 4.98 (1H, t, J= 5.9 Hz), 5.71 (1H, dd, J= 9.0 Hz, 15.7 Hz), 6.41 (1H, d, J= 15.7 Hz), 6.59 (1H, d, J= 3.2 Hz), 6.75 (1H, dd, J= 1.6 Hz, 8.2 Hz), 6.87-7.01 (3H, m), 7.12-7.23 (2H, m), 7.57-7.71 (2H, m), 8.31 (1H, br s), 8.50 (1H, s).

(v) Producción de diclorhidrato de 5-(2-aminoetil)-N-(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar (2-{4-[(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo (536 mg), ácido clorhídrico 6 N (1 ml) y etanol (4 ml) y de la misma manera que en el Ejemplo E-27(ii), se obtuvo el compuesto del título (399 mg) en forma de un sólido amarillo.

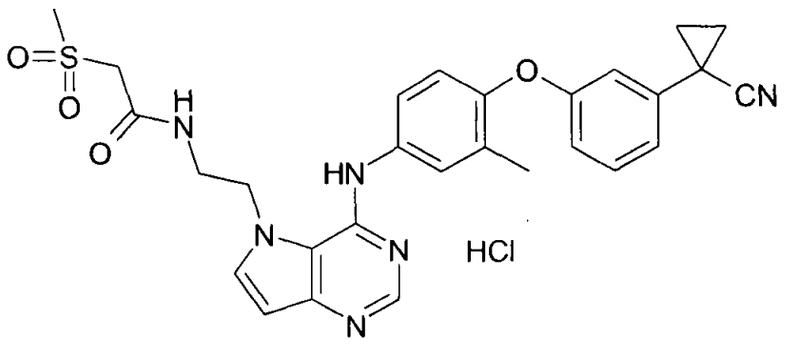
^{1}H-RMN (DMSO-d_6) δ: 0.47-0.55 (2H, m), 0.74-0.84 (2H, m), 1.49-1.64 (1H, m), 2.21 (3H, s), 3.21-3.34 (2H. m), 5.02 (2H, t, J= 6.2 Hz), 5.85 (1H, dd, J= 9.4 Hz, 15.7 Hz), 6.44 (1H, d, J= 15.7 Hz), 6.66-6.74 (2H, m), 6.90-6.99 (2H, m), 7.09 (1H, d, J= 7.8 Hz), 7.27 (1H, t, J= 7.8 Hz), 7.38 (1H, dd, J= 2.6 Hz, 8.7 Hz), 7.48 (1H, d, J= 2.5 Hz), 8.04 (1H, d, J= 3.3 Hz), 8.37 (3H, br s), 8.66 (1H, s), 9.93 (1H, br s).

(vi) Producción de clorhidrato de N-(2-{4-[(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-(4-{3-[(E)-2-ciclopropilvinil]fenoxi}-3-metilfenil)-5H-pirrolo[3,2-d]pirimidin-4-amina (149 mg), ácido metilsulfonilacético (85.1 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (118 mg), trietilamina (0.4 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (178 mg) y solución de cloruro de hidrógeno 4 N/acetato de etilo y de la misma manera que en el Ejemplo E-27(iii), se obtuvo el compuesto del título (123 mg) en forma de cristales amarillos.

^{1}H-RMN (DMSO-d_6) δ: 0.47-0.56 (2H, m), 0.74-0.86 (2H, m), 1.47-1.66 (1H, m), 2.22 (3H, s), 3.06 (3H, m), 3.49-3.63 (2H, m), 4.06 (2H, s), 4.69 (2H, t, J= 6.2 Hz), 5.86 (1H, dd, J= 9.2 Hz, 15.8 Hz), 6.44 (1H, d, J= 15.8 Hz), 6.64 (1H, d, J= 3.0 Hz), 6.70 (1H, dd, J= 1.8 Hz, 8.0 Hz), 6.90-7.00 (2H, m), 7.10 (1H, d, J= 8.0 Hz), 7.28 (1H, t, J= 8.0 Hz), 7.43 (1H, dd, J= 2.5 Hz, 8.6 Hz), 7.52 (1H, d, J= 2.5 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.66 (1H, s), 8.79 (1H, t, J= 5.7 Hz), 9.85 (1H, br s).

Ejemplo E-29



Producción de clorhidrato de N-{2-[4-({4-[3-(1-cianociclopropil)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de {2-[4-({4-[3-(1-cianociclopropil)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (350 mg), 1-[3-(4-amino-2-metilfenoxi)fenil]ciclopropancarbonitrilo (351 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo E-27(i), se obtuvo el compuesto del título (590 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.35-1.43 (2H, m), 1.47 (9H, s), 1.66-1.75 (2H, m), 2.21 (3H, s), 3.43-3.57 (2H, m), 4.41-4.53 (2H, m), 5.01 (1H, t, J= 5.8 Hz), 6.59 (1H, d, J= 3.2 Hz), 6.76-6.83 (1H, m), 6.86-6.95 (2H, m), 6.98-7.05 (1H, m), 7.16 (1H, d, J= 3.2 Hz), 7.24 (1H, t, J= 7.9 Hz), 7.58-7.76 (2H, m), 8.35 (1H, br s), 8.50 (1H, s).

(ii) Producción de diclorhidrato de 1-[3-(4-{[5-(2-

aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarbonitrilo

Al usar {2-[4-({4-[3-(1-cianociclopropil)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (586 mg), ácido clorhídrico 6 N (1 ml) y etanol (6 ml) y de la misma manera que en el Ejemplo E-27(ii), se obtuvo el compuesto del título (478 mg) en forma de cristales blancos.

^{1}H-RMN (DMSO-d_6) δ: 1.47-1.58 (2H, m), 1.71-1.82 (2H, m), 2.21 (3H, s), 3.19-3.49 (2H, m), 4.98 (2H, t, J= 6.1 Hz), 6.71 (1H, d, J= 3.0 Hz), 6.80 (1H, dd, J= 2.3 Hz, 7.7 Hz), 6.98 (1H, t, J= 2.3 Hz), 7.01 (1H, d, J= 8.7 Hz), 7.04-7.09 (1H, m), 7.39 (1H, t, J= 7.7 Hz), 7.42 (1H, dd, J= 2.3 Hz, 8.7 Hz), 7.51 (1H, d, J= 2.3 Hz), 8.01 (1H, d, J= 3.0 Hz), 8.26 (3H, br s), 8.66 (1H, s), 9.81 (1H, br s).

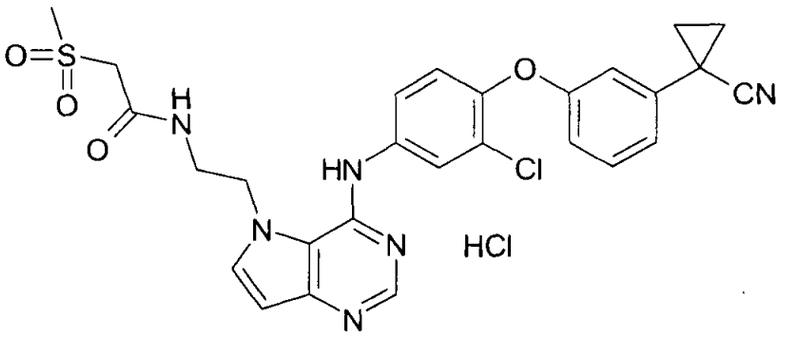
(iii) Producción de clorhidrato de N-{2-[4-({4-[3-(1-cianociclopropil)fenoxi]-3-metilfenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 1-[3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-metilfenoxi)fenil]ciclopropancarbonitrilo (150 mg), ácido metilsulfonilacético (65.2 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (82.1 mg), trietilamina (0.4 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (117 mg) y solución de

cloruro de hidrógeno 4 N/acetato de etilo y de la misma manera que en el Ejemplo E-27(iii), se obtuvo el compuesto del título (133 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.49-1.57 (2H, m), 1.73-1.81 (2H, m), 2.21 (3H, s), 3.05 (3H, s), 3.49-3.60 (2H, m), 4.06 (2H, s), 4.70 (2H, t, J= 6.2 Hz), 6.63 (1H, d, J= 3.0 Hz), 6.79 (1H, dd, J= 2.5 Hz, 8.0 Hz), 6.98 (1H, t, J= 2.5 Hz), 7.01 (1H, d, J= 8.0 Hz), 7.03-7.09 (1H, m), 7.38 (1H, t, J= 8.0 Hz), 7.46 (1H, dd, J= 2.6 Hz, 8.7 Hz), 7.54 (1H, d, J= 2.6 Hz), 7.90 (1H, d, J= 3.0 Hz), 8.66 (1H, s), 8.81 (1H, t, J= 5.5 Hz), 9.87 (1H, s).

Ejemplo E-30



Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

(i) Producción de 1-[3-(2-cloro-4-nitrofenoxi)fenil]ciclopropancarbonitrilo

Al usar 3-cloro-4-fluoronitrobenceno (362 mg), 1-(3-hidroxifenil)ciclopropancarbonitrilo (350 mg), carbonato

de potasio (493 mg) y N,N-dimetilformamida (7 ml) y de la misma manera que en el Ejemplo E-18(iv), se obtuvo el compuesto del título (650 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.39-1.48 (2H, m), 1.74-1.84 (2H, m), 6.90 (1H, d, J= 9 Hz), 6.95-7.01 (1H, m), 7.04 (1H, t, J= 2.0 Hz), 7.20 (1H, d, J= 8.0 Hz), 7.42 (1H, t, J= 8.0 Hz), 8.08 (1H, dd, J= 2.6 Hz, 9.0 Hz), 8.40 (1H, d, J= 2.6 Hz).

(ii) Producción de 1-[3-(4-amino-2-clorofenoxi)fenil]ciclopropancarbonitrilo

Al usar 1-[3-(2-cloro-4-nitrofenoxi)fenil]ciclopropancarbonitrilo (643 mg), hierro reducido (570 mg), cloruro de calcio (113 mg) y etanol (18 ml)/agua (2 ml) y de la misma manera que en el Ejemplo E-18(v), se obtuvo el compuesto del título (508 mg) en forma de un aceite amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.34-1.41 (2H, m), 1.66-1.74 (2H, m), 3.68 (2H, br s), 6.57 (1H, dd, J= 2.8 Hz, 8.5 Hz), 6.68-6.74 (1H, m), 6.78 (1H, d, J= 2.8 Hz), 6.80 (1H, t, J= 2.1 Hz), 6.88 (1H, d, J= 8.5 Hz), 6.95-7.01 (1H, m), 7.23 (1H, t, J= 8.0 Hz).

(iii) Producción de {2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (350 mg), 1-[3-(4-amino-2-

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clorofenoxi)fenil]ciclopropancarbonitrilo (349 mg) y alcohol isopropílico (8 ml) y de la misma manera que en el Ejemplo E-27(i), se obtuvo el compuesto del título (632 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.36-1.45 (2H, m), 1.50 (9H, s), 1.66-1.77 (2H, m), 3.43-3.57 (2H, m), 4.40-4.55 (2H, m), 5.07 (1H, t, J= 5.5 Hz), 6.60 (1H, d, J= 3.0 Hz), 6.84 (1H, dd, J= 2.2 Hz, 8.0 Hz), 6.91 (1H, t, J= 2.2 Hz), 7.03 (1H, d, J= 9.1 Hz), 7.05-7.11 (1H, m), 7.18 (1H, d, J= 3.0 Hz), 7.28 (1H, t, J= 8.0 Hz), 7.87 (1H, dd, J= 2.7 Hz, 9.1 Hz), 8.02 (1H, d, J= 2.7 Hz), 8.51 (1H, s), 8.58 (1H, s).

(iv) Producción de diclorhidrato de 1-[3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)fenil]ciclopropancarbonitrilo

Se disolvió {2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (627 mg) en un solvente mixto de etanol (7 ml)/tetrahidrofurano (1 ml), se añadió ácido clorhídrico 6 N (1 ml), y la mezcla se agitó a 50°C durante 14 h. La mezcla de reacción se concentró a presión reducida, el residuo se disolvió en ácido clorhídrico concentrado (2 ml), y la mezcla se agitó a temperatura ambiente durante 10 min. Se añadió etanol a la mezcla de reacción y el precipitado resultante se recogió por filtración para dar el compuesto del título (433 mg) en forma

de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 1.48-1.60 (2H, m), 1.72-1.84 (2H, m), 3.21-3.37 (2H, m), 5.01 (2H, t, J= 6.4 Hz), 6.74 (1H, d, J= 3.0 Hz), 6.85 (1H, dd, J= 8.0 Hz, 2.2 Hz), 7.03 (1H, t, J= 2.2 Hz), 7.08-7.15 (1H, m), 7.23 (1H, d, J= 8.9 Hz), 7.42 (1H, t, J= 8.0 Hz), 7.61 (1H, dd, J= 2.5 Hz, 8.9 Hz), 7.90 (1H, d, J= 2.5 Hz), 8.05 (1H, d, J= 3.0 Hz), 8.29 (3H, br s), 8.71 (1H, s), 10.05 (1H, br s).

(v) Producción de clorhidrato de N-{2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida

Al usar diclorhidrato de 1-[3-(4-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-2-clorofenoxi)fenil]ciclopropancarbonitrilo (149 mg), ácido metilsulfonilacético (60.0 mg), tetrahidrofurano (0.8 ml)/N,N-dimetilformamida (0.8 ml), 1-hidroxibenzotriazol (77.4 mg), trietilamina (0.4 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (110 mg) y solución de cloruro de hidrógeno 4 N/acetato de etilo y de la misma manera que en el Ejemplo E-27(iii), se obtuvo el compuesto del título (131 mg) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6) δ: 1.50-1.60 (2H, m), 1.74-1.83 (2H, m), 3.06 (3H, s), 3.54 (2H, q, J= 6.0 Hz), 4.06 (2H, s), 4.70 (2H, t, J= 6.0 Hz), 6.66 (1H, d, J= 3.0 Hz), 6.85 (1H, dd, J= 2.2 Hz, 8.0 Hz), 7.02 (1H, t, J= 2.2 Hz), 7.08-7.14

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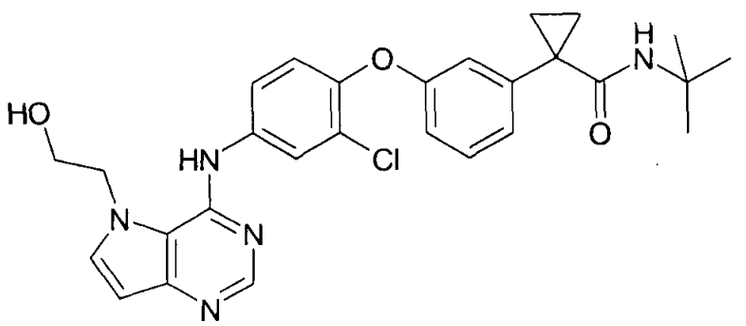
(1H, m), 7.24 (1H, d, J= 9.0 Hz), 7.41 (1H, t, J= 8.0 Hz), 7.64 (1H, dd, J= 2.5 Hz, 9.0 Hz), 7.92 (1H, d, J= 2.5 Hz), 7.93 (1H, d, J= 3.0 Hz), 8.71 (1H, s), 8.77 (1H, t, J= 5.8 Hz), 9.91 (1H, br s).

Ejemplo E-31



Producción de N-(ter-butil)-1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida

(i) Producción de N-(ter-butil)-1-(3-metoxifenil)ciclopropancarboxamida

Se disolvió ácido 1-(3-metoxifenil)ciclopropancarboxílico (400 mg) en tetrahidrofurano (6 ml), se añadieron una cantidad catalítica de N,N-dimetilformamida y cloruro de tionilo (0.4 ml), y la mezcla se agitó a temperatura ambiente durante 6 h. La mezcla de reacción se concentró a presión reducida, y el residuo se disolvió en tetrahidrofurano (4 ml). La solución se añadió gota a gota a una mezcla enfriada hasta 0°C de ter-butilamina (0.25 ml), trietilamina (1 ml) y tetrahidrofurano (3 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se

añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→67:33) para dar el compuesto del título (477 mg) en forma de un aceite de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 0.97 (2H, q, J= 3.7 Hz), 1.22 (9H, s), 1.52 (2H, q, J= 3.7 Hz), 3.82 (3H, s), 5.22 (1H, br s), 6.81-6.87 (1H, m), 6.90-6.94 (1H, m), 6.95-7.01 (1H, m), 7.27 (1H, t, J= 7.9 Hz).

(ii) Producción de N-(ter-butil)-1-(3-hidroxifenil)ciclopropancarboxamida

Al usar N-(ter-butil)-1-(3-metoxifenil)ciclopropancarboxamida (470 mg), benzotrifluoruro (10 ml) y solución de tribromuro de boro 1 N/diclorometano (4 ml) y de la misma manera que en el Ejemplo E-18(iii), se obtuvo el compuesto del título (245 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.95-1.04 (2H, m), 1.22 (9H, s), 1.50-1.58 (2H, m), 5.36 (1H, br s), 6.13 (1H, br s), 6.76-6.88 (2H, m), 6.90-6.98 (1H, m), 7.19-7.29 (1H, m).

(iii) Producción de N-(ter-butil)-1-[3-(2-cloro-4-nitrofenoxi)fenil]ciclopropancarboxamida

Al usar N-(ter-butil)-1-(3-hidroxifenil)ciclopropancarboxamida (242 mg), 3-cloro-4-fluoronitrobenceno (237 mg), carbonato de potasio (223 mg) y N,N-dimetilformamida (5 ml) y de la misma manera que en el Ejemplo E-18(iv), se obtuvo el compuesto del título (397 mg) en forma de cristales blancos.

^{1}H-RMN ($CDCl_3$) δ: 0.96-1.01 (2H, m), 1.23 (9H, s), 1.52-1.59 (2H, m), 5.08 (1H, br s), 6.88 (1H, d, J= 9.1 Hz), 6.98-7.04 (1H, m), 7.08-7.13 (1H, m), 7.27-7.32 (1H, m), 7.43 (1H, t, J= 8.0 Hz), 8.07 (1H, dd, J= 2.8 Hz, 9.1 Hz), 8.40 (1H, d, J= 2.8 Hz).

(iv) Producción de 1-[3-(4-amino-2-clorofenoxi)fenil]-N-(ter-butil)ciclopropancarboxamida

Se disolvió N-(ter-butil)-1-[3-(2-cloro-4-nitrofenoxi)fenil]ciclopropancarboxamida (392 mg) en un solvente mixto de metanol (7.5 ml)/acetato de etilo (7.5 ml), se añadió platino-carbón activado al 5% (44.4 mg) y la mezcla se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 1.5 h. La mezcla de reacción se filtró a través de celite, y el filtrado se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 95:5→50:50) para dar el compuesto del título (324 mg) en forma de un aceite incoloro.

^{1}H-RMN ($CDCl_3$) δ: 0.91-0.98 (2H, m), 1.21 (9H, s),

1.45-1.52 (2H, m), 3.70 (2H, s), 5.17 (1H, br s), 6.59 (1H, dd, J= 2.7 Hz, 8.6 Hz), 6.79 (1H, d, J= 2.7 Hz), 6.81-6.87 (2H, m), 6.91 (1H, d, J= 8.6 Hz), 6.99-7.06 (1H, m), 7.21-7.31 (1H, m).

(v) Producción de N-(ter-butil)-1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (120 mg), 1-[3-(4-amino-2-clorofenoxi)fenil]-N-(ter-butil)ciclopropancarboxamida (160 mg), alcohol isopropílico (4 ml) y solución acuosa 1 N de hidróxido de sodio (1.5 ml) y de la misma manera que en el Ejemplo E-18(vi), se obtuvo el compuesto del título (155 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.96 (2H, q, J= 3.7 Hz), 1.21 (9H, s), 1.49 (2H, q, J= 3.7 Hz), 4.14-4.22 (2H, m), 4.37-4.46 (2H, m), 5.19 (1H, s), 6.06 (1H, br s), 6.19 (1H, d, J= 3.2 Hz), 6.89-6.98 (2H, m), 7.02 (1H, d, J= 3.2 Hz), 7.04-7.11 (2H, m), 7.31 (1H, t, J= 7.8 Hz), 7.52 (1H, dd, J= 2.5 Hz, 8.7 Hz), 7.81 (1H, d, J= 2.5 Hz), 8.29 (1H, s), 9.58 (1H, s).

