Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-177653

54. **TÍTULO** Derivado Heterociclico Fusionado y su uso

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** Takeda Pharmaceutical company

DOMICILIO Osaka, Japon

74. **APODERADO** Luz clemencia de Paez
cc 35.456.344 de usaquen

22. **BOGOTÁ, D.C.,** _____

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-117653- -00000-0000
Fecha: 2010-09-23 11:05:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1408

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

2 SOLICITANTE (71)

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

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

Domicilio: Osaka,
Japón

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

3 REPRESENTANTE O APODERADO

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

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

4 INVENTOR (ES) (72)

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3. **Satoshi SASAKI**
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Japón

4. **Shigeru KONDO**
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Osaka 532-8686,
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2009/054007 Fecha: 25 de febrero de 2009
Publicación Internacional No. WO 2009/107850 A3 Fecha: 03 de septiembre de 2009

6 Título (54)

DERIVADO HETEROCICLICO FUSIONADO Y SU USO (16/10 14/2)

7 Clasificación Internacional (51) C07D 471/004

8 Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	26 de febrero de 2008	2008-045134
JP	01 de octubre de 2008	2008-256755

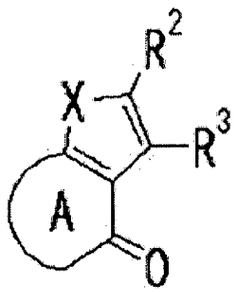
9 **Comprobante de pago No.:** 10-75,703 **Fecha:** 13 de septiembre de 2010
Comprobante de pago No.: 10-75,753 **Fecha:** 13 de septiembre de 2010

10 **Anexos:**

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 554.000.oo.
- [x] Comprobante de pago por 9 reivindicaciones adicionales después de la décima reivindicación por $234.000.oo.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Páez

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

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2009/107850 A3

   Descripción:

   Páginas 727 en el idioma original

   Páginas 635 en español

   Reivindicaciones: Número (s) 19

   Figuras: Número (s)

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

3. ☒ Listado de Secuencias.

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

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

179

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

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

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

Fe

C

14656
08085

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

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

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

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

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, writ mandamus, the prote[illegible] cnal, and administrative [illegible] suits instituted by me (us) [illegible] matters they ma[illegible] r of Attorney, compromise, co[illegible] admit

COPIA TOMADA FIEL DE LA ORIGINAL QUE HE TENIDO A LA VISTA
21 SEP 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas [illegible]
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

© CAVELIER ABOGADOS

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

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

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

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

en/in Osaka, Japan

por/by

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

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C.
21 SEP 2004
NOTARIO
Jaime Vargas
NOTARIO
ENCARGADO
NOTARIA SEXTA DE BOGOTA

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WPPODE01-179 (MINUTA 12.1.1.2.5)

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

REGISTER NUMBER 334 / 2004

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

Dated this 14th day of December, 2004

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

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas Chacón
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

COPIA NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. PARA CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA

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

4. bears the seal/stamp of — Kiyoomi FUJITA, Notary Public

Certified

5. at **Osaka** 6. DEC. 17. 2004

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

8. No. 04149

9. Seal/stamp:

10. Signature:

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

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

21 SEP 2010

NOTARIO ENCARGADO

Jaime Vargas Ch... NOTARIO ENCARGADO NOTARIA SEXTA DE BOGOTA

大阪法務局所属　公証人役場

認証登簿　平成１６年 第　334　号

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

よって、その署名が本人の自筆であることを証する。

平成　16　年　12　月　14　日

大阪市西区江戸堀１丁目１０番８号（帝人殖産ビル内）

公証人　**藤田清臣**　役場において

大阪法務局所属

公証人　藤田清臣

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C.
21 SEP 2010
NOTARIO ENCARGADO
Jaime Vargas Ch[illegible]
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

THE OSAKA CHAMBER OF COMMERCE & INDUSTRY

2-8 HOMMACHIBASHI, CHUO-KU, OSAKA 540-0029, JAPAN.
FAX : (06)6944-6248 TEL : (06)6944-~~6412~~ 6411
URL : http://www.osaka.cci.or.jp/

November 17, 2004

To whom it may concern:

CERTIFICATE OF MEMBERSHIP

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

Company name: Takeda Pharmaceutical Company Limited

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

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

Membership Number: KT-01-00080

The Osaka Chamber of Commerce & Industry

Yoshinobu Kobayashi
Authorized Signatory

COTEJO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:37

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia
CERTIFICA:

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

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

Firma del Encargado de Funciones Consulares)

Derechos:

MINISTERIO DE RELACIONES EXTERIORES

085749

ESTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

RAFAEL RICARDO OROZCO

NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas C.
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

総第 3603 号

証　　明

大阪法務局所属公証人　藤田清臣

平成 16 年 12 月 14 日付

平成 16 年 登簿 第 334 号

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

平成 16 年 12 月 17 日
平成　　年　　月　　日

大阪法務局長　梅津和宏

CERTIFICATE

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

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PUESTO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

12

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

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

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

Firma Ilegible

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

REGISTRO NÚMERO **334** / 2004

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

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

Expedido hoy 14 de diciembre de 2004

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

10-8, Edobori 1-chome

13

Nishi-ku, Osaka, Japón

Firma ilegible

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

DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

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

Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

APOSTILLA

(Convention de La Haye du 5 octubre 1961)

1. País: **JAPÓN**
   Este documento público
2. ha sido firmado por Kiyoomi FUJ
3. actuando en calidad de Director de la Oficina de Asuntos Legales de Tokio
4. lleva el sello/estampilla de Kiyoomi FUJITA, Notario Público

CONSUL NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas Cifuentes
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

14

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

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

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

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

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

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

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO [illegible]
MINISTERIO [illegible]

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

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

Diego Lorenzo

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

SANTAFE DE BOGOTA, 08 FEB 2005

CODEJURIS 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

Diego Lorenzo

CUALQUIERA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

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

21 SEP 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas Ch...
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

15

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 · JAPON ·

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-~~6412~~ 6411
URL: http://www.osaka.cci.or.jp/

Noviembre 17 de 2004

A quién pueda interesar:

CERTIFICADO DE MEMBRESÍA

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

Nombre de la compañía: Takeda Pharmaceutical Company Limited

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

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

Numero de Membresía: KT-01-00080

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO

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

MINISTERIO DE
RELACIONES EXTERIORES

313391

Diego Vargas
ESTA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:39

JEFE DE LEGALIZACIONES
BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA D.C. HAGO CONSTAR QUE LA(S) FIRMA(S) DE
Diego Vargas
ESTAMPADA EN EL PRESENTE DOCUMENTO ES
SEMEJANTE A LA QUE APARECE EN LA(S) CEDULA(S)
DE CIUDADANIA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA
08 FEB 2005

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C.
HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE
CON EL ORIGINAL QUE ME FUE PRESENTADO
BOGOTA D.C.