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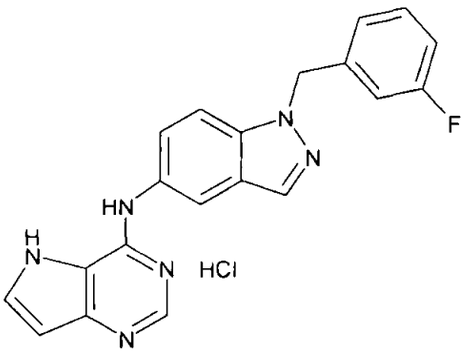
Ejemplo G-1

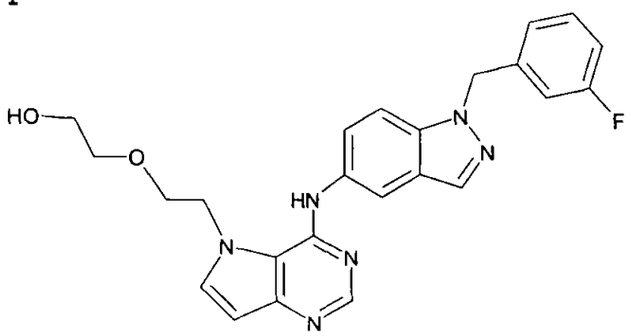


Producción de clorhidrato de N-[1-(3-fluorobencil)-1H-indazol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una solución de 4-cloro-5H-pirrolo[3,2-d]pirimidina (153 mg) y 1-(3-fluorobencil)-1H-indazol-5-amina (362 mg) en N,N-dimetilformamida (2 ml) se agitó a 120°C durante 2.5 h. La mezcla de reacción se enfrió hasta temperatura ambiente, se agregó acetato de etilo (30 ml) y la mezcla se agitó a temperatura ambiente durante 30 min. Los cristales resultantes se recogieron por filtración, se lavaron con acetato de etilo y se secaron a presión reducida para dar el compuesto del título (361 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 5.70 (2H, s), 6.57 (1H, d, J= 2 Hz), 7.00-7.20 (3H, m), 7.36 (1H, m), 7.70-7.90 (3H, m), 8.17 (1H, s), 8.41 (1H, m), 8.59 (1H, s), 10.97 (1H, br s), 12.58 (1H, br s).

Ejemplo G-2



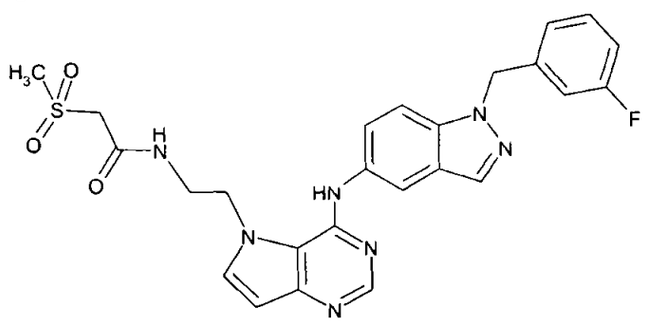
Producción de 2-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (150 mg), 1-(3-fluorobencil)-1H-indazol-5-amina (156 mg) y 1-metil-2-pirrolidona (0.863 ml) se agitó con calentamiento a 140°C durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml), y la capa orgánica se lavó con bicarbonato de sodio acuoso (30 ml), se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 70:30→0:100), y las fracciones objeto se concentraron a presión reducida. El residuo obtenido se disolvió en metanol (1.89 ml), se añadió solución acuosa 1 N de hidróxido de sodio (0.433 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se agregó ácido clorhídrico 1 N (0.433 ml) a la mezcla, y la mezcla se diluyó con acetato de etilo (80 ml), y la capa orgánica se lavó con

salmuera saturada (30 ml), se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→90:10) y se cristalizó en éter isopropílico para dar el compuesto del título (153 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.50 (4H, br s), 3.84 (2H, t, J= 4 Hz), 4.64 (2H, t, J= 4 Hz), 4.69 (1H, m), 5.69 (2H, s), 6.47 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.36 (1H, m), 7.53 (1H, d, J= 9 Hz), 7.60-7.70 (2H, m), 8.05 (1H, s), 8.09 (1H, s), 8.23 (1H, s), 8.76 (1H, br s).

Ejemplo G-3



Producción de N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

(i) Producción de [2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (0.5 g) y 1-(3-

fluorobencil)-1H-indazol-5-amina (608 mg) en alcohol isopropílico (5 ml) se agitó a 80°C durante 12 h. Se agregó bicarbonato de sodio acuoso (30 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (80 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 7:3→acetato de etilo) para dar el compuesto del título (820 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.44 (9H, s), 3.50 (2H, m), 4.46 (2H, m), 5.07 (1H, m), 5.58 (2H, s), 6.57 (1H, d, J= 3 Hz), 6.80-7.00 (3H, m), 7.14 (1H, d, J= 3 Hz), 7.20-7.40 (2H, m), 7.74 (1H, dd, J= 2 Hz, 9 Hz), 7.99 (1H, s), 8.05 (1H, d, J= 1 Hz), 8.45 (1H, s), 8.53 (1H, br s).

(ii) Producción de triclorhidrato de 5-(2-aminoetil)-N-[1-(3-fluorobencil)-1H-indazol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (780 mg), ácido clorhídrico 2 N (11.1 ml) y tetrahidrofurano (22.2 ml) se agitó a 60°C durante 20 h. El solvente se evaporó a presión reducida, se añadió etanol a la mezcla, y la mezcla luego se concentró. El

polvo precipitado se recogió por filtración y se lavó con éter isopropílico para dar el compuesto del título (668 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.32 (2H, m), 5.08 (2H, m), 5.74 (2H, s), 6.72 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.38 (1H, m), 7.52 (1H, dd, J= 2 Hz, 9 Hz), 7.80 (1H, d, J= 9 Hz), 7.91 (1H, d, J= 2 Hz), 8.07 (1H, m), 8.20 (1H, s), 8.45 (3H, br s), 8.60 (1H, s).

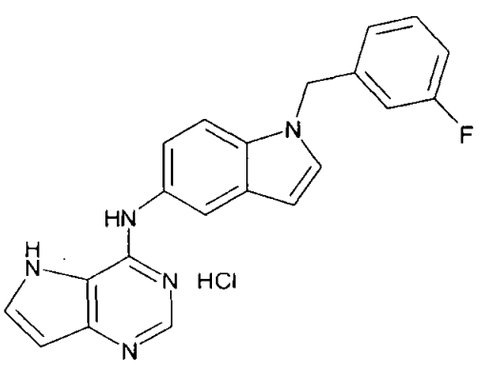
(iii) Producción de N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida

Una mezcla de triclorhidrato de 5-(2-aminoetil)-N-[1-(3-fluorobencil)-1H-indazol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina (183 mg), ácido metilsulfonilacético (74.2 mg), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 90:10) y se cristalizó

en éter isopropílico para dar el compuesto del título (134 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.07 (3H, s), 3.48 (2H, q, J= 6 Hz), 4.04 (2H, s), 4.56 (2H, t, J= 6 Hz), 5.69 (2H, s), 6.45 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.30-7.40 (1H, m), 7.57 (2H, m), 7.68 (1H, d, J= 9 Hz), 7.95 (1H, m), 8.10 (1H, s), 8.21 (1H, s), 8.58 (1H, br s), 8.65 (1H, t, J= 6 Hz).

Ejemplo G-4

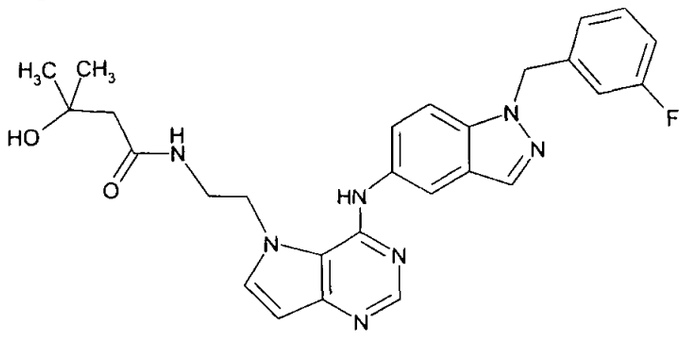


Producción de clorhidrato de N-[1-(3-fluorobencil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una solución de 4-cloro-5H-pirrolo[3,2-d]pirimidina (153 mg) y 1-(3-fluorobencil)-1H-indol-5-amina (360 mg) en N,N-dimetilformamida (2 ml) se agitó a 120°C durante 2 h. La mezcla de reacción se enfrió hasta temperatura ambiente, a ello se añadió acetato de etilo (30 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Los cristales resultantes se recogieron por filtración, se lavaron con acetato de etilo y se secaron a presión reducida para dar el compuesto del título (377 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 5.46 (2H, s), 6.53 (2H, d, J= 3 Hz), 7.05 (3H, m), 7.36 (1H, m), 7.49 (2H, m), 7.56 (1H, d, J= 3 Hz), 7.79 (1H, br s), 8.16 (1H, br s), 8.51 (1H, s), 10.61 (1H, br s), 12.45 (1H, br s).

Ejemplo G-5



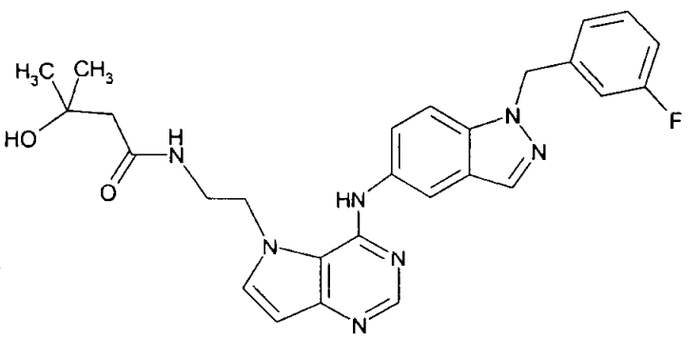
Producción de N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

Una mezcla de triclorhidrato de 5-(2-aminoetil)-N-[1-(3-fluorobencil)-1H-indazol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina (183 mg), ácido 3-hidroxi-3-metilbutanoico (0.058 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por

cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) y se cristalizó en éter isopropílico para dar el compuesto del título (100 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.12 (6H, s), 2.20 (2H, s), 3.44 (2H, q, J= 7 Hz), 4.52 (2H, t, J= 7 Hz), 4.69 (1H, s), 5.69 (2H, s), 6.44 (1H, d, J= 3 Hz), 7.00-7.20 (3H, m), 7.30-7.40 (1H, m), 7.50-7.70 (3H, m), 8.00 (1H, d, J= 2 Hz), 8.09 (1H, s), 8.20 (1H, s), 8.23 (1H, t, J= 7 Hz), 8.76 (1H, br s).

Ejemplo G-6



Producción de 2-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etanol

Una mezcla de benzoato de 2-[2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etoxi]etilo (150 mg), 1-(3-fluorobencil)-1H-indol-5-amina (155 mg) y 1-metil-2-pirrolidona (0.863 ml) se agitó con calentamiento a 140°C durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (80 ml) y se lavó con bicarbonato de sodio acuoso (30 ml). La capa orgánica se separó, se secó sobre sulfato de

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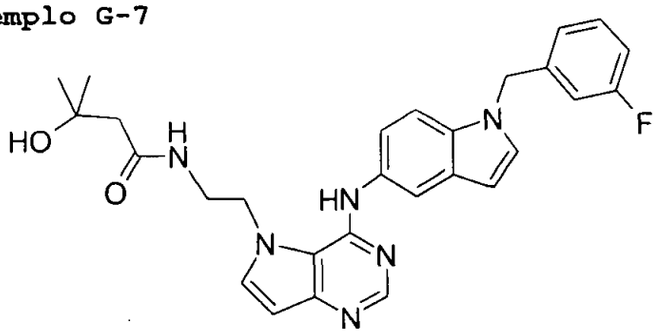
magnesio anhidro, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano:acetato de etilo = 70:30→0:100→acetato de etilo:metanol = 95:5), y las fracciones objeto se concentraron a presión reducida. El residuo obtenido se disolvió en metanol (1.89 ml), se agregó solución acuosa 1 N de hidróxido de sodio (0.433 ml), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido clorhídrico 1 N (0.433 ml) a la mezcla, y la mezcla se diluyó con acetato de etilo (80 ml). La capa orgánica se lavó con salmuera saturada (30 ml), se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo:metanol = 100:0→90:10) y se cristalizó en éter isopropílico/acetato de etilo para dar el compuesto del título (107 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.49 (4H, br s), 3.83 (2H, t, J= 4 Hz), 4.61 (2H, t, J= 4 Hz), 4.67 (1H, t, J= 4 Hz), 5.45 (2H, s), 6.44 (1H, dd, J= 1.5 Hz, 3 Hz), 6.47 (1H, d, J= 3 Hz), 6.90-7.10 (3H, m), 7.25 (1H, d, J= 9 Hz), 7.3-7.5 (2H, m), 7.51 (1H, d, J= 3 Hz), 7.59 (1H, d, J= 3 Hz), 7.81 (1H, s), 8.17 (1H, s), 8.58 (1H, br s).

Ejemplo G-7



Producción de N-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

(i) Producción de [2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Una solución de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (0.5 g) y 1-(3-fluorobencil)-1H-indol-5-amina (606 mg) en alcohol isopropílico (5 ml) se agitó a 80°C durante 12 h. Se agregó bicarbonato de sodio acuoso (30 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo (80 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 7:3→acetato de etilo→acetato de etilo:metanol = 95:5) para dar el compuesto del título (840 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.42 (9H, s), 3.45 (2H, m), 4.38 (2H,t, J= 7 Hz), 5.17 (1H, m), 5.29 (2H, s), 6.51 (1H, dd, J= 1 Hz, 3 Hz), 6.53 (1H, d, J= 3 Hz), 6.78 (1H, d, J= 9 Hz), 6.80-7.00 (2H, m), 7.10 (2H, t, J= 3 Hz), 7.18-7.30 (2H, m), 7.47 (1H, d, J= 9 Hz), 7.89 (1H, br s), 8.20 (1H, br s), 8.43 (1H, s).

(ii) Producción de diclorhidrato de 5-(2-aminoetil)-N-[1-(3-fluorobencil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (830 mg), ácido clorhídrico 2 N (11.8 ml) y tetrahidrofurano (23.6 ml) se agitó a 60°C durante 20 h. El solvente se evaporó a presión reducida, se añadió etanol a la mezcla, y la mezcla luego se concentró. El polvo precipitado se recogió por filtración y se lavó con éter isopropílico para dar el compuesto del título (828 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.27 (2H, m), 5.07 (2H, m), 5.43 (2H, s), 6.50-6.70 (2H, m), 6.80-7.30 (4H, m), 7.37 (1H, m), 7.68 (1H, m), 7.86 (1H, s), 8.04 (1H, d, J= 3 Hz), 8.44 (1H, s), 8.50 (3H, br s), 8.55 (1H, s), 10.01 (1H, br s).

(iii) Producción de N-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida

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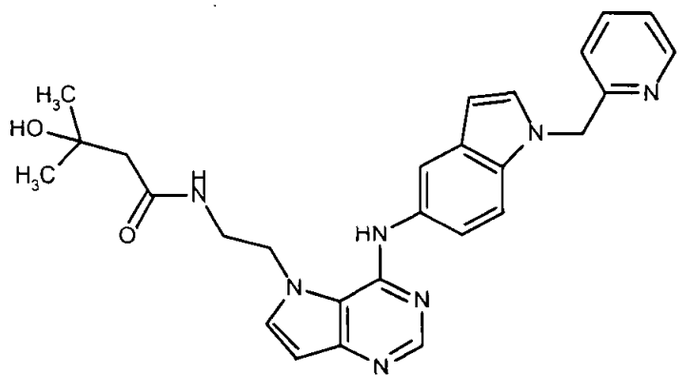
Una mezcla de diclorhidrato de 5-(2-aminoetil)-N-[1-(3-fluorobencil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina (183 mg), ácido 3-hidroxi-3-metilbutanoico (0.058 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (103 mg), 1-hidroxibenzotriazol (72.5 mg), trietilamina (0.15 ml) y N,N-dimetilformamida (6.9 ml) se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo→acetato de etilo:metanol = 85:15) y se cristalizó en éter isopropílico para dar el compuesto del título (43 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.12 (6H, s), 2.20 (2H, s), 3.44 (2H, q, J= 7 Hz), 4.50 (2H, t, J= 7 Hz), 4.70 (1H, br s), 5.46 (2H, s), 6.41 (1H, d, J= 3 Hz), 6.47 (1H, d, J= 3 Hz), 6.9-7.2 (3H, m), 7.20-7.50 (3H, m), 7.52 (2H, t, J= 3 Hz), 7.76 (1H, s), 8.15 (1H, s), 8.19 (1H, t, J= 6 Hz), 8.57 (1H, br s).

Ejemplo G-8



Producción de 3-hidroxi-3-metil-N-[2-(4-{[1-(piridin-2-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]butanamida

(i) Producción de 5-nitro-1-(piridin-2-ilmetil)-1H-indol

A una solución de 5-nitroindol (1.62 g) y 2-(clorometil)clorhidrato de piridina (1.80 g) en N,N-dimetilformamida (20 ml) se añadió carbonato de potasio (3.46 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 16 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (2.05 g) en forma de cristales amarillos.

^{1}H-RMN ($CDCl_3$) δ: 5.49 (2H, s), 6.75-6.80 (2H, m), 7.15-7.25 (1H, m), 7.32 (1H, d, J= 9.0 Hz), 7.36 (1H, d, J=

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3.3 Hz), 7.58 (1H, dt, J= 2.1 Hz, 7.8 Hz), 8.07 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.55-8.65 (2H, m).

(ii) Producción de 1-(piridin-2-ilmetil)-1H-indol-5-amina

A una solución de 5-nitro-1-(piridin-2-ilmetil)-1H-indol (507 mg) en acetato de etilo (10 ml)/metanol (2 ml) se añadió platino-carbón activado al 5% (84.5 mg) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 h. El carbón activado con platino se filtró, y el filtrado se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 70:30→100:0) y luego se recristalizó en acetato de etilo/hexano para dar el compuesto del título (357 mg) en forma de un polvo de color durazno blancuzco.

^{1}H-RMN ($CDCl_3$) δ: 3.48 (2H, br s), 5.38 (2H, s), 6.39 (1H, d, J= 3.0 Hz), 6.55-6.70 (2H, m), 6.94 (1H, s), 7.03 (1H, d, J= 8.7 Hz), 7.10-7.20 (2H, m), 7.49 (1H, t, J= 7.8 Hz), 8.57 (1H, d, J= 4.2 Hz).

(iii) Producción de [2-(4-{[1-(piridin-2-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Una mezcla de [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (297 mg), 1-

(piridin-2-ilmetil)-1H-indol-5-amina (246 mg) y alcohol isopropílico (5.0 ml) se agitó a 80°C durante 16 h. Bajo enfriamiento con hielo, se añadió bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→90:10) para dar el compuesto del título (498 mg) en forma de un polvo de color púrpura pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.43 (9H, s), 3.45-3.55 (2H, m), 4.35-4.45 (2H, m), 4.9-5.0 (1H, m), 5.45 (2H, s), 6.53 (1H, d, J = 3.0 Hz), 6.55 (1H, d, J = 3.0 Hz), 6.71 (1H, d, J = 8.1 Hz), 7.10-7.30 (4H, m), 7.40-7.50 (1H, m), 7.52 (1H, dt, J = 1.8, 7.8 Hz), 7.90 (1H, s), 8.17 (1H, br s), 8.44 (1H, s), 8.58 (1H, d, J = 4.2 Hz).

(iv) Producción de tetraclorhidrato de 5-(2-aminoetil)-N-[1-(piridin-2-ilmetil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Una mezcla de [2-(4-{[1-(piridin-2-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (439 mg) y ácido clorhídrico al 10% (p/p)/metanol (5 ml) se agitó a 65°C durante 18 h. La mezcla de reacción se concentró a presión reducida, y el precipitado se recogió por filtración y se lavó con éter

dietílico para dar el compuesto del título (422 mg) en forma de cristales de color verde pálido.

^{1}H-RMN (DMSO-d_6) δ: 3.2-3.4 (2H, m), 4.90-5.10 (2H, m), 5.63 (2H, s), 6.57 (1H, d, J= 3.3 Hz), 6.69 (1H, d, J= 3.3 Hz), 7.08 (1H, d, J= 7.2 Hz), 7.20 (1H, d, J= 8.7 Hz), 7.35-7.45 (1H, m), 7.52 (1H, d, J= 8.7 Hz), 7.61 (1H, d, J= 3.3 Hz), 7.67 (1H, s), 7.85-7.95 (1H, m), 8.01 (1H, d, J= 2.7 Hz), 8.25-8.4 (3H, m), 8.56 (1H, s), 8.61 (1H, d, J= 5.1 Hz), 9.97 (1H, s).

(v) Producción de 3-hidroxi-3-metil-N-[2-(4-{[1-(piridin-2-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]butanamida

A una solución de tetraclorhidrato de 5-(2-aminoetil)-N-[1-(piridin-2-ilmetil)-1H-indol-5-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 3-hidroxi-3-metilbutanoico (67 mg) y 1-hidroxibenzotriazol (85 mg) en N,N-dimetilformamida (5.0 ml) se añadieron trietilamina (0.52 ml) y clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (120 mg) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel

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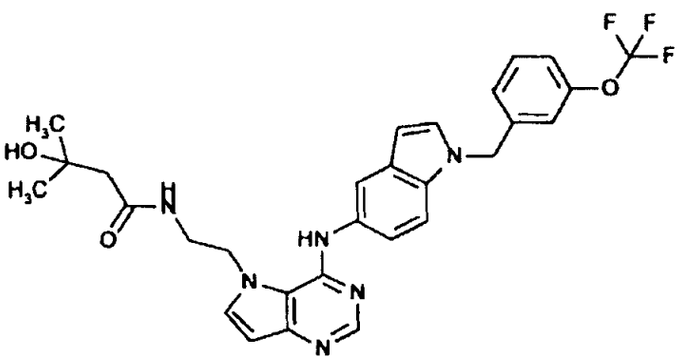
de sílice (eluyente, acetato de etilo:metanol = 100:0→70:30) y luego se recristalizó en acetato de etilo/éter diisopropílico para dar el compuesto del título (85.3 mg) en forma de cristales incoloros.

^{1}H-RMN (DMSO-d_6) δ: 1.26 (6H, s), 2.37 (2H, s), 3.55-3.7 (2H, m), 4.35-4.45 (2H, m), 5.45 (2H, s), 6.55 (2H, dd, J= 3.3 Hz, 7.8 Hz), 6.73 (1H, d, J= 7.8 Hz), 6.75-6.85 (1H, m), 7.1-7.25 (3H, m), 7.39 (1H, dd, J= 1.8 Hz, 8.7 Hz), 7.53 (1H, dt, J= 1.8 Hz, 7.8 Hz), 7.87 (1H, d, J= 1.5 Hz), 8.22 (1H, s), 8.43 (1H, s), 8.58 (1H, d, J= 4.8 Hz).

Ejemplo G-9



Producción de 3-hidroxi-3-metil-N-{2-[4-({1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}butanamida

(i) Producción de 5-nitro-1-[3-(trifluorometoxi)bencil]-1H-indol

Al usar 5-nitroindol (538 mg), 1-(bromometil)-3-(trifluorometoxi)benceno (0.96 g), carbonato de potasio (551 mg) y N,N-dimetilformamida (8.0 ml) y de la misma manera que

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en el Ejemplo G-8(i), se obtuvo el compuesto del título (0.95 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 5.39 (2H, s), 6.76 (1H, d, J= 3.3 Hz), 6.90-7.00 (2H, m), 7.15 (1H, d, J= 8.1 Hz), 7.20-7.30 (2H, m), 7.35 (1H, t, J= 8.1 Hz), 8.09 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.62 (1H, d, J= 2.4 Hz).

(ii) Producción de 1-[3-(trifluorometoxi)bencil]-1H-indol-5-amina

Al usar 5-nitro-1-[3-(trifluorometoxi)bencil]-1H-indol (504 mg), platino-carbón activado al 5% (84 mg) y acetato de etilo (15 ml) y de la misma manera que en el Ejemplo G-8(ii), se obtuvo el compuesto del título (466 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.50 (2H, br s), 5.26 (2H, s), 6.37 (1H, d, J= 3.0 Hz), 6.62 (1H, dd, J= 2.4 Hz, 8.7 Hz), 6.90-7.10 (5H, m), 7.08 (1H, d, J= 8.7 Hz), 7.25-7.35 (1H, m).

(iii) Producción de {2-[4-({1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (405 mg), 1-[3-(trifluorometoxi)bencil]-1H-indol-5-amina (459 mg) y alcohol isopropílico (8.0 ml) y de la misma manera que en el Ejemplo G-8(iii), se obtuvo el compuesto del título (692 mg) en forma

de un amorfo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.42 (9H, s), 3.45-3.55 (2H, m), 4.35-4.45 (2H, m), 4.93 (1H, br s), 5.33 (2H, s), 6.52 (1H, d, J = 3.3 Hz), 6.55 (1H, d, J = 3.0 Hz), 6.95-7.05 (2H, m), 7.10-7.25 (4H, m), 7.30 (1H, t, J = 8.2 Hz), 7.45-7.55 (1H, m), 7.90 (1H, s), 8.18 (1H, br s), 8.44 (1H, s).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-{1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar {2-[4-({1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}carbamato de ter-butilo (675 mg), ácido clorhídrico al 10% (p/p)/metanol (8.0 ml) y metanol (6.0 ml) y de la misma manera que en el Ejemplo G-8(iv), se obtuvo el compuesto del título (568 mg) en forma de un polvo anaranjado.

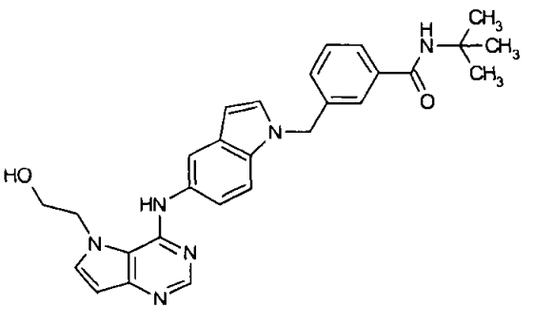
^{1}H-RMN (DMSO-d_6) δ: 3.20-3.35 (2H, m), 4.90-5.10 (2H, m), 5.54 (2H, s), 6.55 (1H, d, J= 3.3 Hz), 6.68 (1H, d, J= 3.0 Hz), 7.15-7.30 (4H, m), 7.46 (1H, t, J= 7.8 Hz), 7.53 (1H, d, J= 8.7 Hz), 7.63 (1H, d, J= 3.3 Hz), 7.67 (1H, s), 8.01 (1H, d, J= 3.0 Hz), 8.25-8.45 (3H, m), 8.55 (1H, s), 9.93 (1H, s).

(v) Producción de 3-hidroxi-3-metil-N-{2-[4-({1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}butanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 3-hidroxi-3-metilbutanoico (62 mg), 1-hidroxibenzotriazol (76 mg), trietilamina (0.48 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (106 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo G-8(v), se obtuvo el compuesto del título (143 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.26 (6H, s), 2.38 (2H, s), 3.55-3.70 (2H, m), 4.35-4.50 (2H, m), 5.32 (2H, s), 6.54 (2H, t, J= 3.6 Hz), 6.80-6.90 (1H, m), 6.95-7.05 (2H, m), 7.10-7.20 (3H, m), 7.20-7.45 (3H, m), 7.88 (1H, s), 8.25 (1H, s), 8.43 (1H, s).

Ejemplo G-10



Producción de N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida

(i) Producción de 3-[(5-nitro-1H-indol-1-il)metil]benzoato de metilo

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Al usar 5-nitroindol (0.87 g), 3-(bromometil)benzoato de metilo (1.35 g), carbonato de potasio (0.89 g) y N,N-dimetilformamida (10 ml) y de la misma manera que en el Ejemplo G-8(i), se obtuvo el compuesto del título (0.83 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.89 (3H, s), 5.41 (2H, s), 6.75 (1H, d, J= 3.3 Hz), 7.20-7.35 (3H, m), 7.39 (1H, t, J= 7.8 Hz), 7.88 (1H, s), 7.97 (1H, d, J= 7.8 Hz), 8.07 (1H, dd, J= 2.4 Hz, 9.1 Hz), 8.60 (1H, d, J= 1.8 Hz).

(ii) Producción de ácido 3-[(5-nitro-1H-indol-1-il)metil]benzoico

A una suspensión de 3-[(5-nitro-1H-indol-1-il)metil]benzoato de metilo (0.75 g) en metanol (12 ml) se añadió solución acuosa 1 N de hidróxido de sodio (12 ml) y la mezcla se agitó a temperatura ambiente durante 1.5 h. Se agregó tetrahidrofurano (12 ml) a la mezcla y la mezcla se agitó a temperatura ambiente durante 5 h. Bajo enfriamiento con hielo, se agregó ácido clorhídrico 1 N (12 ml) a la mezcla de reacción, y la mezcla se concentró a presión reducida. El precipitado se recogió por filtración, y se lavó con etanol y éter diisopropílico para dar el compuesto del título (621 mg) en forma de un polvo amarillo.

^{1}H-RMN (DMSO-d_6) δ: 5.55 (2H, s), 6.80 (1H, d, J= 2.4 Hz), 7.15-7.35 (2H, m), 7.67 (1H, d, J= 9.0 Hz), 7.70-7.85 (3H, m), 7.99 (1H, d, J= 7.8 Hz), 8.57 (1H, s).

(iii) Producción de N-(ter-butil)-3-[(5-nitro-1H-indol-1-il)metil]benzamida

A una suspensión de ácido 3-[(5-nitro-1H-indol-1-il)metil]benzoico (600 mg) y ter-butilamina (222 mg) en N,N-dimetilformamida (5.0 ml) se añadieron trietilamina (0.45 ml) y cianofosfato de dietilo (0.49 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 21 h. Se añadió ter-butilamina (0.32 ml) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 20 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 35:65→70:30) para dar el compuesto del título (266 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 5.39 (2H, s), 5.87 (1H, br s), 6.70-6.75 (1H, m), 7.10 (1H, d, J= 7.8 Hz), 7.25-7.30 (2H, m), 7.33 (1H, t, J= 7.8 Hz), 7.55 (1H, d, J= 7.8 Hz), 7.67 (1H, s), 8.06 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.60 (1H, d, J= 2.1 Hz).

(iv) Producción de 3-[(5-amino-1H-indol-1-il)metil]-N-(ter-butil)benzamida

Al usar N-(ter-butil)-3-[(5-nitro-1H-indol-1-

il)metil]benzamida (263 mg), platino-carbón activado al 5% (44 mg) y acetato de etilo (10 ml) y de la misma manera que en el Ejemplo G-8(ii), se obtuvo el compuesto del título (241 mg) en forma de un amorfo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 3.50 (2H, br s), 5.28 (2H, s), 5.84 (1H, br s), 6.37 (1H, d, J= 3.0 Hz), 6.62 (1H, dd, J= 2.4 Hz, 8.7 Hz), 6.94 (1H, d, J= 2.1 Hz), 7.00-7.15 (3H, m), 7.25-7.35 (1H, m), 7.54 (1H, d, J= 7.5 Hz), 7.60 (1H, s).

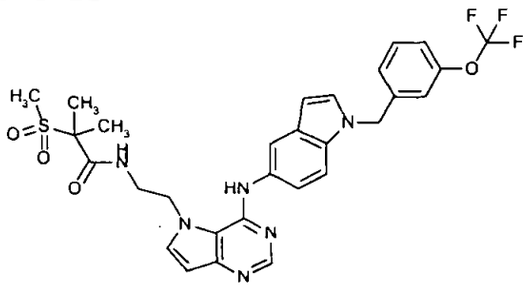
(v) Producción de N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (105 mg), 3-[(5-amino-1H-indol-1-il)metil]-N-(ter-butil)benzamida (123 mg) y alcohol isopropílico (5.0 ml) se agitó a 80°C durante 16 h. Bajo enfriamiento con hielo, se añadió bicarbonato de sodio acuoso a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (1.5 ml) y tetrahidrofurano (3.0 ml) y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se neutralizó con ácido

clorhídrico 1 N, y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se recristalizó en acetato de etilo/metanol para dar el compuesto del título (90 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (9H, s), 4.00-4.10 (2H, m), 4.25-4.35 (2H, m), 5.33 (2H, s), 5.90 (1H, br s), 6.14 (1H, d, J= 3.0 Hz), 6.52 (1H, d, J= 2.7 Hz), 6.87 (1H, d, J= 3.0 Hz), 7.10-7.35 (5H, m), 7.54 (1H, d, J= 7.5 Hz), 7.63 (1H, s), 7.76 (1H, s), 8.19 (1H, s), 9.15 (1H, s).

Ejemplo G-11



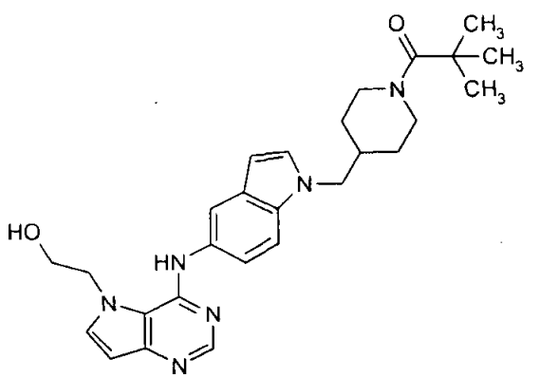
Producción de 2-metil-2-(metilsulfonil)-N-{2-[4-({1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}propanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-{1-[3-(trifluorometoxi)bencil]-1H-indol-5-il}-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 2-metil-2-(metilsulfonil)propanoico (87 mg), 1-hidroxibenzotriazol (76 mg), trietilamina (0.48 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (106 mg) y N,N-

dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo G-8(v), se obtuvo el compuesto del título (100 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.61 (6H, s), 2.84 (3H, s), 3.65-3.75 (2H, m), 4.35-4.45 (2H, m), 5.34 (2H, s), 6.55 (1H, d, J= 3.0 Hz), 6.60 (1H, d, J= 3.0 Hz), 7.00-7.45 (9H, m), 7.86 (1H, s), 7.91 (1H, br s), 8.46 (1H, s).

Ejemplo G-12



Producción de 2-{4-[(1-{[1-(2,2-dimetilpropanoil)piperidin-4-il]metil}-1H-indol-5-il)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

(i) Producción de 4-[(5-nitro-1H-indol-1-il)metil]piperidin-1-carboxilato de ter-butilo

A una solución de 4-(hidroximetil)piperidin-1-carboxilato de ter-butilo (1.29 g) y trietilamina (1.17 ml) en tetrahidrofurano (30 ml) se añadió gota a gota cloruro de metansulfonilo (0.56 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 h. Se agregó bicarbonato de sodio acuoso a la mezcla de reacción bajo

enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida para dar un aceite de color amarillo. A una solución de 5-nitroindol (811 mg) en N,N-dimetilformamida (5.0 ml) se añadió hidruro de sodio (60% en aceite (220 mg)) bajo enfriamiento con hielo, y la mezcla se agitó a 0°C durante 10 min. Bajo enfriamiento con hielo, a la mezcla de reacción se añadió gota a gota una solución del aceite amarillo obtenido con anterioridad en N,N-dimetilformamida (5.0 ml) y la mezcla se agitó a temperatura ambiente durante 1 h, y a 60°C durante 18 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 30:70→50:50) para dar el compuesto del título (1.79 g) como una forma amorfa amarilla.

^{1}H-RMN ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.45 (9H, s), 1.50-1.60 (2H, m), 1.90-2.05 (1H, m), 2.55-2.70 (2H, m), 4.00-4.20 (4H, m), 6.69 (1H, d, J= 3.0 Hz), 7.20 (1H, d, J= 3.0 Hz), 7.34 (1H, d, J= 9.0 Hz), 8.12 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.60 (1H, d, J= 2.1 Hz).

(ii) Producción de 4-[(5-amino-1H-indol-1-

il)metil]piperidin-1-carboxilato de ter-butilo

Al usar 4-[(5-nitro-1H-indol-1-il)metil]piperidin-1-carboxilato de ter-butilo (0.90 g), platino-carbón activado al 5% (0.15 g) y acetato de etilo (10 ml) y de la misma manera que en el Ejemplo G-8(ii), se obtuvo el compuesto del título (0.83 g) en forma de un amorfo rojo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.10-1.25 (2H, m), 1.44 (9H, s), 1.50-1.60 (2H, m), 1.90-2.05 (1H, m), 2.55-2.70 (2H, m), 3.91 (2H, d, J= 7.2 Hz), 4.00-4.20 (2H, m), 6.28 (1H, d, J= 3.0 Hz), 6.67 (1H, dd, J= 2.1 Hz, 8.7 Hz), 6.92 (1H, d, J= 2.1 Hz), 6.96 (1H, d, J= 3.3 Hz), 7.12 (1H, d, J= 8.7 Hz).

(iii) Producción de 4-{[5-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-1H-indol-1-il]metil}piperidin-1-carboxilato de ter-butilo

Una mezcla de benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (686 mg), 4-[(5-amino-1H-indol-1-il)metil]piperidin-1-carboxilato de ter-butilo (824 mg) y alcohol isopropílico (20 ml) se agitó a 80°C durante 12 h. Bajo enfriamiento con hielo, se añadió bicarbonato de sodio acuoso a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (1.04 g) en forma de un polvo

amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.45 (9H, s), 1.50-1.60 (2H, m), 1.95-2.10 (1H, m), 2.55-2.70 (2H, m), 3.98 (2H, d, J= 7.5 Hz), 4.05-4.20 (2H, m), 4.55-4.70 (4H, m), 6.43 (1H, d, J= 3.3 Hz), 6.63 (1H, d, J= 3.3 Hz), 7.04 (1H, d, J= 3.3 Hz), 7.25-7.35 (3H, m), 7.35-7.45 (3H, m), 7.50-7.65 (2H, m), 7.90-8.00 (2H, m), 8.48 (1H, s).

(iv) Producción de diclorhidrato de benzoato de 2-(4-{[1-(piperidin-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etilo

A una solución de 4-{[5-({5-[2-(benzoiloxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)-1H-indol-1-il]metil}piperidin-1-carboxilato de ter-butilo (820 mg) en metanol (10 ml) se añadió ácido clorhídrico al 10% (p/p)/metanol (10 ml) y la mezcla se agitó a temperatura ambiente durante 17 h. La mezcla de reacción se concentró a presión reducida, se añadió etanol, y la mezcla se volvió a concentrar. Esta operación se repitió dos veces. Se añadió éter diisopropílico, y la mezcla se concentró. El polvo obtenido se recogió por filtración, y se lavó con éter diisopropílico para dar el compuesto del título (621 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.35-1.55 (2H, m), 1.60-1.70 (2H, m), 2.05-2.20 (1H, m), 2.70-2.90 (2H, m), 3.20-3.30 (2H, m), 4.14 (2H, d, J= 6.9 Hz), 4.60-4.70 (2H, m), 5.10-5.20

(2H, m), 6.45 (1H, d, J= 3.0 Hz), 6.65 (1H, d, J= 2.7 Hz), 7.15 (1H, d, J= 9.6 Hz), 7.40-7.50 (3H, m), 7.55 (1H, d, J= 8.7 Hz), 7.66 (1H, t, J= 7.5 Hz), 7.81 (2H, d, J= 8.1 Hz), 8.07 (1H, d, J= 3.0 Hz), 8.53 (1H, s), 8.55-8.70 (1H, br m), 8.90-9.00 (1H, br m), 9.90 (1H, br s).