21 SEP 2010

NOTARIO ENCARGADO

NOTARIA SEXTA DE BOGOTA
COLOMBIA
Jaime Vargas C.
NOTARIO
ENCARGADO

CAVELIER
ABOGADOS

EDIFICIO SISKI
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BOGOTA 8, COLOMBIA

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TELEFAX: (57) (1) 217-9211 (57) (1) 310-4995

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Poderdante : **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

Poder conferido el : 14/12/2004

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

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

Señora Jefe,

EMILIO FERRERO
T.P.A. N° 31.929
C.C. N° 438.019 de Usaquén

Acepto:

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

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA
21 SEP 2010
NOTARIO ENCARGADO
REPUBLICA DE COLOMBIA
Jaime Vargas Ortiz
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C. 05 NOV 2009

Ante mi AMPARO QUINTERO ARTURO,

NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ, D.C.

Compareció(eron) Emilio Torres Villaquiran Luz Clemencia Sanchez de Paez

Quien(es) exhibió(eron) la(s) C.C.

4258019 TEP 31929

8545639 VM TP 23565

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

En constancia se firma esta diligencia.

Emilio Torres

Luz Clemencia Sanchez

REPÚBLICA DE COLOMBIA

Amparo Quintero Arturo

NOTARIA

NOTARIA SEXTA DE BOGOTA

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

21 SEP 2010

NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA

Jaime Vargas Cortés

NOTARIO ENCARGADO

NOTARIA SEXTA DE BOGOTA

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

Tel 7

CESION

Yo, (nosotros) abajo firmado (s)
1.
2.

domiciliado(s) en

de la invención:

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

constituida y existente de conformidad con las leyes de

domiciliada en

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

ASSIGNMENT

I (we), the undersigned
1. Nobuhiro FUJII
2. Yuya OGURO
3. Satoshi SASAKI
4. Shigeru KONDO

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

state(s) under oath to be sole and true inventor(s) of the invention:
FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF

state as well, that assign, without reservations or limitations in favour of
Takeda Pharmaceutical Company Limited
a corporation constituted and existing in conformity with the laws of
Japan

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

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

Dado y firmado hoy/Given and signed this
____ day of _____ 2010
en/in _____

Firma/Signature

1. Nobuhiro Fujii Nobuhiro FUJII
2. Yuya Oguro Yuya OGURO
3. Satoshi Sasaki Satoshi SASAKI
4. Shigeru Kondo Shigeru KONDO

© CAVELIER ABOGADOS
WPPODE01-374

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. JUL. 29. 2010

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

8. No. 4403

9. Seal/stamp:

10. Signature:

Naomi ASANO

For the Minister for Foreign Affairs

Naomi ASANO

78

大阪法務局所属　公証人役場

認証登簿　平成２２年 第　349　号

嘱託人　藤井　伸寛　および　近藤　滋　は、本職の面前でこの証書に署名した。

また、嘱託人　大黒　裕哉　および　佐々木　聡　の代理人　小澤　友代　は、本職の面前でこの証書にある嘱託人の署名を自認した。

よって、その署名が本人の自筆であることを証する。

平成　２２　年　７　月　２７　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

REGISTER NUMBER 349 / 2010

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Messrs. Nobuhiro FUJII and Shigeru KONDO.

And, I hereby certify that the signatures of this document applied for has been approved by Ms. Tomoyo KOZAWA in my presence to be the true signatures of Messrs. Yuya OGURO and Satoshi SASAKI

Dated this 27th day of July, 2010

10-8, Edobori 1-chome,

Nishi-ku, Osaka, Japan.

Masaharu Kemma

Masaharu KEMMA

Notary attached

to The Osaka Legal Affairs Bureau

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

20

第　3325　号

証　明

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

平成22年7月29日
平成　年　月　日

大阪法務局長　石　井　寛　明

Registration *No.*

CERTIFICATE

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

Date JUL. 29. 2010

Director of the Osaka Legal Affairs Bureau

21

TRADUCCIÓN OFICIAL 255/2010 DE UN DOCUMENTO EN INGLÉS Y ESPAÑOL POR EL CUAL LOS ABAJO FIRMANTES, 1) NOBUHIRO FUJII, 2) YUYA OGURO; 3. SATOSHI SASAKI Y 4. SHIGERU KONDO, RESIDENTES RESPECTIVAMENTE, 1 Y 4) EN C/O TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, JUSOHONMACHI 2-CHOME, YODOGAWA-KU, OSAKA-SHI, OSAKA 532-8686 JAPÓN, 2 Y 3. c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, WADAI, TSUKUBA-SHI, IBARAKI 300-4293 JAPÓN DECLARAN BAJO JURAMENTO SER LOS INVENTORES ÚNICOS Y VERDADEROS DEL INVENTO DERIVADO HETEROCÍCLICO FUSIONADO Y USO DEL MISMO Y QUE LO CEDEN Y TRANSFIEREN SIN LIMITACIÓN A FAVOR DE LA SOCIEDAD TAKEDA PHARMACEUTICAL COMPANY LIMITED, UNA SOCIEDAD CONSTITUIDA Y EXISTENTE DE CONFORMIDAD CON LAS LEYES DE JAPÓN, DOMICILIADA EN 1-1, DOSHOMACHI 4-CHOME, CHUO-KU, OSAKA-SHI, OSAKA 541-0045, JAPÓN TODOS LOS DERECHOS INHERENTES A DICHA INVENCIÓN Y QUE LA CITADA COMPAÑÍA QUEDA FACULTADA PARA SOLICITAR EN SU NOMBRE LA PATENTE DE INVENCIÓN CORRESPONDIENTE EN LA REPUBLICA DE COLOMBIA.