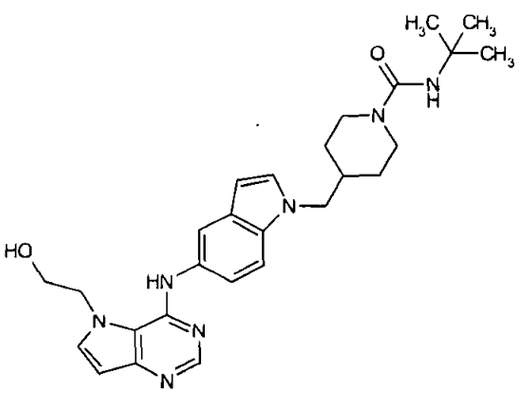
(v) Producción de 2-{4-[(1-{[1-(2,2-dimetilpropanoil)piperidin-4-il]metil}-1H-indol-5-il)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etanol

A una suspensión de diclorhidrato de benzoato de 2-(4-{[1-(piperidin-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (200 mg) en tetrahidrofurano (5.0 ml) se añadieron gota a gota trietilamina (0.23 ml) y cloruro de 2,2-dimetilpropanoílo (0.045 ml) bajo enfriamiento con hielo. La mezcla se agitó a 0°C durante 30 min y a temperatura ambiente durante 30 min. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (1.5 ml) y tetrahidrofurano (4.0 ml) y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N y se añadieron

bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se recristalizó en acetato de etilo/metanol/éter diisopropílico para dar el compuesto del título (104 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.10-1.30 (2H, m), 1.27 (9H, s), 1.55-1.70 (2H, m), 2.05-2.20 (1H, m), 2.60-2.75 (2H, m), 3.98 (2H, d, J= 7.2 Hz), 4.05-4.15 (2H, m), 4.30-4.50 (4H, m), 6.10 (1H, d, J= 3.0 Hz), 6.46 (1H, d, J= 3.0 Hz), 6.85 (1H, d, J= 3.0 Hz), 7.04 (1H, d, J= 3.0 Hz), 7.25-7.35 (1H, m), 7.35-7.45 (1H, m), 7.75 (1H, s), 8.18 (1H, s), 9.27 (1H, br s).

Ejemplo G-13



Producción de N-(ter-butil)-4-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piperidin-1-carboxamida

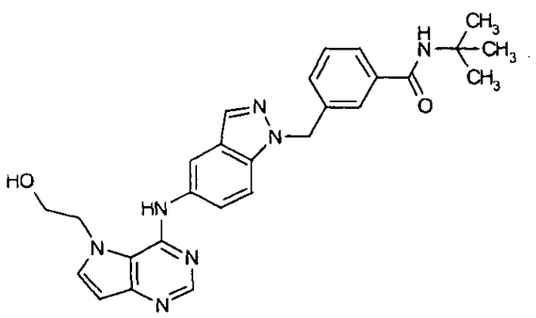
A una suspensión de diclorhidrato de benzoato de 2-

(4-{[1-(piperidin-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (200 mg) en tetrahidrofurano (5.0 ml) se añadieron gota a gota trietilamina (0.23 ml) y 2-isocianat-2-metilpropano (0.045 ml) bajo enfriamiento con hielo. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, se añadió agua a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5). Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (1.6 ml) y tetrahidrofurano (4.0 ml) y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N y se añadieron bicarbonato de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se recristalizó en acetato de etilo/metanol/éter diisopropílico para dar el compuesto del título (112 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.15-1.30 (2H, m), 1.34 (9H, s), 1.50-1.65 (2H, m), 1.95-2.10 (1H, m), 2.55-2.70 (2H, m), 3.85-3.95 (2H, m), 3.99 (2H, d, J= 7.2 Hz), 4.05-4.15 (2H,

m), 4.29 (1H, s), 4.30-4.40 (2H, m), 6.19 (1H, d, J= 3.0 Hz), 6.45-6.50 (1H, m), 6.90-6.95 (1H, m), 7.05-7.10 (1H, m), 7.25-7.45 (2H, m), 7.75 (1H, s), 8.23 (1H, s), 9.20 (1H, br s).

Ejemplo G-14



Producción de N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indazol-1-il)metil]benzamida

(i) Producción de 3-[(5-nitro-1H-indazol-1-il)metil]benzoato de metilo

A una solución de 5-nitroindazol (816 mg) y 3-(bromometil)benzoato de metilo (2.29 g) en N,N-dimetilformamida (10 ml) se añadió carbonato de potasio (2.07 g) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice

LLS.

(eluyente, acetato de etilo:hexano = 20:80→50:50) para dar el compuesto del título (805 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.90 (3H, s), 5.68 (2H, s), 7.30-7.45 (3H, m), 7.90-8.00 (2H, m), 8.23 (1H, dd, J= 1.8 Hz, 9.0 Hz), 8.20-8.25 (1H, m), 8.74 (1H, d, J= 1.8 Hz).

(ii) Producción de ácido 3-[(5-nitro-1H-indazol-1-il)metil]benzoico

Al usar 3-[(5-nitro-1H-indazol-1-il)metil]benzoato de metilo (0.79 g), solución acuosa 1 N de hidróxido de sodio (12 ml), metanol (15 ml) y tetrahidrofurano (15 ml) y de la misma manera que en el Ejemplo G-10(ii), se obtuvo el compuesto del título (732 mg) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 5.86 (2H, s), 7.40-7.55 (2H, m), 7.75-7.90 (2H, m), 8.00 (1H, d, J= 9.3 Hz), 8.25 (1H, dd, J= 2.1 Hz, 9.3 Hz), 8.48 (1H, s), 8.86 (1H, d, J= 2.1 Hz), 13.07 (1H, br s).

(iii) Producción de N-(ter-butil)-3-[(5-nitro-1H-indazol-1-il)metil]benzamida

A una suspensión de ácido 3-[(5-nitro-1H-indazol-1-il)metil]benzoico (595 mg) en tetrahidrofurano (10 ml) se añadieron N,N-dimetilformamida (una gota) y cloruro de tionilo (0.144 ml) y la mezcla se agitó a temperatura ambiente durante 3.5 h. A una solución de ter-butilamina

(0.73 g) y trietilamina (0.25 g) en N,N-dimetilformamida (4.0 ml) se añadió la mezcla de reacción antes mencionada bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 4.5 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 30:70→50:50) para dar el compuesto del título (0.56 g) en forma de una forma amorfa de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 5.66 (2H, s), 5.88 (1H, br s), 7.20-7.30 (1H, m), 7.35 (1H, t, J= 7.5 Hz), 7.40 (1H, d, J= 9.0 Hz), 7.56 (1H, d, J= 7.5 Hz), 7.73 (1H, s), 8.23 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.25 (1H, s), 8.74 (1H, d, J= 2.1 Hz).

(iv) Producción de 3-[(5-amino-1H-indazol-1-il)metil]-N-(ter-butil)benzamida

Al usar N-(ter-butil)-3-[(5-nitro-1H-indazol-1-il)metil]benzamida (0.55 g), platino-carbón activado al 5% (92 mg) y acetato de etilo (20 ml) y de la misma manera que en el Ejemplo G-8(ii), se obtuvo el compuesto del título (0.47 g) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 1.44 (9H, s), 3.61 (2H, br s), 5.55 (2H, s), 5.86 (1H, br s), 6.81 (1H, d, J= 9.0 Hz), 6.95-

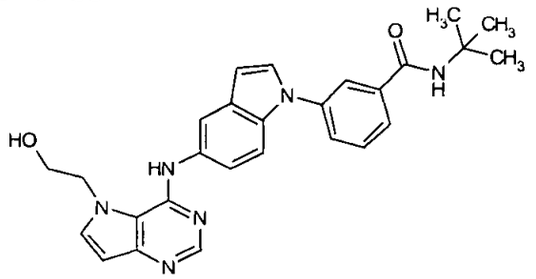
7.00 (1H, m), 7.14 (1H, d, J= 8.7 Hz), 7.20 (1H, d, J= 7.5 Hz), 7.30 (1H, t, J= 7.5 Hz), 7.56 (1H, d, J= 8.1 Hz), 7.63 (1H, s), 7.83 (1H, s).

(v) Producción de N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indazol-1-il)metil]benzamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (151 mg), 3-[(5-amino-1H-indazol-1-il)metil]-N-(ter-butil)benzamida (177 mg), alcohol isopropílico (8.0 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y tetrahidrofurano (4.0 ml) y de la misma manera que en el Ejemplo G-10(v), se obtuvo el compuesto del título (169 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.59 (2H, s), 5.92 (1H, br s), 6.18 (1H, d, J= 3.0 Hz), 6.93 (1H, d, J= 3.6 Hz), 7.25-7.35 (4H, m), 7.40-7.50 (1H, m), 7.56 (1H, d, J= 7.2 Hz), 7.65 (1H, s), 7.88 (1H, s), 7.98 (1H, s), 8.22 (1H, s), 9.33 (1H, br s).

Ejemplo G-15



Producción de N-(ter-butil)-3-(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)benzamida

(i) Producción de 3-(5-nitro-1H-indol-1-il)benzoato de etilo

Una solución mixta de 5-nitroindol (1.62 g), 3-yodobenzoato de etilo (3.04 g), N,N-dimetilenodiamina (0.97 g), carbonato de potasio (1.66 g), yoduro de cobre (I) (0.19 g) y tolueno (10 ml) se agitó a 120°C durante 24 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60) para dar el compuesto del título (0.95 g) en forma de un polvo amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.43 (3H, t, J= 7.0 Hz), 4.44 (2H, q, J= 7.0 Hz), 6.89 (1H, d, J= 3.3 Hz), 7.50-7.55 (2H, m), 7.60-7.75 (2H, m), 8.10-8.20 (3H, m), 8.66 (1H, d, J= 2.4 Hz).

(ii) Producción de ácido 3-(5-nitro-1H-indol-1-il)benzoico

Al usar 3-(5-nitro-1H-indol-1-il)benzoato de etilo (0.95 g), solución acuosa 1 N de hidróxido de sodio (15 ml), etanol (15 ml) y tetrahidrofurano (15 ml) y de la misma manera que en el Ejemplo G-10(ii), se obtuvo el compuesto del título (0.71 g) en forma de un polvo amarillo.

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^{1}H-RMN (DMSO-d_6) δ: 6.95-7.05 (1H, m), 7.60-7.75 (2H, m), 7.83 (1H, d, J= 7.2 Hz), 7.90-8.10 (4H, m), 8.68 (1H, s).

(iii) Producción de N-(ter-butil)-3-(5-nitro-1H-indol-1-il)benzamida

Al usar ácido 3-(5-nitro-1H-indol-1-il)benzoico (565 mg), cloruro de tionilo (0.144 ml), tetrahidrofurano (10 ml), ter-butilamina (0.73 g), trietilamina (0.25 g) y N,N-dimetilformamida (4.0 ml) y de la misma manera que en el Ejemplo G-14(iii), se obtuvo el compuesto del título (0.32 g) en forma de un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 5.99 (1H, br s), 6.89 (1H, d, J= 3.3 Hz), 7.50-7.65 (4H, m), 7.65-7.75 (1H, m), 7.93 (1H, s), 8.13 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.66 (1H, d, J= 2.4 Hz).

(iv) Producción de 3-(5-amino-1H-indol-1-il)-N-(ter-butil)benzamida

Al usar N-(ter-butil)-3-(5-nitro-1H-indol-1-il)benzamida (0.32 g), platino-carbón activado al 5% (0.05 g) y acetato de etilo (20 ml) y de la misma manera que en el Ejemplo G-8(ii), se obtuvo el compuesto del título (253 mg) en forma de una amorfo de color rosa pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.49 (9H, s), 3.58 (2H, br s), 5.94 (1H, br s), 6.51 (1H, d, J= 3.0 Hz), 6.68 (1H, dd, J= 2.1 Hz, 8.7 Hz), 6.96 (1H, d, J= 2.1 Hz), 7.20-7.30 (1H, m),

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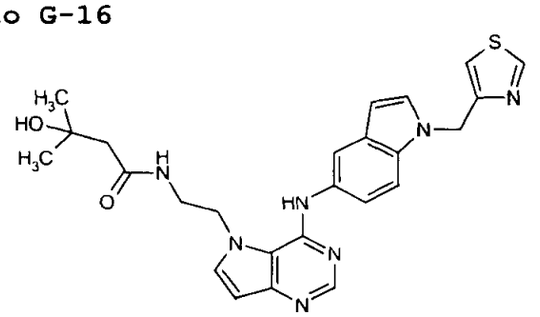
7.37 (1H, d, J= 8.7 Hz), 7.50-7.65 (3H, m), 7.84 (1H, s).

(v) Producción de N-(ter-butil)-3-(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)benzamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (164 mg), 3-(5-amino-1H-indol-1-il)-N-(ter-butil)benzamida (200 mg), alcohol isopropílico (8.0 ml), solución acuosa 1 N de hidróxido de sodio (2.5 ml) y tetrahidrofurano (5.0 ml) y de la misma manera que en el Ejemplo G-10(v), se obtuvo el compuesto del título (154 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.51 (9H, s), 4.10-4.15 (2H, m), 4.35-4.45 (2H, m), 6.03 (1H, br s), 6.17 (1H, d, J= 3.3 Hz), 6.67 (1H, d, J= 3.3 Hz), 6.91 (1H, d, J= 3.3 Hz), 7.30-7.40 (2H, m), 7.50-7.70 (4H, m), 7.80-7.85 (1H, m), 7.89 (1H, s), 8.23 (1H, s), 9.24 (1H, br s).

Ejemplo G-16



Producción de 3-hidroxi-3-metil-N-[2-(4-{[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]butanamida

(i) Producción de 5-nitro-1-(1,3-tiazol-4-ilmetil)-

1H-indol

Al usar 5-nitroindol (1.62 g), clorhidrato de 4-(clorometil)-1,3-tiazol (1.87 g), carbonato de potasio (4.15 g) y N,N-dimetilformamida (20 ml) y de la misma manera que en el Ejemplo G-8(i), se obtuvo el compuesto del título (1.98 g) en forma de un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ: 5.54 (2H, s), 6.74 (1H, d, J= 3.3 Hz), 6.95-7.00 (1H, m), 7.30-7.45 (2H, m), 8.10 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.60 (1H, d, J= 2.1 Hz), 8.81 (1H, d, J= 2.1 Hz).

(ii) Producción de 1-(1,3-tiazol-4-ilmetil)-1H-indol-5-amina

A una solución de 5-nitro-1-(1,3-tiazol-4-ilmetil)-1H-indol (519 mg) en acetato de etilo (20 ml)/metanol (4 ml) se añadió platino-carbón activado al 5% (87 mg) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 3 días bajo una atmósfera de hidrógeno. Bajo una atmósfera de nitrógeno, se añadió 10% de paladio/carbón (87 mg), y la mezcla se agitó a temperatura ambiente durante 9 h bajo una atmósfera de hidrógeno. El catalizador se filtró, y el filtrado se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 60:40→100:0) para dar el compuesto del título (424 mg) en forma de un aceite rojo.

^{1}H-RMN ($CDCl_3$) δ: 3.50 (2H, br s), 5.44 (2H, s), 6.37 (1H, d, J= 3.3 Hz), 6.64 (1H, dd, J= 2.1 Hz, 8.4 Hz), 6.75-6.80 (1H, m), 6.94 (1H, d, J= 2.1 Hz), 7.10-7.15 (2H, m), 8.77 (1H, d, J= 1.8 Hz).

(iii) Producción de [2-(4-{[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (446 mg), 1-(1,3-tiazol-4-ilmetil)-1H-indol-5-amina (414 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo G-8(iii), se obtuvo el compuesto del título (697 mg) en forma de un amorfo rojo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.43 (9H, s), 3.45-3.55 (2H, m), 4.35-4.45 (2H, m), 4.92 (1H, br s), 5.51 (2H, s), 6.51 (1H, d, J = 3.0 Hz), 6.56 (1H, d, J = 3.0 Hz), 6.81 (1H, s), 7.13 (1H, d, J = 3.3 Hz), 7.20 (1H, d, J = 3.0 Hz), 7.28 (1H, d, J = 8.7 Hz), 7.48 (1H, d, J = 7.2 Hz), 7.88 (1H, s), 8.18 (1H, br s), 8.44 (1H, s), 8.79 (1H, d, J = 2.1 Hz).

(iv) Producción de diclorhidrato de 5-(2-aminoetil)-N-[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar [2-(4-{[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (675 mg), ácido clorhídrico al 10% (p/p)/metanol

(10 ml) y metanol (8.0 ml) y de la misma manera que en el Ejemplo G-8(iv), se obtuvo el compuesto del título (610 mg) en forma de un polvo verde pálido.

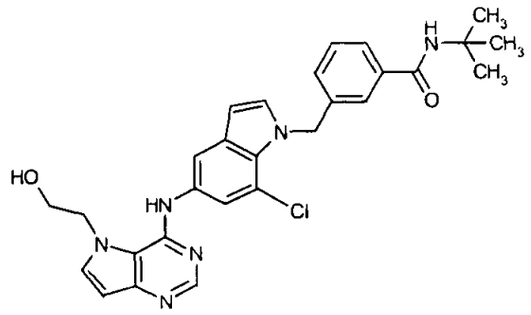
^{1}H-RMN (DMSO-d_6) δ: 3.25-3.35 (2H, m), 4.90-5.10 (2H, m), 5.57 (2H, s), 6.50 (1H, d, J= 3.3 Hz), 6.69 (1H, d, J= 3.0 Hz), 7.20 (1H, dd, J= 1.8 Hz, 8.4 Hz), 7.50-7.65 (4H, m), 8.01 (1H, d, J= 3.0 Hz), 8.25-8.45 (3H, m), 8.55 (1H, s), 9.05 (1H, d, J= 1.8 Hz), 9.97 (1H, s).

(v) Producción de 3-hidroxi-3-metil-N-[2-(4-{[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]butanamida

Al usar diclorhidrato de 5-(2-aminoetil)-N-[1-(1,3-tiazol-4-ilmetil)-1H-indol-5-il]-5H-pirrolo[3,2-d]pirimidin-4-amina (200 mg), ácido 3-hidroxi-3-metilbutanoico (71 mg), 1-hidroxibenzotriazol (88 mg), trietilamina (0.56 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (123 mg) y N,N-dimetilformamida (5.0 ml) y de la misma manera que en el Ejemplo G-8(v), se obtuvo el compuesto del título (118 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.27 (6H, s), 2.38 (2H, s), 3.55-3.70 (2H, m), 4.35-4.50 (2H, m), 5.50 (2H, s), 6.50-6.60 (2H, m), 6.65-6.75 (1H, m), 6.82 (1H, s), 7.13 (1H, d, J= 3.3 Hz), 7.15-7.45 (4H, m), 7.83 (1H, s), 8.25 (1H, s), 8.42 (1H, s), 8.78 (1H, d, J= 1.5 Hz).

Ejemplo G-17



Producción de N-(ter-butil)-3-[(7-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida

(i) Producción de 7-cloro-5-nitroindolina

Una solución mixta de 5-nitroindolina (3.28 g), N-clorosuccimida (2.94 g) y acetonitrilo (100 ml) se calentó a reflujo durante 19 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 30:70→50:50) para dar el compuesto del título (2.09 g) en forma de un polvo amarillo.

^{1}H-RMN ($CDCl_3$) δ: 3.23 (2H, t, J= 8.7 Hz), 3.84 (2H, t, J= 8.7 Hz), 4.68 (1H, br s), 7.85-7.90 (1H, m), 8.05-8.10 (1H, m).

(ii) Producción de 7-cloro-5-nitro-1H-indol

A una solución de 7-cloro-5-nitroindolina (2.09 g)

en acetato de etilo (100 ml) se añadió óxido de manganeso (9.13 g), y la mezcla se agitó a 60°C durante 15 h. Se filtró el óxido de manganeso, y el filtrado se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo) y se lavó con hexano para dar el compuesto del título (1.92 g) en forma de un polvo de color marrón pálido.

^{1}H-RMN ($CDCl_3$) δ: 6.79-6.82 (1H, m), 7.40-7.45 (1H, m), 8.15 (1H, d, J= 1.8 Hz), 8.53 (1H, d, J= 1.8 Hz), 8.65-8.85 (1H, m).

(iii) Producción de 3-[(7-cloro-5-nitro-1H-indol-1-il)metil]benzoato de metilo

Al usar 7-cloro-5-nitro-1H-indol (950 mg), 3-(bromometil)benzoato de metilo (1.22 g), carbonato de potasio (0.80 g) y N,N-dimetilformamida (15 ml) y de la misma manera que en el Ejemplo G-8(i), se obtuvo el compuesto del título (1.43 g) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 3.89 (3H, s), 5.84 (2H, s), 6.80 (1H, d, J= 3.3 Hz), 7.13 (1H, dd, J= 0.9 Hz, 7.8 Hz), 7.25-7.30 (1H, m), 7.38 (1H, t, J= 7.8 Hz), 7.79 (1H, s), 7.95 (1H, d, J= 8.1 Hz), 8.07 (1H, d, J= 2.1 Hz), 8.50 (1H, d, J= 2.1 Hz).