DADO Y FIRMADO POR LOS CUATRO INVENTORES ARRIBA MENCIONADOS

NÚMERO DE REGISTRO 349/2010

Por la presente certifico que este documento fue firmado ante mi y que las firmas que aparecen en el mismo son las firmas verídicas de los señores NOBUHIRO FUJII y SHIGERU KONDO. Además certifico que las firmas de este documento solicitado han sido aprobadas por la señora TOMOYO KOZAWA en mi presencia por ser las firmas verídicas de los señores YUYA OGURO Y SATOSHI SASAKI. Fechado hoy 27 de julio de 2010.

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

Eduardo Calado N.

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

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

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

CERTIFICACIÓN

Por la presente se certifica que la certificación notarial adjunta ha sido firmada por un notario debidamente autorizado y practicante en Osaka, Japón y que el sello oficial que aparece en la misma es genuino. 29 de julio de 2010.

Director de la Oficina de Asuntos jurídicos de Osaka.

APOSTILLA

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

1. PAIS: JAPON

Este documento público

2. ha sido firmado por MASAHARU KEMMA

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

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

CERTIFICADO

5. En OSAKA. 6. el 29 de julio de 2010

7. Por el Ministerio de Asuntos Exteriores

8. No. 4403

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

10. Firma: NAOMI ASANO, a nombre del Ministro de Asuntos Exteriores, COLO-14656-841-061-8 . 380 palabras. 1 hora

ECN\ECN\ID-177855\WPCL002G

Bogotá, 6 de septiembre de 2010.

Eduardo Calado M.

TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FUJII, Nobuhiro** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). **OGURO, Yuya** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki, 3004293 (JP). **SASAKI, Satoshi** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 10, Wadai, Tsukuba-shi, Ibaraki, 3004293 (JP). **KONDO, Shigeru** [—/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP).

(74) Agent: **TAKASHIMA, Hajime**; Meiji Yasuda Seimei Osaka Midosuji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410044 (JP).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

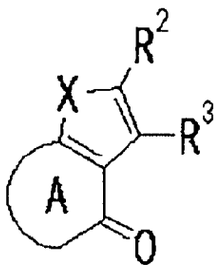
Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

[Continued on next page]

(54) Title: FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF



(I)

(57) Abstract: The present invention provides a compound having a superior Smo inhibitory activity and lower toxicity, which is sufficiently satisfactory as a pharmaceutical product.The present invention provides a compound represented by the formula (I) wherein ring A is 5- to 7-membered ring optionally having substituent(s), where substituents are optionally bonded to each other to form a ring; X is O, S or NR^1 (R^1 is a hydrogen atom or a hydrocarbon group optionally having substituent(s)); R^2 is carbamoyl optionally having substituent(s); and R^3 is hydroxy optionally having substituent(s), or a salt thereof.

WO 2009/107850 A3

WO 2009/107850 A3

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
28 January 2010

DESCRIPTION

FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF

Technical Field

[0001]

The present invention relates to a fused heterocyclic derivative and use thereof. More particularly, the present invention relates to a compound having a strong Smo inhibitory activity and useful for the prophylaxis or treatment of cancer and the like, and use thereof.

[0002]

(Background of the Invention)

The study of morphogenesis during the developmental stage has been conducted based on the screening of variant using Drosophila. Hedgehog gene (hh) was found as one of the genes that cause morphological abnormality of Drosophila embryo due to mutation thereof. Hedgehog gene product (Hh) is a secretory protein, which is produced as an about 45 kDa precursor and then divided, due to autolysis, into a 20 kDa N-terminal side domain, which is a main active principle, and a 25 kDa C-terminal side domain. The 20 kDa N-terminal side domain, which is a main active principle, is modified by fatty acid on the N-terminal and cholesterol on the C-terminal thereof. The Hedgehog signal transduction system is formed by the protein group described below. Hh receptor is Patched (Ptch), which is a twelve-transmembrane-type protein. Ptch acts on Smoothened (Smo), which is a seven-transmembrane-type protein, and suppresses the function of Smo in the absence of Hh. When Hh is bound to the receptor Ptch, suppression of Smo is released and Smo is activated. The signal produced by the activation of Smo activates transcription factor Ci, which regulates the expression of the gene group involved in the morphogenesis (non-patent document 1).

A pathway corresponding to the Drosophila Hedgehog signal transduction system has been confirmed also in mammals. In human, for example, three types of gene products, sonic

hedgehog (Shh), indian hedgehog (Ihh) and deseart hedgehog (Dhh), are known to correspond to Drosophila Hh, and undergo post-translational modification as in Drosophila Hh (non-patent document 2). In human Shh, a 19 kDa active principle is cleaved out from a 45 kDa precursor protein by autolysis, and fatty acid and cholesterol are added to the N-terminal and C-terminal thereof, respectively (non-patent document 3). Such modification is considered to be essential for the maintenance of Shh activity and, for example, 40 times enhanced activity was achieved by the addition of palmitic acid to Escherichia coli recombinant human Shh free of N-terminal modification with fatty acid, and 160 times enhanced activity was achieved by the addition of myristic acid thereto (non-patent document 4). On the other hand, as a human gene corresponding to Drosophila Smo, human Smo is known, and as a human gene corresponding to Drosophila Ptch, 2 types of Ptch1 and Ptch2 are known. In addition, a transcription factor corresponding to Drosophila Ci is considered to be Gli in human, and 3 types of Gli1, Gli2 and Gli3 are known (non-patent document 5). Shh/Ihh/Dhh are each bound to Ptch1 and activate Smo by inhibiting the bond between Ptch1 and Smo. Shh/Ihh/Dhh are also bound to Ptch2, Hip1, Gas1 and Cdo/Boc, besides Ptch1, and regulate the activation of Smo. A signal transduction from Smo induces nuclear localization of Gli1 and Gli2, and activate transcription of Gli1 (non-patent document 6).