(iv) Producción de ácido 3-[(7-cloro-5-nitro-1H-indol-1-il)metil]benzoico

Al usar 3-[(7-cloro-5-nitro-1H-indol-1-

il)metil]benzoato de metilo (1.30 g), solución acuosa 1 N de hidróxido de sodio (20 ml), metanol (20 ml) y tetrahidrofurano (30 ml) y de la misma manera que en el Ejemplo G-10(ii), se obtuvo el compuesto del título (1.20 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 5.92 (2H, s), 6.99 (1H, d, J= 3.0 Hz), 7.26 (1H, d, J= 7.5 Hz), 7.44 (1H, t, J= 7.5 Hz), 7.56 (1H, s), 7.82 (1H, d, J= 7.5 Hz), 7.88 (1H, d, J= 3.0 Hz), 7.98 (1H, d, J= 1.8 Hz), 8.62 (1H, d, J= 1.8 Hz), 12.90-13.10 (1H, br).

(v) Producción de N-(ter-butil)-3-[(7-cloro-5-nitro-1H-indol-1-il)metil]benzamida

Al usar ácido 3-[(7-cloro-5-nitro-1H-indol-1-il)metil]benzoico (595 mg), cloruro de tionilo (0.13 ml), tetrahidrofurano (10 ml), ter-butilamina (0.66 g), trietilamina (0.23 g) y N,N-dimetilformamida (4.0 ml) y de la misma manera que en el Ejemplo G-14(iii), se obtuvo el compuesto del título (460 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 5.83 (2H, s), 5.86 (1H, br s), 6.79 (1H, t, J= 3.3 Hz), 7.02 (1H, d, J= 7.8 Hz), 7.20-7.30 (1H, m), 7.33 (1H, t, J= 7.8 Hz), 7.53 (1H, d, J= 7.8 Hz), 7.58 (1H, s), 8.07 (1H, d, J= 2.4 Hz), 8.49 (1H, d, J= 2.4 Hz).

(vi) Producción de 3-[(5-amino-7-cloro-1H-indol-1-

il)metil]-N-(ter-butil)benzamida

Se suspendió N-(ter-butil)-3-[(7-cloro-5-nitro-1H-indol-1-il)metil]benzamida (212 mg) en etanol (10 ml)/agua (1 ml), se añadió cloruro de calcio (30.5 mg), y la mezcla se disolvió a 90°C. Se añadió hierro reducido (184 mg) a la mezcla, y la mezcla se agitó a 90°C durante 4 h. La mezcla de reacción se dejó retornar hasta temperatura ambiente, y el material insoluble se filtró. El filtrado se concentró a presión reducida, se añadió acetato de etilo, y la mezcla se lavó con salmuera. La mezcla se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida para dar el compuesto del título (203 mg) como una forma amorfa amarilla.

^{1}H-RMN ($CDCl_3$) δ: 1.44 (9H, s), 3.45-3.60 (2H, br), 5.69 (2H, s), 5.84 (1H, br s), 6.37 (1H, d, J= 3.3 Hz), 6.61 (1H, d, J= 2.0 Hz), 6.82 (1H, d, J= 2.0 Hz), 6.95-7.05 (1H, m), 7.02 (1H, d, J= 3.3 Hz), 7.29 (1H, t, J= 7.8 Hz), 7.50-7.55 (1H, m), 7.53 (1H, d, J= 7.8 Hz).

(vii) Producción de N-(ter-butil)-3-[(7-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (151 mg), 3-[(5-amino-7-cloro-1H-indol-1-il)metil]-N-(ter-butil)benzamida (196 mg), alcohol isopropílico (8.0 ml), solución acuosa 1 N de hidróxido de

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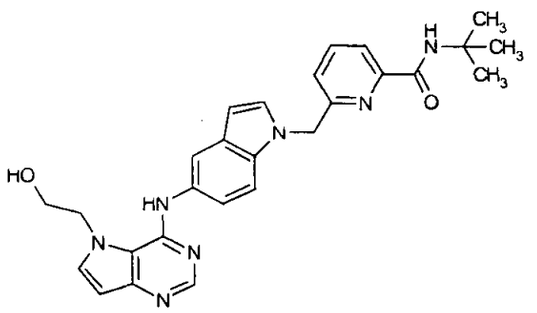
sodio (2.0 ml) y tetrahidrofurano (4.0 ml) y de la misma manera que en el Ejemplo G-10(v), se obtuvo el compuesto del título (157 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.45 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.75 (2H, s), 5.89 (1H, s), 6.17 (1H, d, J= 3.0 Hz), 6.53 (1H, d, J= 3.0 Hz), 6.92 (1H, d, J= 3.0 Hz), 7.05 (1H, d, J= 7.2 Hz), 7.09 (1H, d, J= 3.0 Hz), 7.25-7.35 (2H, m), 7.50-7.55 (2H, m), 7.65-7.70 (1H, m), 8.22 (1H, s), 9.22 (1H, s).

Ejemplo G-18



Producción de N-(ter-butil)-6-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piridin-2-carboxamida

(i) Producción de 6-(hidroximetil)piridin-2-carboxilato de etilo

A una solución de piridin-2.6-dicarboxilato de dietilo (4.46 g) en etanol (50 ml) se añadió borohidruro de sodio (454 mg) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió salmuera, y la mezcla se extrajo con

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acetato de etilo. La capa acuosa se saló, y la mezcla se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio anhidro, y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→100:0) para dar el compuesto del título (2.42 g) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.44 (3H, t, J= 7.2 Hz), 3.53 (1H, t, J= 5.4 Hz), 4.46 (2H, q, J= 7.2 Hz), 4.86 (2H, d, J= 5.4 Hz), 7.49 (1H, d, J= 7.8 Hz), 7.84 (1H, t, J= 7.8 Hz), 8.02 (1H, d, J= 7.8 Hz).

(ii) Producción de 6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxilato de etilo

A una solución de 6-(hidroximetil)piridin-2-carboxilato de etilo (1.00 g) y trietilamina (0.84 ml) en tetrahidrofurano (20 ml) se añadió gota a gota cloruro de metansulfonilo (0.43 ml) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1.5 h. Bajo enfriamiento con hielo, a la mezcla de reacción se añadieron bicarbonato de sodio acuoso y salmuera, y la mezcla se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. Al compuesto obtenido se añadieron 5-nitroindol (757 mg), carbonato de potasio (0.97 g) y N,N-dimetilformamida (10 ml) y la mezcla se agitó a temperatura

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ambiente durante 24 h a 60°C durante 20 h, y a 80°C durante 1 h. Bajo enfriamiento con hielo, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa acuosa se saló, y la mezcla se extrajo con acetato de etilo. Las capas orgánicas combinadas se secaron sobre sulfato de magnesio anhidro, se concentraron a presión reducida, y el residuo se recristalizó en acetato de etilo para dar el compuesto del título (1.31 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.47 (3H, t, J= 7.2 Hz), 4.51 (2H, q, J= 7.2 Hz), 5.62 (2H, s), 6.76 (1H, d, J= 7.8 Hz), 6.79 (1H, d, J= 3.0 Hz), 7.30 (1H, d, J= 9.0 Hz), 7.36 (1H, d, J= 3.0 Hz), 7.70 (1H, t, J= 7.8 Hz), 8.02 (1H, d, J= 7.8 Hz), 8.08 (1H, dd, J= 2.1 Hz, 9.0 Hz), 8.63 (1H, d, J= 2.1 Hz).

(iii) Producción de ácido 6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxílico

Al usar 6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxilato de etilo (1.20 g), solución acuosa 1 N de hidróxido de sodio (20 ml), etanol (20 ml) y tetrahidrofurano (40 ml) y de la misma manera que en el Ejemplo G-10(ii), se obtuvo el compuesto del título (1.01 g) en forma de un polvo de color amarillo pálido.

^{1}H-RMN (DMSO-d_6) δ: 5.68 (2H, s), 6.80-6.85 (1H, m), 6.89 (1H, d, J= 7.2 Hz), 7.67 (1H, d, J= 8.1 Hz), 7.70-7.90 (3H, m), 7.99 (1H, d, J= 9.0 Hz), 8.60 (1H, s).

(iv) Producción de N-(ter-butil)-6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxamida

Al usar ácido 6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxílico (0.95 g), cloruro de tionilo (0.23 ml), tetrahidrofurano (20 ml), ter-butilamina (1.17 g), trietilamina (0.40 g) y N,N-dimetilformamida (8.0 ml) y de la misma manera que en el Ejemplo G-14(iii), se obtuvo el compuesto del título (636 mg) en forma de un amorfo de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.41 (9H, s), 5.51 (2H, s), 6.78 (1H, d, J= 3.3 Hz), 6.98 (1H, d, J= 7.8 Hz), 7.30-7.40 (2H, m), 7.66 (1H, br s), 7.76 (1H, t, J= 7.8 Hz), 8.05-8.15 (2H, m), 8.63 (1H, d, J= 2.1 Hz).

(v) Producción de 6-[(5-amino-1H-indol-1-il)metil]-N-(ter-butil)piridin-2-carboxamida

A una solución de N-(ter-butil)-6-[(5-nitro-1H-indol-1-il)metil]piridin-2-carboxamida (211 mg) en acetato de etilo (8.0 ml) se añadió platino-carbón activado al 5% (35 mg) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 h. Bajo una atmósfera de nitrógeno, se añadió 10% de paladio/carbón (69 mg) a la mezcla de reacción, y la mezcla se siguió agitando bajo una atmósfera de hidrógeno a temperatura ambiente durante 2.5 h. El catalizador se filtró, y el filtrado se concentró a presión reducida. El residuo se

separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 50:50→80:20) para dar el compuesto del título (160 mg) en forma de una amorfo de color rosa pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.48 (9H, s), 3.52 (2H, br s), 5.39 (2H, s), 6.41 (1H, d, J= 3.0 Hz), 6.64 (1H, dd, J= 2.4 Hz, 8.7 Hz), 6.82 (1H, d, J= 8.1 Hz), 6.97 (1H, d, J= 2.4 Hz), 7.00-7.10 (1H, m), 7.11 (1H, d, J= 3.0 Hz), 7.68 (1H, t, J= 7.5 Hz), 7.89 (1H, br s), 8.03 (1H, d, J= 7.5 Hz).

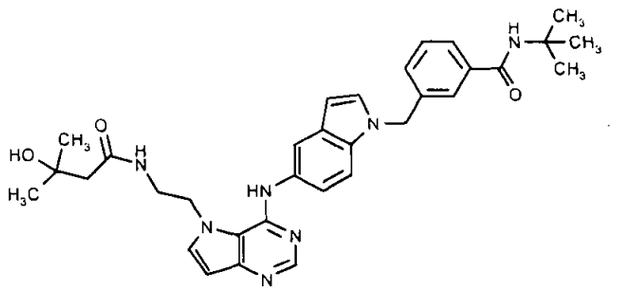
(vi) Producción de N-(ter-butil)-6-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piridin-2-carboxamida

Al usar benzoato de 2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etilo (136 mg), 6-[(5-amino-1H-indol-1-il)metil]-N-(ter-butil)piridin-2-carboxamida (160 mg), alcohol isopropílico (8.0 ml), solución acuosa 1 N de hidróxido de sodio (2.0 ml) y tetrahidrofurano (4.0 ml) y de la misma manera que en el Ejemplo G-10(v), se obtuvo el compuesto del título (137 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.50 (9H, s), 4.05-4.15 (2H, m), 4.30-4.40 (2H, m), 5.46 (2H, s), 6.16 (1H, d, J= 3.0 Hz), 6.57 (1H, d, J= 3.0 Hz), 6.85-6.90 (2H, m), 7.19 (1H, d, J= 3.0 Hz), 7.20-7.30 (1H, m), 7.35 (1H, d, J= 9.0 Hz), 7.69 (1H, t, J= 7.5 Hz), 7.81 (1H, s), 7.92 (1H, s), 8.04 (1H, d,

J= 7.5 Hz), 8.20 (1H, s), 9.15 (1H, br s).

Ejemplo G-19



Producción de N-(ter-butil)-3-({5-[(5-{2-[(3-hidroxi-3-metilbutanoil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-1H-indol-1-il}metil)benzamida

(i) Producción de (2-{4-[(1-{3-[(ter-butilamino)carbonil]bencil}-1H-indol-5-il)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo

Al usar [2-(4-cloro-5H-pirrolo[3,2-d]pirimidin-5-il)etil]carbamato de ter-butilo (297 mg), 3-[(5-amino-1H-indol-1-il)metil]-N-(ter-butil)benzamida (354 mg) y alcohol isopropílico (8.0 ml) y de la misma manera que en el Ejemplo G-8(iii), se obtuvo el compuesto del título (478 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.43 (9H, s), 1.46 (9H, s), 3.45-3.55 (2H, m), 4.35-4.50 (2H, m), 4.93 (1H, br s), 5.33 (2H, s), 5.88 (1H, s), 6.49 (1H, d, J = 3.0 Hz), 6.55 (1H, d, J = 2.4 Hz), 7.10-7.30 (4H, m), 7.30 (1H, t, J = 7.8 Hz), 7.40-7.50 (1H, m), 7.54 (1H, d, J = 8.1 Hz), 7.64 (1H, s), 7.86 (1H, s), 8.16 (1H, br s), 8.43 (1H, s).

(ii) Producción de diclorhidrato de 3-[(5-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]-N-(ter-butil)benzamida

Al usar (2-{4-[(1-{3-[(ter-butilamino)carbonil]bencil}-1H-indol-5-il)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)carbamato de ter-butilo (449 mg) y ácido clorhídrico al 10% (p/p)/metanol (5.0 ml) y de la misma manera que en el Ejemplo G-8(iv), se obtuvo el compuesto del título (400 mg) en forma de un polvo de color anaranjado pálido.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 3.25-3.35 (2H, m), 4.90-5.05 (2H, m), 5.51 (2H, s), 6.56 (1H, d, J= 3.0 Hz), 6.69 (1H, d, J= 3.3 Hz), 7.20 (1H, d, J= 9.0 Hz), 7.29 (1H, d, J= 7.2 Hz), 7.37 (1H, t, J= 7.8 Hz), 7.51 (1H, d, J= 9.0 Hz), 7.62 (1H, d, J= 3.0 Hz), 7.65-7.70 (2H, m), 7.68 (1H, s), 7.99 (1H, d, J= 3.0 Hz), 8.15-8.30 (3H, m), 8.58 (1H, s), 9.89 (1H, s).

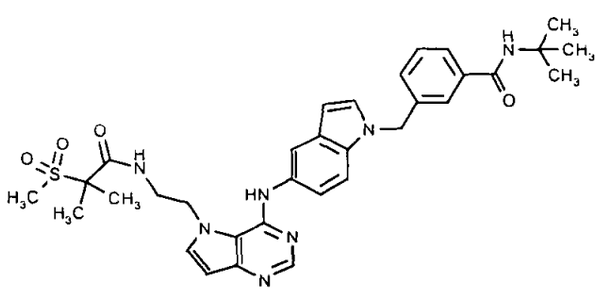
(iii) Producción de N-(ter-butil)-3-({5-[(5-{2-[(3-hidroxi-3-metilbutanoil)amino]etil}-5H-pirrolo[3,2-d]pirimidin-4-il)amino]-1H-indol-1-il}metil)benzamida

Al usar diclorhidrato de 3-[(5-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]-N-(ter-butil)benzamida (150 mg), ácido 3-hidroxi-3-metilbutanoico (48 mg), 1-hidroxibenzotriazol (59 mg), trietilamina (0.38 ml), clorhidrato de 1-etil-3-(3-

dimetilaminopropil)carbodiimida (83 mg) y N,N-dimetilformamida (4.0 ml) y de la misma manera que en el Ejemplo G-8(v), se obtuvo el compuesto del título (80 mg) en forma de cristales de color amarillo pálido.

^{1}H-RMN ($CDCl_3$) δ: 1.25 (6H, s), 1.46 (9H, s), 2.44 (2H, s), 3.55-3.65 (2H, m), 4.45-4.55 (2H, m), 5.30 (2H, s), 5.99 (1H, s), 6.51 (1H, d, J= 3.0 Hz), 6.57 (1H, d, J= 3.3 Hz), 7.10-7.35 (6H, m), 7.55 (1H, d, J= 8.1 Hz), 7.64 (1H, s), 7.75-7.80 (1H, m), 8.05-8.10 (1H, m), 8.28 (1H, s), 9.55-9.65 (1H, br).

Ejemplo G-20



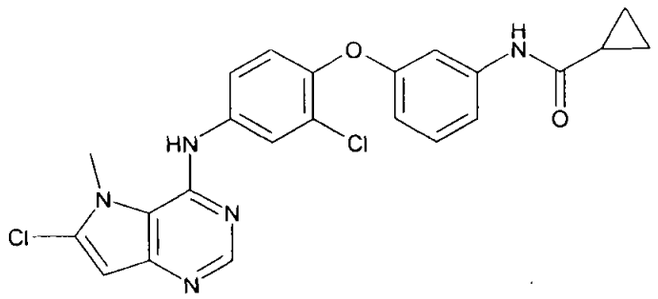
Producción de N-(ter-butil)-3-[(5-{[5-(2-{[2-metil-2-(metilsulfonil)propanoil]amino}etil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida

Al usar diclorhidrato de 3-[(5-{[5-(2-aminoetil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]-N-(ter-butil)benzamida (150 mg), ácido 2-metil-2-(metilsulfonil)propanoico (68 mg), 1-hidroxibenzotriazol (59 mg), trietilamina (0.38 ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (83 mg) y N,N-

dimetilformamida (4.0 ml) y de la misma manera que en el Ejemplo G-8(v), se obtuvo el compuesto del título (91 mg) en forma de cristales incoloros.

^{1}H-RMN ($CDCl_3$) δ: 1.46 (6H, s), 1.60 (9H, s), 2.84 (3H, s), 3.60-3.75 (2H, m), 4.30-4.45 (2H, m), 5.34 (2H, s), 5.90 (1H, s), 6.51 (1H, d, J= 2.7 Hz), 6.55-6.60 (1H, m), 7.00-7.10 (1H, m), 7.10-7.40 (6H, m), 7.53 (1H, d, J= 7.5 Hz), 7.65 (1H, s), 7.81 (1H, s), 7.89 (1H, s), 8.44 (1H, s).

Ejemplo H-1



Producción de N-(3-{2-cloro-4-[(6-cloro-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida

(i) Producción de 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina

A una solución de diisopropilamina (540 mg) en tetrahidrofurano (12 ml) se añadió n-butil-litio (2.7 ml) a 0°C. Tras agitar durante 30 min, la mezcla se enfrió hasta -78°C, y se añadió 4-cloro-5-metil-5H-pirrolo[3,2-d]pirimidina (500 mg). La mezcla de reacción se agitó durante 1 h, se agregó cloruro de p-toluensulfonilo (690 mg), y la mezcla se

dejó llegar hasta -40°C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→30:70). Después de concentrar a presión reducida, los cristales resultantes se recogieron por filtración, y se lavó con éter diisopropílico para dar el compuesto del título (191 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 4.13 (3H, s), 6.72 (1H, s), 8.68 (1H, s).

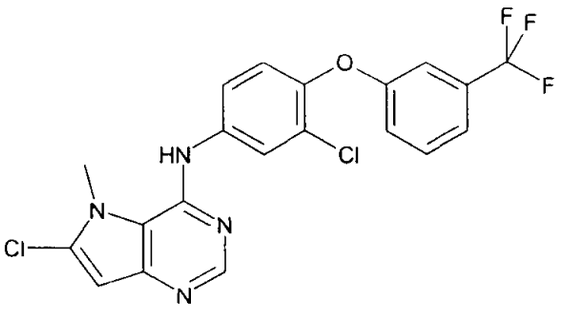
(ii) Producción de N-(3-{2-cloro-4-[(6-cloro-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida

Una mezcla de 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (98 mg), N-[3-(4-amino-2-clorofenoxi)fenil]ciclopropancarboxamida (167 mg) y alcohol isopropílico (7.0 ml) se agitó a 80°C durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadieron agua e carbonato ácido de sodio acuoso saturado y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida y el

residuo obtenido se sometió a cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→0:100). Las fracciones objeto se concentraron a presión reducida. El residuo se cristalizó en acetato de etilo-hexano para dar el compuesto del título (146 mg) en forma de un polvo blanco.

^{1}H-RMN ($CDCl_3$) δ: 0.78-0.84 (2H, m), 0.99-1.05 (2H, m), 1.47-1.54 (1H, m), 4.07 (3H, s), 6.60 (1H, s), 6.75-6.77 (2H, m), 7.01-7.04 (2H, m), 7.20-7.26 (3H, m), 7.62 (1H, s), 8.10 (1H, br s), 8.47 (1H, s).