The Hedgehog signal is involved in the morphogenesis in the developmental stages also in mammals. In human, for example, patients with Holoprosencephaly, which is a congenital developmental abnormality, showed mutation in Shh (non-patent document 7). Moreover, a natural compound Cyclopamine derived from white hellebore known as a compound inducing Cyclopus in sheep (non-patent document 8) was confirmed to inhibit Smo as action mechanism thereof (non-patent document 9). Furthermore, an Shh knockout mouse was prepared, and its phenotype was found to include Cyclopus,

malformation of extremities (non-patent document 10), and neural plate malformation (non-patent document 11).

Hedgehog signal is inherently a developmental signal, which is promoted in tumor tissues and functions as a cancer cell growth and survival signal. Hedgehog signal is considered to function for the growth and survival of cancer cells in an autocrine mode, or function between cancer cells and cancer interstitial cells in a paracrine mode, in tumor tissues (non-patent document 12). In an autocrine mode, it works for the growth and maintenance of cancer cells, via transcription activation by Gli-1, by abnormal cell cycle control due to increased expression of Cyclin D and decreased expression of p21, promotion of proliferation signal by activation of EGFR pathway and the like. On the other hand, in a paracrine mode, since Shh expressed in cancer cells acts on Smo in cancer interstitial cells, growth factors such as insulin-like growth factor-1, fibroblast growth factor, platelet-derived growth factor and the like are transmitted from cancer interstitial cells to cancer cells, and function for the growth and survival of cancer cells. It is also considered that promotion of VEGF, PDGF pathway and the like by Gli-1 promotes tumor angiogenesis (non-patent document 13). As to the mechanism of promotion of Hedgehog signal, a cancer in which Hedgehog signal is promoted due to mutation of Ptch1 and a cancer which is promoted by overexpression of Shh, which is one of the ligands, have been reported (non-patent document 14). As a cancer in which Hedgehog signal is promoted due to mutation, basal cell cancer and medulloblastoma are known, and mutation of Ptch1 observed in these cancers activates Hedgehog signal in a ligand independent manner (non-patent document 15). As a cancer in which Hedgehog signal is promoted by overexpression of Shh, pancreatic cancer (non-patent document 16) and the like have been reported. In a transgenic mouse in which Shh is forcedly expressed in the pancreas, Hedgehog signal is suggested to be involved not only in the growth and

maintenance of cancer, but also carcinogenic process, since a PanIN-like lesion in the initial stages of cancer progress was found in the pancreas (non-patent document 17). Furthermore, Hedgehog signal is considered to function for the growth and survival of cancer stem cells, and play a key role in the metastasis or postoperative recurrence of tumor and the like (non-patent document 18).

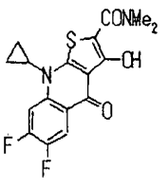
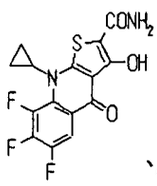
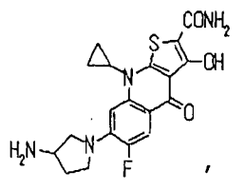
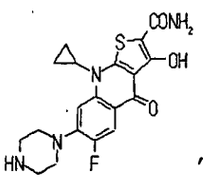
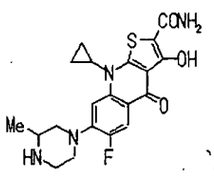
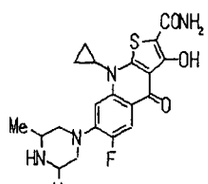
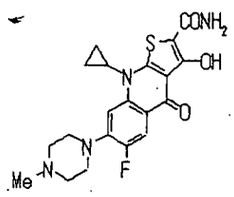
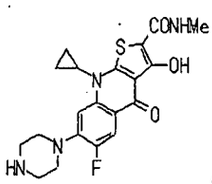
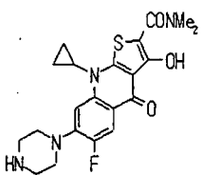
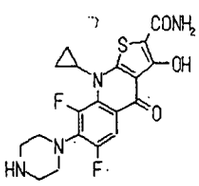
As the Hedgehog signal inhibitor, the following are known. Cyclopamine, which is a naturally occurring Smo inhibitory compound, has been reported to show a tumor growth suppressive effect on glioma (non-patent document 19) and the like. As a synthetic low-molecular-weight compound inhibiting Smo, CUR-61414 (non-patent document 20) and SANT-1, 2, 3, 4 (non-patent document 21) have been reported. It has been reported with regard to the Hedgehog signal inhibitory antibody that administration of an anti-Shh antibody to a cancer-bearing nude mouse transplanted with colorectal cancer cell line HT-29 resulted in cancer regression (patent document 1).

[0003]

As a compound similar to the compound described in the present specification, patent document 2 discloses the following compounds having an antibacterial activity.

[0004]

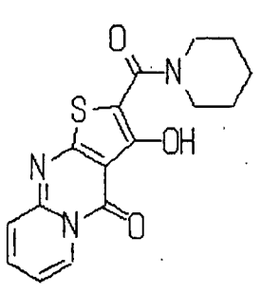
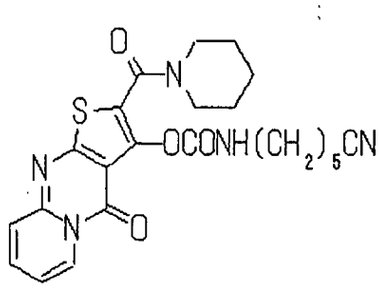


[0005]

As a compound having an antibacterial activity, patent document 3 discloses the following compounds.