Ejemplo H-2



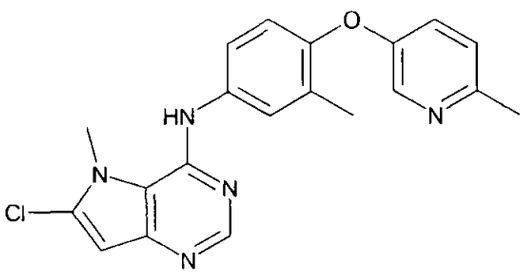
Producción de 6-cloro-N-{3-cloro-4-[3-(trifluorometil)fenoxi]fenil}-5-metil-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (70 mg), 3-cloro-4-[3-(trifluorometil)fenoxi]anilina (109 mg) y alcohol isopropílico (7.0 ml) y de la misma manera que en el Ejemplo H-1(ii), se obtuvo el compuesto del título (61 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 4.07 (3H, s), 6.73 (1H, s),

7.21-7.33 (3H, m), 7.46-7.67 (3H, m), 7.93 (1H, br s), 8.40 (1H, br s), 8.97 (1H, br s).

Ejemplo H-3

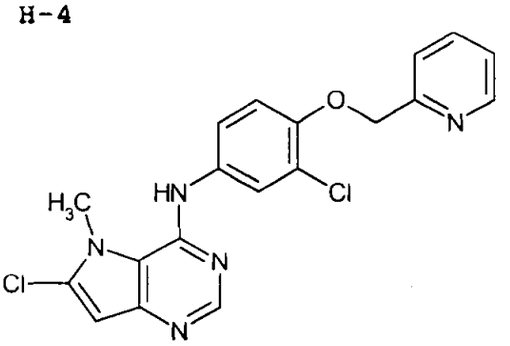


Producción de 6-cloro-5-metil-N-{3-metil-4-[(6-metilpiridin-3-il)oxi]fenil}-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (150 mg), 3-metil-4-[(6-metilpiridin-3-il)oxi]anilina (160 mg) y alcohol isopropílico (8.0 ml) y de la misma manera que en el Ejemplo H-1(ii), se obtuvo el compuesto del título (116 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 2.17 (3H, s), 2.43 (3H, s), 4.04 (3H, s), 6.65 (1H, s), 6.94 (1H, d, J= 8.3 Hz), 7.16-7.25 (2H, m), 7.44-7.51 (2H, m), 7.16 (1H, d, J= 2.7 Hz), 8.28 (1H, s), 8.57 (1H, s).

Ejemplo H-4



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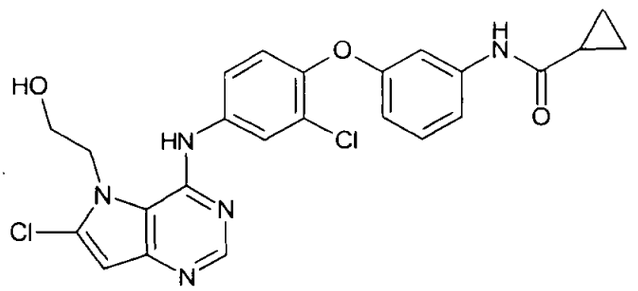
Producción de 6-cloro-N-[3-cloro-4-(piridin-2-ilmetoxi)fenil]-5-metil-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (150 mg), 3-cloro-4-(piridin-2-ilmetoxi)anilina (210 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo H-1(ii), se obtuvo el compuesto del título (170 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 4.03 (3H, s), 5.27 (2H, s), 6.64 (1H, s), 7.20-7.91 (6H, m), 8.25 (1H, s), 8.54 (1H, br s), 8.58-8.62 (1H, m).

Ejemplo H-5



Producción de N-[3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida

(i) Producción de 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina

4-cloro-5H-pirrolo[3,2-d]pirimidina (2.00 g), (2-bromoetoxi)(ter-butil)dimetilsilano (4.00 g) y carbonato de cesio (6.40 g) se disolvieron en N,N-dimetilformamida (10 ml)

y la mezcla se agitó a temperatura ambiente durante 4 h. Bajo enfriamiento con hielo, se añadió salmuera a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:hexano = 20:80→40:60) para dar el compuesto del título (3.02 g) en forma de un sólido marrón.

^{1}H-RMN (DMSO-d_6) δ: -0.24 (6H, s), 0.69 (9H, s), 3.90-3.93 (2H, m), 4.61-4.64 (2H, m), 6.76 (1H, s), 8.00 (1H, s), 8.61 (1H, s).

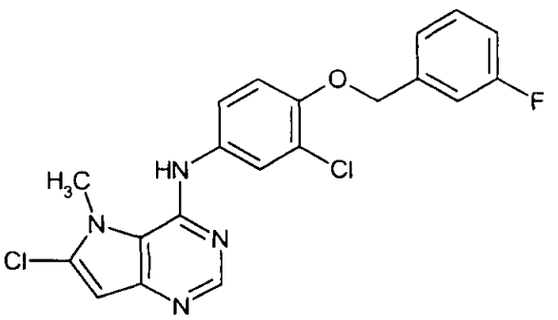
(ii) Producción de N-[3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]ciclopropancarboxamida

Al usar diisopropilamina (2.20 g), n-butil-litio 1.6 M (14 ml), tetrahidrofurano (50 ml), 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina (500 mg), cloruro de p-toluensulfonilo (6.10 g), N-[3-(4-amino-2-clorofenoxi)fenil]ciclopropancarboxamida (190 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo H-1(i) y (ii), se obtuvo un compuesto. El compuesto obtenido se disolvió en metanol (10 ml), se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml), y la mezcla se agitó a 80°C durante 18 h. Bajo

enfriamiento con hielo, a la mezcla de reacción se añadió bicarbonato de sodio acuoso, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (73 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 0.75-0.77 (4H, m), 1.69-1.75 (1H, m), 3.88-3.91 (2H, m), 4.53-4.55 (2H, m), 6.62-6.68 (1H, m), 6.72 (1H, s), 7.20-7.96 (6H, m), 8.37 (1H, s), 9.87-9.97 (1H, m), 10.24 (1H, s).

Ejemplo H-6

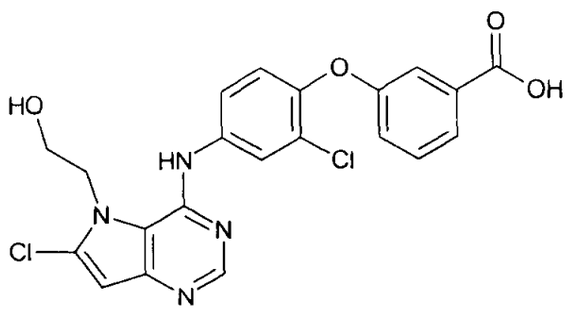


Producción de 6-cloro-N-{3-cloro-4-[(3-fluorobencil)oxi]fenil}-5-metil-5H-pirrolo[3,2-d]pirimidin-4-amina

Al usar 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (150 mg), 3-cloro-4-[(3-fluorobencil)oxi]anilina (167 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo H-1(ii), se obtuvo el compuesto del título (61 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 4.03 (3H, s), 5.24 (2H, s), 6.64 (1H, s), 7.14-7.50 (6H, m), 7.71-7.72 (1H, m), 8.26 (1H, s), 8.52 (1H, s).

Ejemplo H-7



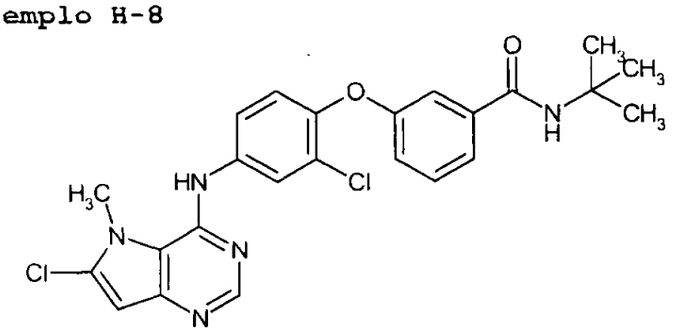
Producción de ácido 3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzoico

Al usar diisopropilamina (2.00 g), n-butil-litio 1.6 M (13 ml), tetrahidrofurano (50 ml), 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina (450 mg), cloruro de p-toluensulfonilo (6.01 g), 3-(4-amino-2-clorofenoxi)benzoato de metilo (190 mg), alcohol isopropílico (10 ml), metanol (10 ml) y solución de cloruro de hidrógeno 4 N/acetato de etilo (3.0 ml) y de la misma manera que en el Ejemplo H-1(i), (ii) y Ejemplo H-5(ii), se obtuvo un compuesto. Al compuesto obtenido se añadieron solución acuosa 1 N de hidróxido de sodio (0.8 ml) y tetrahidrofurano (4.0 ml) y la mezcla se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N y a ello se añadieron bicarbonato

de sodio acuoso y salmuera. La mezcla se extrajo con acetato de etilo, y la capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (127 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 3.83-3.91 (2H, m), 4.54-4.57 (2H, m), 6.49 (1H, br s), 6.73 (1H, s), 7.24-7.68 (6H, m), 7.98 (1H, s), 9.97 (1H, s), 13.14 (1H, br s).

Ejemplo H-8



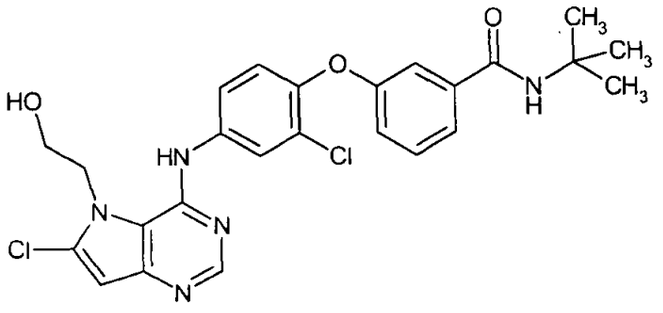
Producción de N-(ter-butil)-3-{2-cloro-4-[(6-cloro-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}benzamida

Al usar 4.6-dicloro-5-metil-5H-pirrolo[3,2-d]pirimidina (110 mg), 3-(4-amino-2-clorofenoxi)-N-(ter-butil)benzamida (197 mg) y alcohol isopropílico (10 ml) y de la misma manera que en el Ejemplo H-1(ii), se obtuvo el compuesto del título (86 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 4.06 (3H, s), 6.69

(1H, s), 7.06-7.64 (6H, m), 7.81 (1H, s), 7.89 (1H, br s), 8.34 (1H, s), 8.81 (1H, s).

Ejemplo H-9



Producción de N-(ter-butil)-3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

Al usar diisopropilamina (2.80 g), n-butil-litio 1.6 M (16 ml), tetrahidrofurano (50 ml), 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina (800 mg), cloruro de p-toluensulfonilo (7.10 g), 3-(4-amino-2-clorofenoxi)-N-(ter-butil)benzamida (811 mg) y alcohol isopropílico (16 ml) y de la misma manera que en el Ejemplo H-1(i) y (ii), se obtuvo un compuesto. El compuesto obtenido se disolvió en metanol (10 ml), se añadió solución de cloruro de hidrógeno 4 N/acetato de etilo (10 ml), y la mezcla se agitó a 80°C durante 18 h. Bajo enfriamiento con hielo, a la mezcla de reacción se añadió bicarbonato de sodio acuoso, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por

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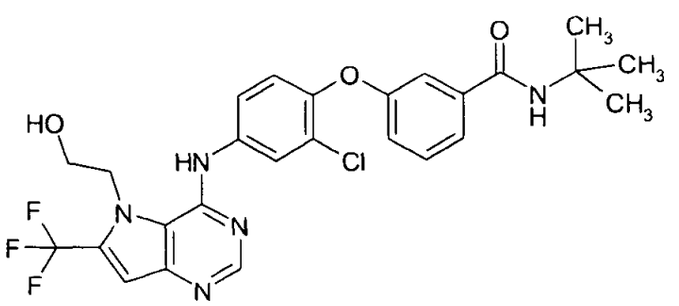
cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (576 mg) en forma de cristales.

^{1}H-RMN (DMSO-d_6) δ: 1.36 (9H, s), 3.88-3.91 (2H, m), 4.53-4.57 (2H, m), 6.72 (1H, s), 7.06-7.61 (6H, m), 7.81 (1H, s), 7.96-7.97 (1H, m), 8.37 (1H, s), 9.52-10.53 (1H, m).

Ejemplo H-10



Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-6-(trifluorometil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

(i) Producción de 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-6-(trifluorometil)-5H-pirrolo[3,2-d]pirimidina

A una solución de diisopropilamina (300 mg) en tetrahidrofurano (20 ml) se añadió n-butil-litio 1.6 M (2.0 ml) a 0°C. Tras agitar durante 30 min, la mezcla se enfrió hasta -78°C, y se agregó 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-5H-pirrolo[3,2-d]pirimidina (520 mg). La mezcla de reacción se agitó durante 1 h, trifluorometansulfonato de S-

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(trifluorometil)dibenzotiofenio (2.00 g), y la mezcla se dejó llegar hasta -40°C durante 1 h. Se añadió agua a la mezcla de reacción y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con agua y salmuera saturada, y se secó sobre sulfato de magnesio. Después de concentrar a presión reducida, el residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, hexano:acetato de etilo = 80:20→30:70). Después de concentrar a presión reducida, los cristales resultantes se recogieron por filtración y se lavó con éter diisopropílico para dar el compuesto del título (29 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 0.02 (6H, s), 0.74 (9H, s), 3.92-3.96 (2H, m), 4.74-4.78 (2H, m), 7.17 (1H, s), 8.79 (1H, s).

(ii) Producción de N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-6-(trifluorometil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida

Al usar 5-(2-{[ter-butil(dimetil)silil]oxi}etil)-4-cloro-6-(trifluorometil)-5H-pirrolo[3,2-d]pirimidina (25 mg), 3-(4-amino-2-clorofenoxi)-N-(ter-butil)benzamida (26 mg) y alcohol isopropílico (1.5 ml) y de la misma manera que en el Ejemplo H-2(ii), se obtuvo un compuesto. El compuesto obtenido se disolvió en metanol (2.0 ml), se agregó solución de cloruro de hidrógeno 4 N/acetato de etilo (1.0 ml), y la mezcla se agitó a 80°C durante 18 h. Se agregó bicarbonato de

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sodio acuoso a la mezcla de reacción bajo enfriamiento con hielo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. El residuo se separó y se purificó por cromatografía en columna de gel de sílice (eluyente, acetato de etilo:metanol = 100:0→95:5) para dar el compuesto del título (9.2 mg) en forma de cristales.

^{1}H-RMN ($CDCl_3$) δ: 1.36 (9H, s), 3.92-3.96 (2H, m), 4.61-4.64 (2H, m), 7.06-7.45 (5H, m), 7.55-7.61 (2H, m), 7.82 (1H, s), 7.97 (1H, s), 8.44 (1H, s), 9.50-10.55 (1H, m).

Ejemplo de formulación 1 (cantidad por comprimido)

(1) Compuesto obtenido en el Ejemplo A-1	10.0 mg
(2) Lactosa	60.0 mg
(3) Almidón de maíz	35.0 mg
(4) Gelatina	3.0 mg
(5) Estearato de magnesio	2.0 mg

Una mezcla de 10.0 mg del compuesto obtenido en el Ejemplo A-1, 60.0 mg de lactosa y 35.0 mg de almidón de maíz se granula a través de un tamiz de 1 mm de malla usando 0.03 ml de una solución acuosa al 10% en peso de gelatina (3.0 mg de gelatina), tras lo cual los gránulos se secan a 40°C y se vuelven a filtrar. Los gránulos obtenidos se mezclan con 2.0 mg de estearato de magnesio y se comprimen. Los núcleos de los comprimidos obtenidos se recubren con una cobertura de

azúcar que comprende una suspensión de sacarosa, dióxido de titanio, talco y goma arábiga y se lustra con cera de abejas para obtener comprimidos recubiertos con azúcar.

Ejemplo de formulación 2 (dosis por comprimido)

(1) Compuesto obtenido en el Ejemplo A-1	10.0 mg
(2) Lactosa	70.0 mg
(3) Almidón de maíz	50.0 mg
(4) Almidón soluble	7.0 mg
(5) Estearato de magnesio	3.0 mg

Se granulan 10.0 mg del compuesto obtenido en Ejemplo A-1 y 3.0 mg de estearato de magnesio usando 0.07 ml de una solución acuosa de almidón soluble (7.0 mg de almidón soluble), tras lo cual estos gránulos se secan y mezclan con 70.0 mg de lactosa y 50.0 mg de almidón de maíz. Esta mezcla se comprime para obtener comprimidos.

Ejemplo experimental 1A Clonación de gen HER2 humano y preparación de baculovirus recombinantes

Se clonó el gen HER2 humano por RT-PCR al usar ARN total preparado de células MCF7 como una plantilla. El cebador usado para RT-PCR se preparó a partir de una información de secuencias de nucleótidos (acceso a Genbank N° M11730) del gen HER2 por adición de una secuencia de nucleótidos que codifican el péptido DYKDDDD y una secuencia de reconocimiento de enzimas de restricción en una secuencia

de nucleótidos (2176-3918 de acceso de Genbank N° M11730) que codifica la región del dominio intracelular de HER2, de modo que la proteína contenga una etiqueta de péptido DYKDDDD N-terminal. La secuencia de nucleótidos del cebador se indica a continuación.

HER2-U:5'-AATTAAGTCGACATGGACTACAAAGACGATGACGACAAGCGACGGCAGCAGAAGATCCGGAAGTAC-3' (SEC ID NO:1)

y

HER2-L:

5'-AATTAAGCATGCTCACACTGGCACGTCCAGACCCAGGTACTC-3' (SEC ID NO:2)

La reacción RT se realizó con un sistema de Síntesis SuperScript First-Strand para RT-PCR (Invitrogen) y la reacción de PCR se realizó con un kit KOD-plus (TOYOBO). El producto de PCR obtenido se sometió a electroforesis en gel de agarosa (1%), el fragmento de ADN amplificado por PCR se recuperó el gel y luego se digirió con enzimas de restricción Sal I y Sph I. El ADN tratado con las enzimas de restricción se sometió a electroforesis en gel de agarosa (1%), y el fragmento de ADN obtenido se recuperó y ligó a pFASTBAC1 de plásmido (Invitrogen) digerido con las enzimas de restricción Sal I y Sph I para dar el plásmido de expresión pFB-HER2. La secuencia de nucleótidos del fragmento de inserción fue confirmada y se halló que era idéntica a la

secuencia de nucleótidos (2176-3918 de acceso de Genbank M11730) de dominio intracelular HER2. Además, mediante el sistema de expresión de baculovirus BAC-TO-BAC (Invitrogen), se preparó baculovirus recombinante BAC-HER2.

Ejemplo experimental 1B Preparación de proteína de dominio intracelular HER2

Células SF-21 se sembraron como 1×10^6 células/ml en medio Sf-900II SFM (1 L, Invitrogen) que contiene 10% de suero fetal bovino (trazas), 50 mg/l de gentamicina (Invitrogen) y 0.1% de Pluronic F-68 (Invitrogen), y se realizó cultivo con agitación en un frasco Erlenmeyer de 2 L de volumen a 27°C, 100 rpm. Después de cultivar durante 24 se agregó baculovirus recombinante BAC-HER2 (13.4 ml), y la mezcla luego se cultivó durante 3 días. El medio de cultivo se centrifugó a 2,000 rpm durante 5 min para dar células infectadas por virus. Las células infectadas se lavaron con una solución fisiológica con regulador de pH fosfato (Invitrogen), centrifugada en las mismas condiciones, y las células se conservaron a -80°C. Las células crioconservadas se descongelaron sobre hielo, se suspendieron en regulador de pH A (50 mM regulador de pH Tris (30 ml, pH 7.4) que contiene 20% de glicerol, 0.15 M de NaCl) complementado con inhibidor de proteasa completo (Boehringer), y se descompusieron tres veces con un homogeneizador Polytron (Kinematica) a 20,000 rpm durante 30 s. El medio de ruptura se clarificó por

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centrifugación a 40,000 rpm durante 30 min., y se filtró con un filtro de 0.45 μm. El filtrado se pasó a través de una columna empaquetada con gel de afinidad Anti-FLAG M2 (4 ml, Sigma) con una velocidad de flujo de aproximadamente 0.5 ml/min. La columna se lavó con regulador de pH A, y se eluyó con regulador de pH A que contiene 100 μg/ml de péptido FLAG. Eluido se concentró con Vivaspin 20 (Vivascience) con un corte de peso molecular de 30K. El concentrado se purificó por filtración en gel con Hi Load Superdex 200pg 16/60 (Amersham Bioscience) equilibrado con regulador de pH A. Se juntaron las fracciones que contienen un dominio intracelular HER2, se añadió glicerol a la concentración final de 50% y se crioconservó a -80°C.

Ejemplo experimental 1C Determinación de actividad inhibitoria de HER2 cinasa

Un compuesto de prueba disuelto en dimetilsulfóxido (DMSO) se diluyó con un regulador de pH para reacción de cinasa (50 mM Tris-HCl (pH 7.5), 5 mM de $MgCl_2$, 5 mM de $MnCl_2$, 2 mM de ditiotreitol, 0.01% de Tween-20). A esta solución de compuesto (10 μL) se añadió un regulador de pH para reacción de cinasa (20 μL) que contiene 5 μg/ml de dominio intracelular HER2 obtenido en el Ejemplo experimental 1B y 12.5 μg/ml de sustrato de polipéptido poli-Glu:Tir (4:1) (Sigma). A la mezcla obtenida se añadió 20 μL de solución de ATP (1.25 μM de ATP, 0.05 de μCi [γ-^{32}P]ATP), la mezcla se

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dejó reaccionar a 25°C durante 10 min. y la reacción se reguló en pH con 50 µl de 20% de solución de TCA. La solución de reacción se dejó reposar a 4°C durante 20 min., y la fracción ácida insoluble se transfirió a un filtro GF/C (PerkinElmer) con un recolector de células (PerkinElmer) y se lavó con 250 mM de solución de ácido fosfórico. Después de lavar, se secó la placa a 45°C durante 60 min., y se agregó 35 µL de MicroScinti 0 (PerkinElmer). Se midió la radiactividad con TopCount (PerkinElmer). Se calculó la tasa inhibitoria de HER2 cinasa (%) del compuesto de prueba, según la siguiente fórmula:

Tasa inhibitoria (%)=(1-(recuento de compuesto de prueba - blanco)÷(control - blanco))×100

El recuento de la solución que reaccionó sin adición del compuesto se usó como "control", y el recuento de la solución sin el compuesto y el dominio intracelular HER2 se usó como "blanco". Los resultados de la tasa inhibitoria de los compuestos se muestran en la Tabla 1.

De lo anterior, se demostró que los compuestos de la presente invención inhibieron fuertemente la actividad de HER2 cinasa.

Tabla 1

Ejemplo N° (compuesto N°)	Tasa de inhibición (%) a 1.0 μM
A-1	98
A-15	99
B-1	99
C-26	98
C-45	97
C-89	100
E-22	99
G-5	93
G-14	100

Ejemplo experimental 2 Acción inhibitoria sobre proliferación de células de cáncer de mama BT-474 *in vitro*

Una suspensión de células de cáncer de mama humano BT-474 (100 μl (6,000 células)) se sembró para su fijación en una microplaca de 96 cavidades y se cultivaron en una incubadora (37°C, 5% de dióxido de carbono). Al día siguiente, se añadieron 100 μl de una solución de cada compuesto de prueba diluida previamente en forma seriada por mitades, para dar la dosis indicada, y las células se cultivaron durante 5 días. Después de extraer el medio de cultivo que contiene el compuesto de prueba, las células se lavaron y se fijaron con 50% de ácido tricloroacético,

después de lo cual a 0.4% (p/v) de solución SRB (disuelto en 1% de ácido acético) se añadió una tintura a la proteína celular (Skehan y otros, Journal of the National Cancer Institute, Vol. 82, pp. 1107-1112, 1990). Después de lavar con una solución al 1% de ácido acético, se añadieron 100 µl de solución Tris (10 mM) para extraër el pigmento y se midió la absorbancia con una longitud de onda de 550 nm para cuantificar la cantidad de células como contenido de proteínas. Si se toma como 100% el contenido de proteína del grupo control, que no recibió solución de compuesto de prueba, se determinó la relación de contenido de proteína residual para cada grupo de tratamiento, y se calculó la concentración de compuesto requerida para obtener 50% de supresión del contenido células residuales respecto del control (valor IC_{50}). Los resultados se muestran en la Tabla 2.

Tabla 2

Ejemplo N° (compuesto N.°)	IC_{50}(nM)
A-1	<100
C-45	<100
C-97	<100
C-116	<100
G-5	<100

1256.

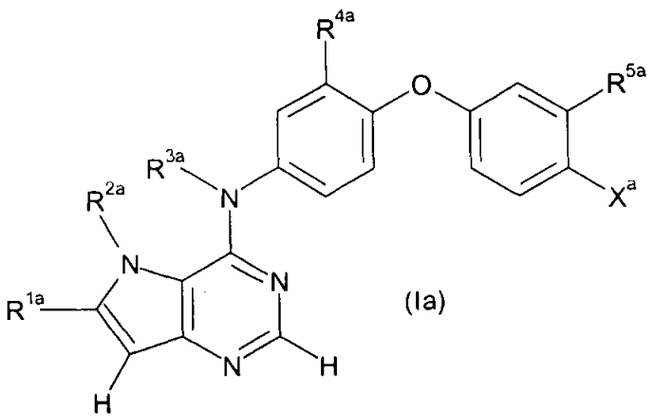
Aplicabilidad industrial

De acuerdo con la presente invención, se proveen compuestos pirrolo[3,2-d]pirimidina y pirazolo[4,3-d]pirimidina, uno de sus métodos de producción y su uso. Estos compuestos fusionados de pirimidina tienen superior acción inhibitoria de tirosina cinasa, son muy seguros, y son suficientemente satisfactorios como productos farmacéuticos.

Esta solicitud se basa en la solicitud de patentes N° 2005-349858 y 2006-060648 presentada en Japón, cuyo contenido se incorpora en su totalidad en la presente como referencia.

REIVINDICACIONES

1.- Un compuesto representado por la fórmula:



caracterizado porque

R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6a}-CO-(CH_2)_n-SO_2-$

en donde n es un número entero de 1 a 4, R^{6a} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3a} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

R^{4a} es un átomo de halógeno o un grupo alquilo de C_{1-6},

R^{5a} es un átomo de halógeno o un grupo alquilo de C_{1-6}, y

X^a es un átomo de hidrógeno o un átomo de halógeno,

o una de sus sales,

con la condición de que se excluya N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado porque X^a es un átomo de hidrógeno.

3.- El compuesto de conformidad con la reivindicación 2, caracterizado porque

R^{1a} es un átomo de hidrógeno,

R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-$alquilo de C_{1-4}

en donde R^{6aa} es un átomo de hidrógeno o un grupo metilo, R^{7a} y R^{8a} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo metilo,

R^{3a} es un átomo de hidrógeno,

R^{4a} es un átomo de cloro o un grupo metilo, y

R^{5a} es un átomo de flúor, un átomo de cloro o un grupo metilo.

4.- El compuesto de conformidad con la reivindicación 3, caracterizado porque R^{7a} y R^{8a} son grupos metilo.

5.- Un compuesto, caracterizado porque se selecciona de los siguientes:

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-

1159.

pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida,

N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N,2-dimetil-2-(metilsulfonil)propanamida,

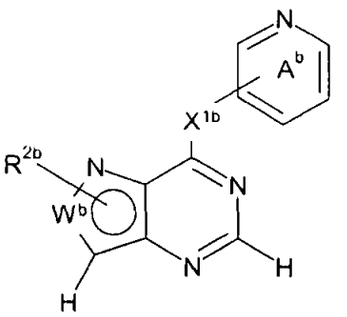
N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida, y

N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,

o una de sus sales, o uno de sus hidratos.

6.- Un compuesto representado por la fórmula:



(Ib)

caracterizado porque

W^b es $C(R^{1b})$ o N,

el anillo A^b es un anillo piridina opcionalmente sustituido,

X^{1b} es $-NR^{3b}-Y^{1b}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ o $-CHR^{3b}-$

en donde R^{3b} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3b} está opcionalmente unido al átomo de carbono en el anillo piridina para el anillo A^b para formar una estructura de anillo opcionalmente sustituida, e Y^{1b} es un enlace, o un alquileno de C_{1-4} u $-O-$(alquileno de C_{1-4})$-$, cada uno de los cuales está opcionalmente sustituido, y

R^{1b} es un átomo de hidrógeno, un átomo de halógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2b} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1b} y R^{2b}, o R^{2b} y R^{3b} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

o una de sus sales.

7.- El compuesto de conformidad con la reivindicación 6, caracterizado porque es representado por la fórmula:

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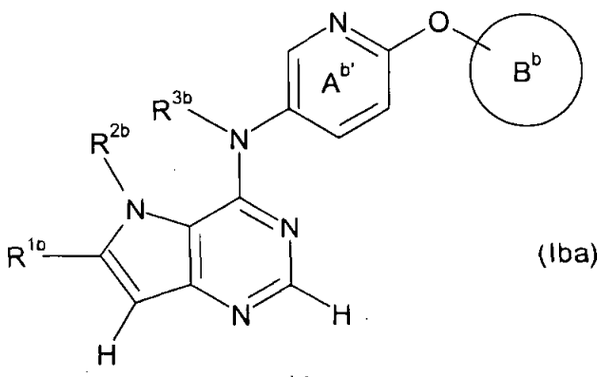


(Iba)

en donde el anillo $A^{b'}$ es un anillo piridina también opcionalmente sustituido, el anillo B^b es un grupo arilo de C_{6-14} opcionalmente sustituido, y los otros símbolos son como se definen en la reivindicación 6.

8.- El compuesto de conformidad con la reivindicación 7, caracterizado porque

R^{1b} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2b} es un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(i) $-NR^{6ba}-CO-(CH_2)_{n1}-SO_2-$alquilo de C_{1-4}

en donde R^{6ba} es un átomo de hidrógeno o un grupo metilo, n1 es un número entero de 1 a 4, y $-(CH_2)_{n1}-$ está opcionalmente sustituido con alquilo de C_{1-4},

(ii) $-NR^{6bb}-CO-(CH_2)_{n2}-OH$

en donde R^{6bb} es un átomo de hidrógeno o un grupo metilo, n2 es un número entero de 1 a 4, y $-(CH_2)_{n2}-$ está opcionalmente sustituido con alquilo de C_{1-4},

1162.

(iii) $-O-(CH_2)_{n3}-OH$

en donde n3 es un número entero de 1 a 4, y $-(CH_2)_{n3}-$ está opcionalmente sustituido con alquilo de C_{1-4}, y

(iv) hidroxi,

R^{3b} es un átomo de hidrógeno,

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno y metilo, y

el anillo B^b es un grupo fenilo opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoilo y halógeno.

9.- El compuesto de conformidad con la reivindicación 7, caracterizado porque

el anillo $A^{b'}$ es un anillo piridina opcionalmente sustituido con halógeno, y

el anillo B^b es un grupo fenilo opcionalmente sustituido en la posición 3 por sustituyentes seleccionados del grupo que consiste en alquilo de C_{1-6} opcionalmente halogenado, alcoxi de C_{1-6} opcionalmente halogenado, alquil de C_{1-6}-carbamoílo y halógeno.

10.- Un compuesto, caracterizado porque se selecciona de los siguientes:

2-{2-[4-({5-cloro-6-[3-

(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol,

N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

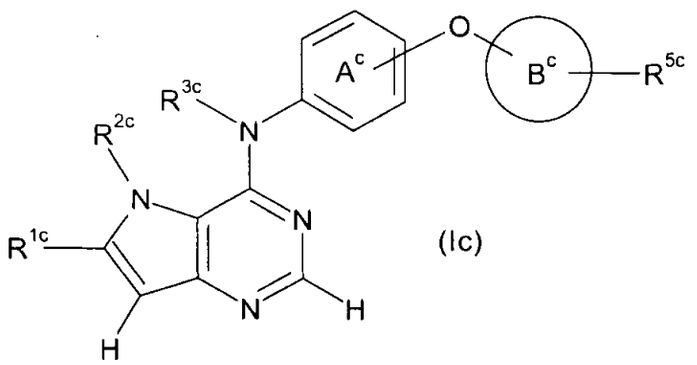
N-{2-[4-({5-cloro-6-[3-(trifluorometil)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

N-{2-[4-({5-cloro-6-[3-(trifluorometoxi)fenoxi]piridin-3-il}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida, y

N-(ter-butil)-3-[(3-cloro-5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}piridin-2-il)oxi]benzamida,

o una de sus sales.

11.- Un compuesto representado por la fórmula:



(Ic)

caracterizado porque

R^{1c} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de

carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2c} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1c} y R^{2c}, o R^{2c} y R^{3c} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3c} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3c} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^c es un anillo benceno opcionalmente sustituido,

R^{5c} es

(i) un grupo amino opcionalmente sustituido,

(ii) un grupo carbamoilo opcionalmente sustituido,

(iii) un grupo ureido opcionalmente sustituido,

(iv) un grupo sulfamoilo opcionalmente sustituido,

(v) un grupo heterocíclico opcionalmente sustituido,

(vi) un grupo alcoxi de C_{2-6} opcionalmente sustituido,

(vii) un grupo aminometilo opcionalmente sustituido,

(viii) un grupo carbamoilmetilo opcionalmente sustituido,

(ix) un grupo alquilsulfonilo opcionalmente

LL65

sustituido, o

(x) un grupo ciano, y

el anillo B^c es un grupo arilo de C_{6-14} o un grupo cicloalquilo de C_{5-8}, cada uno de los cuales está también opcionalmente sustituido además de R^{5c},

o una de sus sales,

con la condición de que se excluyan

clorhidrato de N-(ter-butil)-4-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida,

4-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2,2-dimetilpropil)benzamida,

3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzonitrilo,

3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzonitrilo,

clorhidrato de 3-[2-cloro-4-(6.7-dihidro-9H-pirimido[4',5':4.5]pirrolo[2.1-c][1.4]oxazin-4-ilamino)fenoxi]benzonitrilo, y

(2E)-N-[(2E)-3-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5-metil-5H-pirrolo[3,2-d]pirimidin-6-il)prop-2-en-1-il]-4-(dimetilamino)but-2-enamida.

12.- El compuesto de conformidad con la reivindicación 11, caracterizado porque R^{1c} es un átomo de

hidrógeno.

13.- Un compuesto, caracterizado porque se selecciona de los siguientes:

2-{2-[4-({3-cloro-4-[3-(1,3-tiazol-5-il)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etoxi}etanol,

N-(ter-butil)-3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]benzamida,

3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]-N-(2-hidroxi-1,1-dimetiletil)benzamida,

N-(ter-butil)-3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

N-(3-{2-cloro-4-[(6-ciano-5-metil-5H-pirrolo[3,2-d]pirimidin-4-il)amino]fenoxi}fenil)ciclopropancarboxamida,

N-(ter-butil)-5-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)-2-fluorobenzamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-3-hidroxi-3-metilbutanamida,

N-{2-[4-({3-cloro-4-[3-(dimetilamino)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-(ter-butil)-2-[3-(2-cloro-4-{[5-(2-hidroxietil)-

5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]acetamida,

N-{2-[4-({3-cloro-4-[3-(ciclopropilmetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

N-{2-[4-({3-cloro-4-[3-(2,2-dimetilpropoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

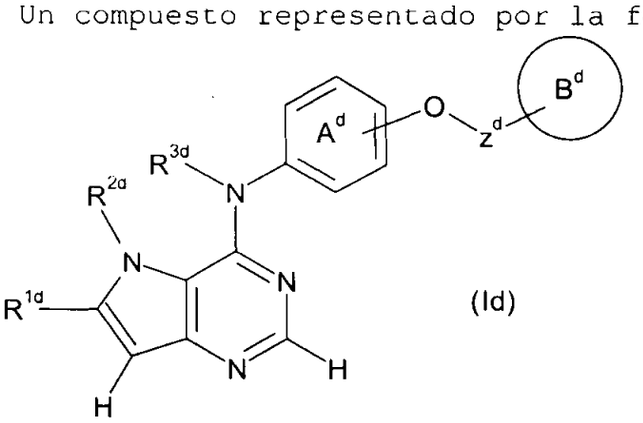
2-(metilsulfonil)-N-{2-[4-({3-metil-4-[3-(2,2,2-trifluoroetoxi)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etil}acetamida,

2-[4-({3-cloro-4-[3-(isopropilsulfonil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol, y

N-[2-(4-{[3-cloro-4-(3-cianofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

o una de sus sales.

14.- Un compuesto representado por la fórmula:



(Id)

caracterizado porque

1168.

R^{1d} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2d} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1d} y R^{2d}, o R^{2d} y R^{3d} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3d} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3d} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^d es un anillo benceno opcionalmente sustituido,

Z^d es un alquileno de C_{1-3} opcionalmente sustituido,

el anillo B^d es un grupo heterocíclico opcionalmente sustituido,

o una de sus sales,

con la condición de que se excluyan

5-[(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)metil]-2-furoato de etilo,

ácido 5-[(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)metil]-2-furancarboxílico,

2-[2-(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-

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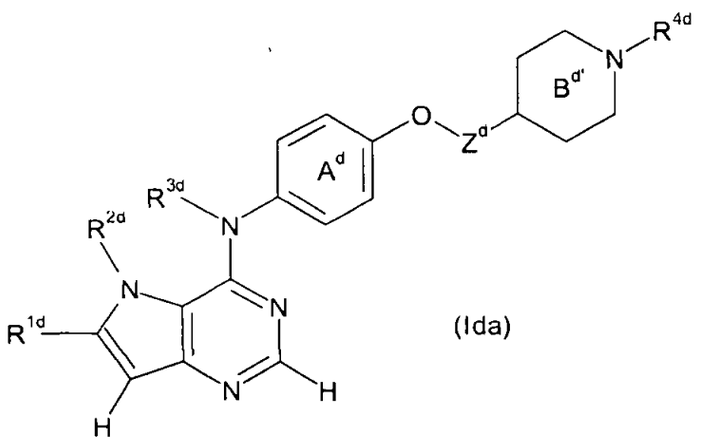
il)etoxi]etanol, y

N-[2-(4-{[3-cloro-4-(piridin-2-ilmetoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida.

15.- El compuesto de conformidad con la reivindicación 14, representado por la fórmula:



(Ida)

caracterizado porque R^{4d} es un grupo acilo o un grupo ureido opcionalmente sustituido, el anillo $B^{d'}$ es un grupo piperidilo también opcionalmente sustituido además de R^{4d}, y los otros símbolos son de conformidad con la reivindicación 14.

16.- Un compuesto, caracterizado porque se selecciona de los siguientes:

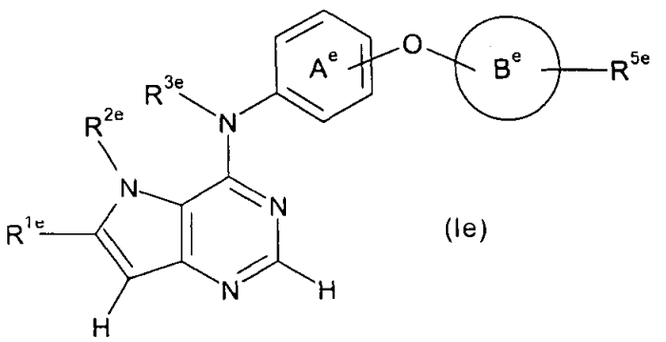
4-{[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]metil}piperidin-1-carboxilato de ter-butilo, y

4-[(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)metil]piperidin-1-carboxilato

de ter-butilo,

o una de sus sales.

17.- Un compuesto representado por la fórmula:



(Ie)

caracterizado porque

R^{1e} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de oxígeno,

R^{2e} es un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1e} y R^{2e}, o R^{2e} y R^{3e} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

R^{3e} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3e} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

el anillo A^e es un anillo benceno opcionalmente sustituido,

R^{5e} es

(i) un grupo alquilo lineal sustituido con grupo

heterocíclico opcionalmente sustituido,

(ii) un grupo alquilo lineal sustituido con imino opcionalmente sustituido,

(iii) un grupo alquilo lineal sustituido con arilo opcionalmente sustituido, que está también opcionalmente halogenado o hidroxilado,

(iv) un grupo alquilo ramificado opcionalmente sustituido,

(v) un grupo alquenilo opcionalmente sustituido,

(vi) un grupo hidroxi sustituido con arilo opcionalmente sustituido,

(vii) un grupo hidroxi sustituido con alquilo de C_{1-6},

(viii) un grupo hidroxi sustituido con alquilo de C_{2-6} halogenado,

(ix) un grupo alquilo de C_{2-6} halogenado,

(x) un grupo cicloalquilo opcionalmente sustituido, o

(xi) un grupo alquil de C_{1-6}-carbonilo opcionalmente sustituido con arilo opcionalmente sustituido, y

el anillo B^e es un grupo arilo de C_{6-14} también opcionalmente sustituido además de R^{5e},

o una de sus sales,

con la condición de que se excluyan

diclorhidrato de 2-(2-{4-[(3-cloro-4-{4-[3-(1H-

imidazol-1-il)propil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol,

2-(2-{4-[(3-cloro-4-{4-[4-(1H-1.2,3-triazol-1-il)butil]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etoxi)etanol, y

1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}etanona.