[0006]

[0007]

patent document 1: WO2004/020599

patent document 2: JP-A-3-223289

patent document 3: WO93/13664

non-patent document 1: Curr. Opin. Genet. Dev., vol. 12, pages 503-511 (2002)

non-patent document 2: Cell, vol. 103, pages 371-374 (2000)

non-patent document 3: J. Biol. Chem., vol. 273, pages 14037-14045 (1998)

non-patent document 4: Biochemistry, vol. 40, pages 4359-4371 (2001)

non-patent document 5: Nature Rev. Cancer, vol. 2, pages 361-372 (2002)

non-patent document 6: Curr. Opin. Cell Biol., vol. 19, pages 159-165 (2007)

non-patent document 7: Nat. Genet., vol. 14, pages 357-360 (1996)

non-patent document 8: Am. J. Vet. Res., vol. 24, pages 1164-1175 (1963)

non-patent document 9: Development, vol. 125, pages 3553-3562 (1998)

non-patent document 10: Nature, vol. 383, pages 407-413 (1996)

non-patent document 11: Cell, vol. 111, pages 63-75 (2002)

non-patent document 12: Nat. Rev. Drug Discov., vol. 5, pages 1026-1033 (2006)

non-patent document 13: Clin Cancer Res., vol. 12, pages 5924-5928 (2006)

non-patent document 14: Nature Rev. Cancer, vol. 3, pages 903-911 (2003)

non-patent document 15: Am. J. Med. Gen., vol. 123A, pages 5-28 (2003)

non-patent document 16: Nature, vol. 425, pages 846-851 (2003)

non-patent document 17: Nature, vol. 425, pages 851-856 (2003)

non-patent document 18: Trends Cell Biol., vol. 17, pages 438-227 (2007)

non-patent document 19: Development, vol. 128, pages 5201-5212 (2001)

non-patent document 20: Proc. Natl. Acad. Sci. U.S.A., vol. 100, pages 4616-4621 (2003)

non-patent document 21: Proc. Natl. Acad. Sci. U.S.A., vol. 99, pages 14071-14076 (2002)

Disclosure of the Invention

Problems to be Solved by the Invention

[0008]

An object of the present invention is to provide a compound having a superior Smo inhibitory activity, low toxicity

and sufficiently satisfactory as a pharmaceutical product.

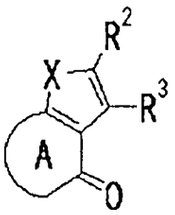
[0009]

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a compound represented by the following formula and a salt thereof have a superior Smo inhibitory activity, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] A compound represented by the formula

[0010]



(I)

[0011]

wherein

ring A is a 5- to 7-membered ring optionally having substituent(s), where substituents are optionally bonded to each other to form a ring;

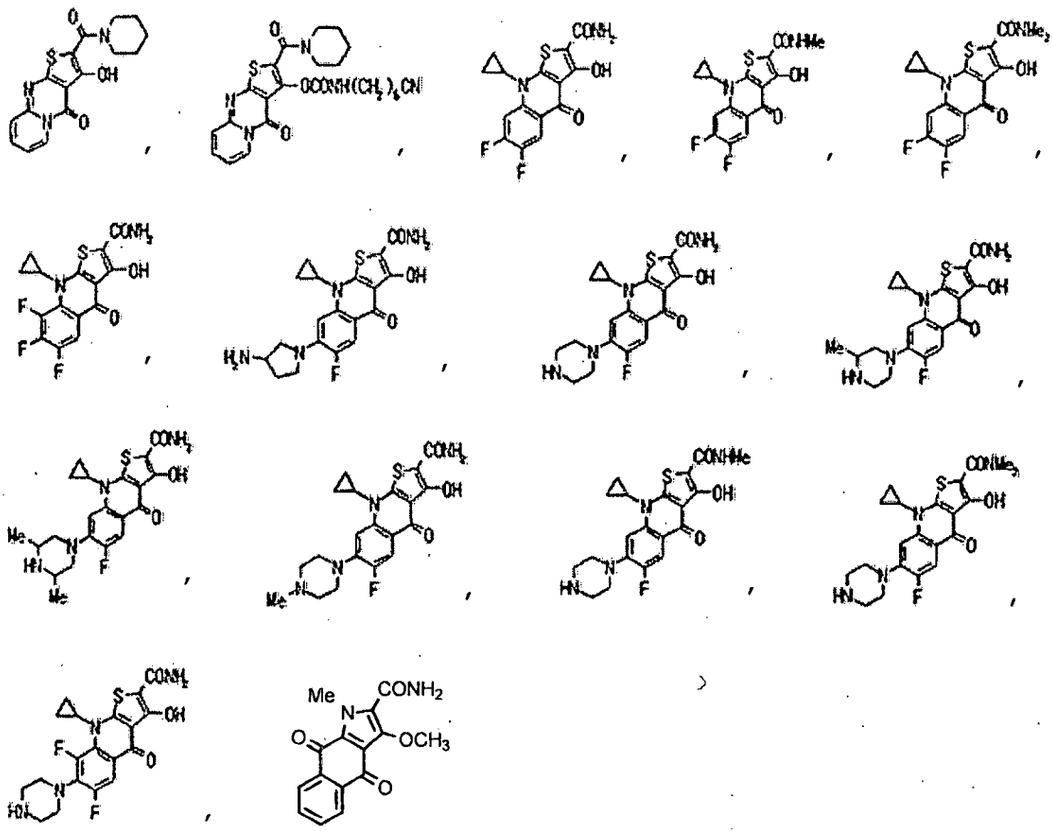
X is O, S or NR^1 (R^1 is a hydrogen atom or a hydrocarbon group optionally having substituent(s));

R^2 is carbamoyl optionally having substituent(s); and

R^3 is hydroxy optionally having substituent(s),

except the following compounds;

[0012]

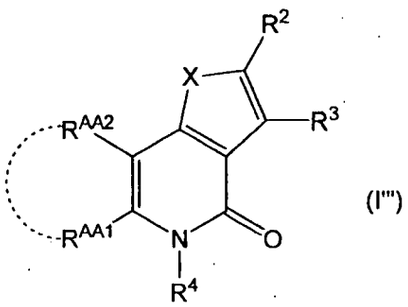


[0013]

(hereinafter sometimes to be abbreviated as compound (I)) or a salt thereof.

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

[0014]



(I'')

[0015]

wherein

X, R^2 and R^3 are as defined in the above-mentioned [1],

R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent, or R^{AA1} and R^{AA2} are optionally bonded to each other to form a 5- to 7-membered ring optionally having

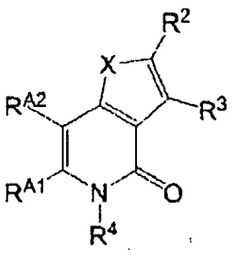
substituent(s), and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s)

(hereinafter sometimes to be abbreviated as compound (I"').

[3] The compound of the above-mentioned [2], which is represented by the formula

[0016]



(I")

[0017]

wherein

X, R^2 and R^3 are as defined in the above-mentioned [1],

R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent, and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s)

(hereinafter sometimes to be abbreviated as compound (I")).

[4] The compound of the above-mentioned [3], wherein X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s),

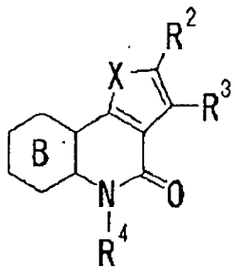
R^{A1} is a hydrogen atom or a C_{1-6} alkyl group,

R^{A2} is a hydrogen atom or a C_{1-6} alkyl group, and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s).

[5] The compound of the above-mentioned [1], which is represented by the formula

[0018]



(I')

[0019]

wherein

X, R^2 and R^3 are as defined in the above-mentioned [1],

ring B is a 6-membered ring optionally having substituent(s); and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s)

(hereinafter sometimes to be abbreviated as compound (I')).

[6] The compound of the above-mentioned [5], wherein ring B is a 6-membered ring optionally having substituent(s),

X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s), and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s).

[7] N-[1-(2-Hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide or a salt thereof.

[8] N-[1-(Hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide or a salt thereof.

[9] 3-Ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

[10] N-[1-(Hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

[11] 6-Ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-

oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

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

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

[14] The pharmaceutical agent of the above-mentioned [13], which is an Smo inhibitor.

[15] The pharmaceutical agent of the above-mentioned [13], which is an agent for the prophylaxis or treatment of cancer.

[16] A method of inhibiting Smo in a mammal, which comprises administering an effective amount of the compound of the above-mentioned [1] or a prodrug thereof to the mammal.

[17] 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 [1] or a prodrug thereof to the mammal.

[18] Use of the compound of the above-mentioned [1] or a prodrug thereof for the production of an Smo inhibitor.

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

In the present specification, compound (I) encompasses compound (I'), compound (I") and compound (I"').

[0020]

(Effect of the Invention)

Since the compound of the present invention has a strong Smo inhibitory action, it can provide a clinically useful agent for the prophylaxis or treatment of cancer, a cancer growth inhibitor and a cancer metastasis suppressive agent.

[0021]

(Detailed Description of the Invention)

The present invention is explained in detail in the following.

In compound (I), X is O, S or NR^1 (R^1 is a hydrogen atom

or a hydrocarbon group optionally having substituent(s)).

Examples of the "hydrocarbon group optionally having substituent(s)" for R^1 include alkyl optionally having substituent(s), alkenyl optionally having substituent(s), alkynyl optionally having substituent(s), cycloalkyl optionally having substituent(s), aryl optionally having substituent(s) and the like.

[0022]

Examples of the "alkyl" of the above-mentioned "alkyl optionally having substituent(s)" include C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) and the like.

Examples of the substituent that the above-mentioned "alkyl optionally having substituent(s)" may have include the following "substituent group A" and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s):

(substituent group A)

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

(2) cyano,

(3) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl) optionally having 1 to 3 substituents selected from

(1') C_{6-10} aryl (e.g., phenyl, naphthyl),

(2') amino,

(3') C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino),

(4') hydroxy,

(5') C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy), and

(6') heterocyclic group (e.g., pyrrolidinyl, benzodioxolyl),

(4) C_{2-6} alkenyl (e.g., vinyl, allyl),

(5) C_{2-6} alkynyl (e.g., ethynyl, propargyl),

(6) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) optionally having one hydroxy,

(7) C_{6-10} aryl (e.g., phenyl, naphthyl) optionally having 1 to 3 substituents selected from

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

(b) hydroxy,

(c) cyano,

(d) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl), and

(e) C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

(8) C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, butylcarbonyl) optionally having 1 to 3 substituents selected from

(1') hydroxy,

(2') C_{1-6} alkoxy (e.g., methoxy, ethoxy),

(3') amino,

(4') C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino),

(5') C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl), and

(6') C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(9) C_{6-10} aryl-carbonyl (e.g., benzoyl, naphthoyl) optionally having 1 to 3 substituents selected from

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

(b) C_{1-6} alkoxy (e.g., methoxy),

(10) carbamoyl,

(11) C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl) optionally having one hydroxy,

(12) di-C_{1-6} alkyl-carbamoyl (e.g., dimethylcarbamoyl, diethylcarbamoyl),

(13) C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl),

(14) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-piperazinylcarbonyl, 4-morpholinylcarbonyl, 4-thiomorpholinylcarbonyl, 1-homopiperazinylcarbonyl),

(15) carboxyl,

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

butoxycarbonyl),

(17) C_{6-10} aryloxy-carbonyl (e.g., phenoxycarbonyl),

(18) amino optionally having 1 or 2 substituents selected from

(a) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(b) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(19) C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino),

(20) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino) optionally having one hydroxy,

(21) C_{1-6} alkyl-carbonylamino (e.g., acetylamino, ethylcarbonylamino) optionally having 1 to 3 substituents selected from

(a) C_{1-6} alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),

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

(c) hydroxy,

(22) di-(C_{1-6} alkyl-carbonyl)amino (e.g., di-(acetyl)amino, di-(ethylcarbonyl)amino, di-(propylcarbonyl)amino),

(23) C_{1-6} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, tert-butoxycarbonylamino),

(24) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-methylamino, N-acetyl-N-ethylamino),

(25) ureido,

(26) C_{1-6} alkyl-ureido (e.g., methylureido, ethylureido),

(27) hydroxy,

(28) C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy) optionally having 1 to 3 C_{6-10} aryl (e.g., phenyl),