18.- Un compuesto, caracterizado porque es seleccionado de los siguientes:

2-[4-({3-cloro-4-[3-(1,1-difluoroetil)fenoxi]fenil}amino)-5H-pirrolo[3,2-d]pirimidin-5-il]etanol,

O-etiloxima de (1Z)-1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ona,

1-{3-[2-cloro-4-({5-[2-(2-hidroxietoxi)etil]-5H-pirrolo[3,2-d]pirimidin-4-il}amino)fenoxi]fenil}-2,2-dimetilpropan-1-ol,

1-[3-(2-cloro-4-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)fenil]-3,3-dimetilbutan-1-ona,

N-(2-{4-[(3-metil-4-{3-[(1E)-3-metilbut-1-en-1-il]fenoxi}fenil)amino]-5H-pirrolo[3,2-d]pirimidin-5-il}etil)-2-(metilsulfonil)acetamida, y

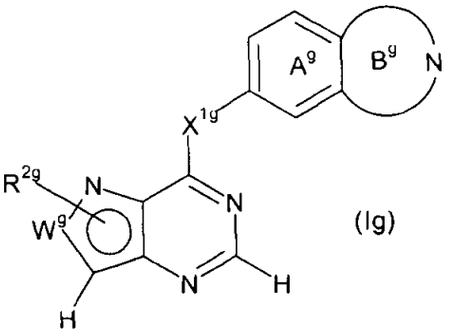
N-{2-[4-({3-cloro-4-[3-(1-cianociclopropil)fenoxi]fenil}amino)-5H-pirrolo[3,2-

1173

d]pirimidin-5-il]etil}-2-(metilsulfonil)acetamida,

o una de sus sales.

19.- Un compuesto representado por la fórmula:



caracterizado porque

W^g es $C(R^{1g})$ o N,

el anillo A^g es un anillo benceno opcionalmente sustituido,

el anillo B^g es un heterociclo con contenido de nitrógeno opcionalmente sustituido,

X^{1g} es $-NR^{3g}-Y^{1g}-$, -O-, -S-, -SO-, $-SO_2-$ o $-CHR^{3g}-$

en donde R^{3g} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3g} está opcionalmente unido al átomo de carbono en el anillo Benceno para el anillo A^g para formar una estructura de anillo opcionalmente sustituida, e Y^{1g} es un enlace, o un alquileno de C_{1-4} u -O-(alquileno de C_{1-4})-, cada uno de los cuales está opcionalmente sustituido, y

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono, un átomo de nitrógeno o un átomo de

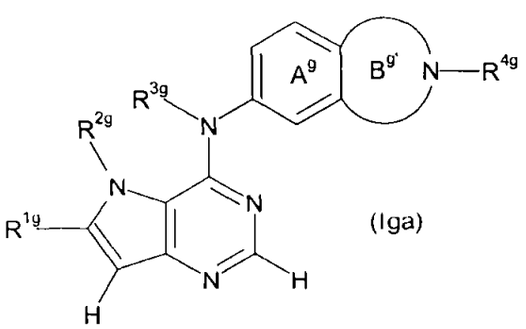
oxígeno,

R^{2g} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1g} y R^{2g}, o R^{2g} y R^{3g} se unen opcionalmente para formar una estructura de anillo opcionalmente sustituida,

o una de sus sales.

20.- El compuesto de conformidad con la reivindicación 19, que es un compuesto representado por la fórmula:



(Iga)

caracterizado porque R^{4g} es un grupo hidrocarburo opcionalmente sustituido, el anillo $B^{g'}$ es un heterociclo con contenido de nitrógeno de 5 ó 6 miembros también opcionalmente sustituido además de R^{4g}, y los otros símbolos son de conformidad con la reivindicación 19.

21.- El compuesto de conformidad con la reivindicación 20, caracterizado porque

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6} opcionalmente sustituido,

R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},

R^{4g} es (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, (iii) un grupo alquilo de C_{1-8}, o (iv) un grupo arilo de C_{6-14} opcionalmente sustituido.

22.- El compuesto de conformidad con la reivindicación 20, caracterizado porque

R^{1g} es un átomo de hidrógeno, un átomo de halógeno, un grupo ciano o un grupo alquilo de C_{1-6} opcionalmente halogenado,

R^{2g} es

(i) un átomo de hidrógeno,

(ii) un grupo alquilo de C_{1-6}, o

(iii) un grupo alquilo de C_{1-6} sustituido con sustituyentes seleccionados del grupo que consiste en

(a) $-O-(CH_2)_n-OH$,

(b) $-NR^{5g}-CO-(CH_2)_n-OH$,

(c) $-NR^{5g}-CO-(CH_2)_n-SO_2$-alquilo de C_{1-4} opcionalmente halogenado,

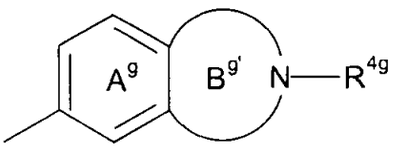
(d) hidroxi, y

(e) amino

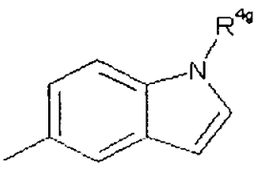
en donde n es un número entero de 1 a 4, R^{5g} es un

átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},

R^{3g} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},



es la fórmula



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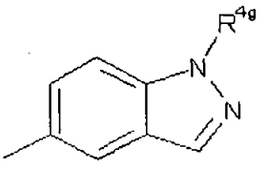


y

R^{4g} es (i) un grupo aril C_{6-14}-alquilo de C_{1-8} opcionalmente sustituido con sustituyentes seleccionados del grupo que consiste en halógeno, alquil de C_{1-6}-carbamoilo y haloalcoxi de C_{1-6}, (ii) un grupo heterociclil-alquilo de C_{1-8} opcionalmente sustituido, o (iii) un grupo arilo de C_{6-14} opcionalmente sustituido.

23.- Un compuesto, caracterizado porque se selecciona de los siguientes:

N-[2-(4-{[1-(3-fluorobencil)-1H-indazol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,

N-[2-(4-{[1-(3-fluorobencil)-1H-indol-5-il]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-3-hidroxi-3-metilbutanamida,

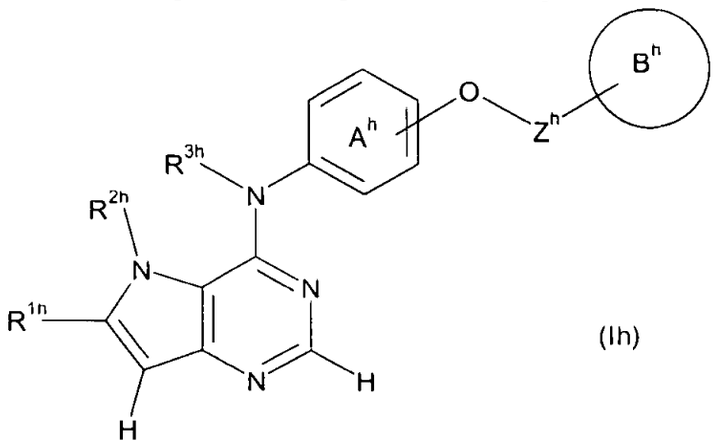
N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]benzamida,

N-(ter-butil)-3-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indazol-1-il)metil]benzamida, y

N-(ter-butil)-6-[(5-{[5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}-1H-indol-1-il)metil]piridin-2-carboxamida,

o una de sus sales.

24.- Un compuesto representado por la fórmula:



(Ih)

caracterizado porque

R^{1h} es un átomo de halógeno o un grupo alquilo de C_{1-6} halogenado,

R^{2h} es un átomo de hidrógeno, o un grupo opcionalmente sustituido unido a través de un átomo de carbono o un átomo de azufre, o

R^{1h} y R^{2h}, o R^{2h} y R^{3h} están unidos para formar una

estructura de anillo opcionalmente sustituida,

R^{3h} es un átomo de hidrógeno o un grupo hidrocarburo alifático opcionalmente sustituido, o R^{3n} está opcionalmente unido al átomo de carbono en el anillo Benceno adyacente para formar una estructura de anillo opcionalmente sustituida,

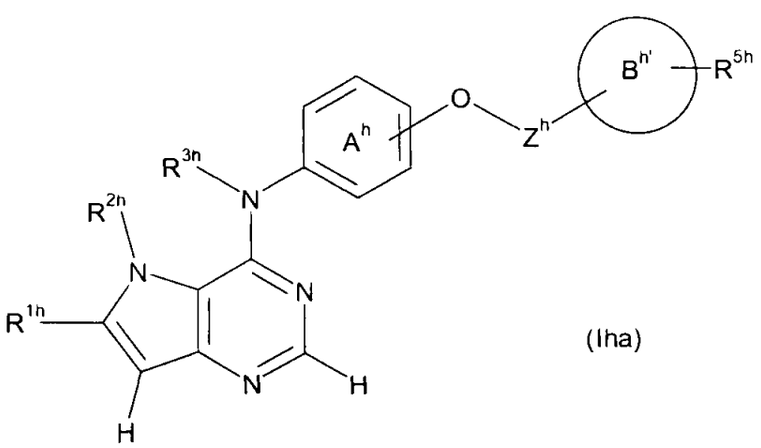
Z^h es un enlace o un alquileno de C_{1-3} opcionalmente sustituido,

el anillo A^h es un anillo benceno opcionalmente sustituido, y

el anillo B^h es (i) un grupo arilo de C_{6-14} opcionalmente sustituido, (ii) un grupo heterocíclico opcionalmente sustituido, o (iii) un grupo cicloalquilo de C_{5-8} opcionalmente sustituido,

o una de sus sales.

25.- El compuesto de conformidad con la reivindicación 24, representado por la fórmula:



(Iha)

caracterizado porque

R^{5h} es

1180.

il]amino}fenoxi)fenil]ciclopropancarboxamida, y

N-(ter-butil)-3-(2-cloro-4-{[6-cloro-5-(2-hidroxietil)-5H-pirrolo[3,2-d]pirimidin-4-il]amino}fenoxi)benzamida,

o una de sus sales.

27.- Un profármaco, caracterizado porque es del compuesto de conformidad con cualquiera de las reivindicaciones 1 a 26.

28.- Un agente farmacéutico, caracterizado porque comprende cualquiera de las reivindicaciones 1 a 26 o una de sus sales o uno de sus profármacos.

29.- El agente farmacéutico de conformidad con la reivindicación 28, caracterizado porque es un inhibidor de la tirosina cinasa.

30.- El agente farmacéutico de conformidad con la reivindicación 28, caracterizado porque es un agente para la prevención o el tratamiento del cáncer.

31.- El agente farmacéutico de conformidad con la reivindicación 30, caracterizado porque el cáncer es cáncer de mama, cáncer de ovario, cáncer colorectal, cáncer gástrico, cáncer de esófago, cáncer de próstata, cáncer de pulmón, cáncer de páncreas o cáncer de riñón.

32.- Un método para la prevención o el tratamiento de cáncer en un mamífero, caracterizado porque comprende la administración de una cantidad efectiva del compuesto de

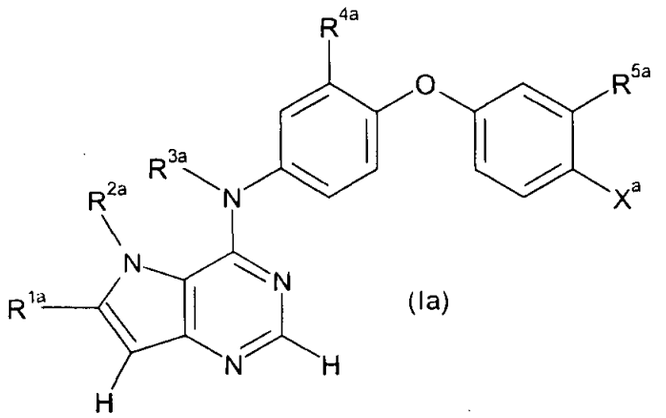
conformidad con cualquiera de las reivindicaciones 1 a 26 o una de sus sales o uno de sus profármacos al mamífero.

33.- Uso del compuesto de conformidad con cualquiera de las reivindicaciones 1 a 26 o una de sus sales o uno de sus profármacos, para la producción de un agente para la prevención o el tratamiento del cáncer.

1182

RESUMEN DE LA INVENCION

La presente invención provee un compuesto representado por la fórmula:



(Ia)

en donde R^{1a} es un átomo de hidrógeno, R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6a}-CO-(CH_2)_n-SO_2-$ en donde n es un número entero de 1 a 4, R^{6a} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4}, R^{3a} es un átomo de hidrógeno o un grupo alquilo de C_{1-6}, R^{4a} es un átomo de halógeno o un grupo alquilo de C_{1-6}, R^{5a} es un átomo de halógeno o un grupo alquilo de C_{1-6}, y X^a es un átomo de hidrógeno o un átomo de halógeno, o una de sus sales. El compuesto de la presente invención tiene una acción inhibidora de la tirosina cinasa superior, es muy seguro y es suficientemente satisfactorio como producto farmacéutico.

LISTADO DE SECUENCIAS

<110> TAKEDA PHARMACEUTICAL COMPANY LIMITED

<120> COMPUESTO HETEROCÍCLICO FUSIONADO

<130> 09983

<150> JP 2005-349858
<151> 2005-12-02

<150> JP 2006-06648
<151> 2006-03-07

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<170> PatentIn versión 3.3

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2006/324499

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/118588 A (TAKEDA PHARMACEUTICAL COMPANY [JP]; ISHIKAWA TOMOYASU [JP]; TANIGUCHI) 15 December 2005 (2005-12-15) claim 1	1-33
P,X	WO 2006/010264 A (METHYLGENE INC [CA]; VAISBURG ARKADII [CA]; WILLIAM STEPHEN [CA]; RAEP) 2 February 2006 (2006-02-02) claim 1	1-33
E	WO 2007/004749 A (TAKEDA PHARMACEUTICAL COMPANY [JP]; IMAMURA SHINICHI [JP]; OGURO YUYA) 11 January 2007 (2007-01-11) claim 1	1-33

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			CA	2358998 A1	03-08-2000
			CN	1333758 A	30-01-2002
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			HR	20010542 A2	31-08-2002
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			JP	2002535391 T	22-10-2002
			JP	2005002125 A	06-01-2005
			MA	26712 A1	20-12-2004
			NO	20013671 A	26-09-2001
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			UA	71945 C2	17-01-2005
			ZA	200105867 A	17-07-2002
WO 2005118588	A	15-12-2005	AU	2005250285 A1	15-12-2005
			CA	2569016 A1	15-12-2005
			EP	1752457 A1	14-02-2007
WO 2006010264	A	02-02-2006	AU	2005266803 A1	02-02-2006
			CA	2573538 A1	02-02-2006
WO 2007004749	A	11-01-2007	NONE		

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***Prioridad*** (32) ***Fecha*** (33) ***País***
2005-349858 **02/12/2005** **JP**
2006-060648 **07/03/2006** **JP**

(51) Int Cl: **C07D 487/004**

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

(72) Inventor(es) **TOMOYASU ISHIKAWA Y OTROS**

(74) Apoderado: **EMILIO FERRERO**

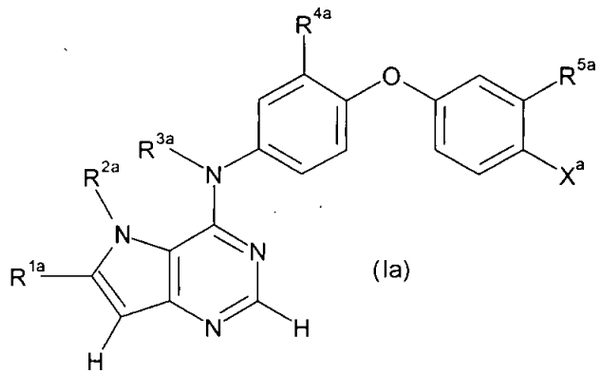
(85) Fecha limite inicio fase nacional: 02/07/2008
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 01/12/2006
No. de solicitud PCT/JP2006/324499

(87) Publicación internacional
Fecha: 07/06/2007
N° publicación: ***WO 2007/064045***

(54) Titulo: **COMPUESTO HETEROCICLICO FUSIONADO**

Reivindicación(es):

1.- Un compuesto representado por la fórmula:



(Ia)

caracterizado porque
R^{1a} es un átomo de hidrógeno,
R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por alquilo de C_{1-4} opcionalmente halogenado con $-NR^{6a}-CO-(CH_2)_n-SO_2-$
en donde n es un número entero de 1 a 4, R^{6a} es un átomo de hidrógeno o un grupo alquilo de C_{1-4}, y $-(CH_2)_n-$ está opcionalmente sustituido con alquilo de C_{1-4},
R^{3a} es un átomo de hidrógeno o un grupo alquilo de C_{1-6},
R^{4a} es un átomo de halógeno o un grupo alquilo de C_{1-6},
R^{5a} es un átomo de halógeno o un grupo alquilo de C_{1-6}, y
X^a es un átomo de hidrógeno o un átomo de halógeno,
o una de sus sales,
con la condición de que se excluya N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida.

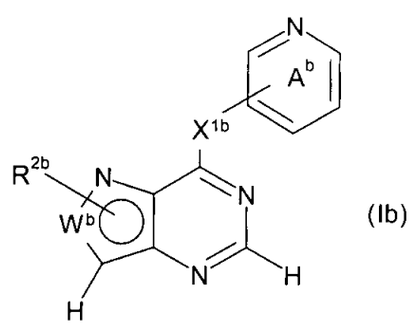
2.- El compuesto de conformidad con la reivindicación 1, caracterizado porque X^a es un átomo de hidrógeno.

3.- El compuesto de conformidad con la reivindicación 2, caracterizado porque
R^{1a} es un átomo de hidrógeno,
R^{2a} es un grupo alquilo de C_{1-6} sustituido con un grupo representado por $-NR^{6aa}-CO-CR^{7a}R^{8a}-SO_2-$alquilo de C_{1-4}
en donde R^{6aa} es un átomo de hidrógeno o un grupo metilo, R^{7a} y R^{8a} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo metilo,
R^{3a} es un átomo de hidrógeno,
R^{4a} es un átomo de cloro o un grupo metilo, y
R^{5a} es un átomo de flúor, un átomo de cloro o un grupo metilo.

4.- El compuesto de conformidad con la reivindicación 3, caracterizado porque R^{7a} y R^{8a} son grupos metilo.

5.- Un compuesto, caracterizado porque se selecciona de los siguientes:
N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,
N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(etilsulfonil)acetamida,
N-[2-(4-{[3-cloro-4-(3-clorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-N,2-dimetil-2-(metilsulfonil)propanamida,
N-[2-(4-{[3-cloro-4-(3-metilfenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida,
N-[2-(4-{[3-cloro-4-(3-fluorofenoxi)fenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-(metilsulfonil)acetamida, y
N-[2-(4-{[4-(3-clorofenoxi)-3-metilfenil]amino}-5H-pirrolo[3,2-d]pirimidin-5-il)etil]-2-metil-2-(metilsulfonil)propanamida,
o una de sus sales, o uno de sus hidratos.

6.- Un compuesto representado por la fórmula:



(Ib)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-067245- -00000-0000

Fecha: 2008-07-01 17:07:26 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 11189

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 46,143
FECHA : JUNIO 9 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678328	09/06/2008	89,445,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
			TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

261656-84-034-5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-067245- -00000-0000

Fecha: 2008-07-01 17:07:26 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1189

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

1490

Firma Responsable

Fecha 01-07-08

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 1191

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	08 67245
	Solicitud internacional	PCT/JP2006/324499
	Fecha inicio fase nacional	02/07/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	6527
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá D.C., 25 JUL. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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