(29) C_{6-10} aryloxy (e.g., phenoxy, naphthoxy),

(30) heterocyclic group (e.g., 5- or 6-membered aromatic heterocyclic group such as 1-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrazolyl, 1-imidazolyl, 2-imidazolyl, 2-pyrazinyl, 2-furyl, 2-thiazolyl, 4-pyrimidinyl and the like;

3- to 8-membered nonaromatic heterocyclic group such as 3-azetidinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, morpholino, 2-tetrahydrofuryl, tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl, 3-azepanyl, 4-azepanyl and the like; a group obtained by fusing a nonaromatic heterocyclic group such as 1,3-benzodioxol-5-yl and the like and a benzene ring) optionally having 1 to 3 (preferably 1 or 2) substituents selected from

(1') C_{1-6} alkyl (e.g., methyl, ethyl, propyl) optionally having 1 to 3 substituents selected from

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

(b) hydroxy,

(2') hydroxy,

(3') oxo,

(4') cyano,

(5') carbamoyl,

(6') C_{1-6} alkoxy (e.g., methoxy),

(7') C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl),

(8') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(9') C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having 1 to 3 substituents selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy),

(c) amino,

(d) C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino),

(e) di-C_{1-6} alkylamino (e.g., dimethylamino), and

(f) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(31) oxo,

(32) thioxo,

(33) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl),

(34) heterocyclyl-carbonyl (e.g., pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl).

[0023]

Examples of the "alkenyl" of the above-mentioned "alkenyl optionally having substituent(s)" include C_{2-6} alkenyl (e.g., vinyl, allyl) and the like.

Examples of the substituent of the above-mentioned "alkenyl optionally having substituent(s)" include the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

[0024]

Examples of the "alkynyl" of the above-mentioned "alkynyl optionally having substituent(s)" include C_{2-6} alkynyl (e.g., ethynyl, propargyl) and the like.

Examples of the substituent that the above-mentioned "alkynyl optionally having substituent(s)" may have include the above-mentioned substituent group A and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

[0025]

Examples of the "cycloalkyl" of the above-mentioned "cycloalkyl optionally having substituent(s)" include C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) and the like.

Examples of the substituent that the above-mentioned "cycloalkyl optionally having substituent(s)" may have include

(1) the above-mentioned substituent group A,

(2) C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A

and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

Moreover, the "cycloalkyl optionally having substituent(s)" may be a group obtained by fusing C_{3-6} cycloalkyl and a benzene ring (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl).

[0026]

Examples of the "aryl" of the above-mentioned "aryl

optionally having substituent(s)" include C_{6-10} aryl (e.g., phenyl, naphthyl) and the like.

Examples of the substituent that the above-mentioned "aryl optionally having substituent(s)" may have include (1) the above-mentioned substituent group A (except oxo and thioxo),

(2) C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A

and the like, and 1 to 5 (preferably 1 to 3) substituents may be present at substitutable position(s).

[0027]

X is preferably O, S or $NR^{1'}$ ($R^{1'}$ is alkyl optionally having substituent(s)), and particularly preferably O, S or N(C_{1-6} alkyl) (particularly, N(methyl)).

[0028]

R^2 is carbamoyl optionally having substituent(s). Examples of the "carbamoyl optionally having substituent(s)" for R^2 include

(1) carbamoyl optionally having 1 or 2 substituent(s) selected from "hydrocarbon group optionally having substituent(s)" and "heterocyclic group optionally having substituent(s)",

(2) cyclic carbamoyl optionally having substituent(s)

and the like.

Examples of the above-mentioned "hydrocarbon group optionally having substituent(s)" include those similar to the aforementioned "hydrocarbon group optionally having substituent(s)" for R^1.

Examples of the "heterocyclic group" of the above-mentioned "heterocyclic group optionally having substituent(s)", and the "heterocyclic group" recited as an example of the substituent that the above-mentioned "alkyl optionally having substituent(s)" may have and the like include aromatic heterocyclic group and saturated or unsaturated nonaromatic heterocyclic group (aliphatic heterocyclic group), each containing, as a ring system-

constituting atom (ring atom), 1 to 3 kinds (preferably 1 or 2 kinds) of at least one (preferably 1 to 4, more preferably 1 or 2) hetero atom selected from oxygen atom, sulfur atom (the sulfur atom may be oxidized) and nitrogen atom, and a group having a bond at carbon atom and the like are used.

Examples of the "aromatic heterocyclic group" include (1) 5- or 6-membered monocyclic aromatic heterocyclic group such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like, and

(2) 8- to 12-membered condensed polycyclic aromatic heterocyclic group such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzoisooxazolyl, benzothiazolyl, benzopyranyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acrydinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenathrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl and the like,

and the like.

[0029]

Examples of the "nonaromatic heterocyclic group" include (1) 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) nonaromatic heterocyclic group (aliphatic heterocyclic group) such as oxiranyl,

azepanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like,

(2) nonaromatic heterocyclic group wherein the double bond in the above-mentioned monocyclic aromatic heterocyclic group or condensed polycyclic aromatic heterocyclic group is partly or entirely saturated, such as 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl and the like, and

(3) a group wherein nonaromatic heterocyclic group such as benzodioxolyl and the like and benzene ring are fused and the like.

Examples of the "substituent" of the above-mentioned "heterocyclic group optionally having substituent(s)" include (1) the above-mentioned substituent group A,

(2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)

and the like, and substituents in a substitutable number may be present at substitutable position(s).

As cyclic carbamoyl of the "cyclic carbamoyl optionally having substituent(s)", 5- to 7-membered cyclic carbamoyl is used, and examples thereof include pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, piperazin-1-ylcarbonyl, morpholin-4-ylcarbonyl, thiomorpholin-4-ylcarbonyl, homopiperazin-1-ylcarbonyl and the like.

Examples of the "substituent" of the "cyclic carbamoyl optionally having substituent(s)" include the above-mentioned substituent group A and the like, and 1 to 3 substituents may be present at substitutable position(s).

In addition, the substituents of the cyclic carbamoyl optionally having substituent(s) may be bonded to each other to form a 5- to 7-membered ring. In other words, the 5- to 7-membered ring and cyclic carbamoyl may form a fused ring

system. The fused ring system includes a spiro fused ring system.

Examples of the 5- to 7-membered ring include (1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and (2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran, 1,3-dioxole). Among these, cyclohexane ring, benzene ring and 1,3-dioxole ring are preferable.

[0030]

As R^2,

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl optionally having 1 or 2 (preferably 1) substituents selected from

(1') halogen atom,

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino,

(5') di-C_{1-6} alkylamino optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino,

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl,

(9') 5- to 7-membered cyclic carbamoyl,

(10') heterocyclic group optionally having 1 to 3 (preferably 1) substituents selected from

(a) hydroxy,

(b) C_{1-6} alkyl optionally having one hydroxy,

(c) oxo,

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

(e) C_{1-6} alkyl-carbonyl optionally having 1 to 3 (preferably 1) substituents selected from C_{1-6} alkyl-carbonyloxy and hydroxy,

(11') C_{1-6} alkoxy-carbonyl,

(12') C_{3-6} cycloalkyl optionally having one hydroxy,

(13') C_{1-6} alkoxy,

(14') C_{2-6} alkynyl,

(15') C_{6-10} aryl optionally having 1 to 3 (preferably 1 or 2) C_{1-6} alkoxy,

(16') carbamoyl, and

(17') C_{1-6} alkyl-carbonyl-amino optionally having 1 to 3 (preferably 1) substituents selected from

(a) C_{1-6} alkyl-carbonyloxy,

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

(c) hydroxy,

(2) C_{3-6} cycloalkyl or 1,2,3,4-tetrahydronaphthalenyl optionally having 1 or 2 substituents selected from

(1') amino optionally having one substituent selected from

(a) C_{1-6} alkoxy-carbonyl, and

(b) C_{1-6} alkyl-carbonyl optionally having 1 to 3 (preferably 1) substituents selected from hydroxy and C_{1-6} alkyl-carbonyloxy,

(2') hydroxy,

(3') carboxy,

(4') C_{1-6} alkoxy-carbonyl,

(5') C_{1-6} alkyl-carbamoyl optionally having one hydroxy,

(6') C_{1-6} alkyl optionally having one hydroxy, and

(7') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(3) C_{6-10} aryl, and

(4) heterocyclic group optionally having 1 to 4 (preferably 1) substituents selected from

(1') C_{1-6} alkyl optionally having 1 to 5 substituents selected from

(a) C_{6-10} aryl,

(b) hydroxy, and

(c) halogen atom,

(2') C_{1-6} alkyl-carbonyl optionally having 1 to 3 (preferably 1) substituents selected from

(a) C_{1-6} alkyl-carbonyloxy,

(b) hydroxy,

(c) C_{1-6} alkoxy,

(d) C_{1-6} alkyl-sulfonyl, and

(e) amino,

(3') C_{1-6} alkoxy-carbonyl, and

(4') 5- or 6-membered aromatic heterocyclic group optionally having 1 to 3 (preferably 1) substituents selected from

(a) C_{1-6} alkyl optionally having 1 to 3 halogen atoms,

(b) cyano,

(c) carbamoyl,

(d) C_{1-6} alkoxy, and

(e) C_{1-6} alkyl-carbamoyl,

(5') oxo,

(6') C_{1-6} alkyl-carbamoyl,

(7') C_{1-6} alkyl-sulfonyl,

(8') C_{6-10} aryl optionally having 1 to 3 (preferably 1) substituents selected from

(a) hydroxy,

(b) cyano, and

(c) C_{1-6} alkyl-sulfonyl,

(9') heterocyclyl-carbonyl, and

(10') C_{6-10} aryloxy-carbonyl (e.g., phenoxycarbonyl),

(B) 5- to 7-membered cyclic carbamoyl optionally having 1 to 3 (preferably 1) substituents selected from

(1) C_{1-6} alkyl optionally having 1 to 3 (preferably 1) substituents selected from

(a) heterocyclic group,

(b) amino,

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

(d) C_{6-10} aryl,

(2) amino optionally having one C_{1-6} alkyl-carbonyl,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino,

(4) heterocyclic group,

(5) C_{1-6} alkyl-carbonyl optionally having one substituent

selected from

(a) hydroxy,

(b) C_{1-6} alkoxy,

(c) amino,

(d) C_{1-6} alkylamino,

(e) di-C_{1-6} alkylamino, and

(f) C_{1-6} alkyl-carbonyloxy,

(6) C_{6-10} aryl, and

(7) oxo, or

(C) 5- to 7-membered cyclic carbamoyl fused with 5- to 7-membered ring

is preferable.

[0031]

R^3 is hydroxy optionally having substituent(s). As the "substituent" of the "hydroxy optionally having substituent(s)" for R^3, the aforementioned "hydrocarbon group optionally having substituent(s)" for R^1, the aforementioned "heterocyclic group optionally having substituent(s)" and the like can be mentioned.

As R^3, hydroxy optionally having alkyl optionally having substituent(s) is preferable,

hydroxy optionally having

(1) C_{1-6} alkyl optionally having one C_{1-6} alkoxy,

(2) C_{1-6} alkyl optionally having 1 to 5 (preferably 1 to 3) halogen atoms,

(3) C_{1-6} alkyl optionally having one C_{6-10} aryl, or

(4) C_{1-6} alkyl optionally having one heterocyclic group

is more preferable, and

hydroxy substituted by

(1) C_{1-6} alkyl optionally having one C_{1-6} alkoxy,

(2) C_{1-6} alkyl optionally having 1 to 5 (preferably 1 to 3) halogen atoms,

(3) C_{1-6} alkyl optionally having one C_{6-10} aryl, or

(4) C_{1-6} alkyl optionally having one heterocyclic group

is still more preferable.

[0032]

Ring A is a 5- to 7-membered ring optionally having substituent(s). As the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A,
(1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and
(2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran, 1,3-dioxole)
can be mentioned.

Examples of the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have include
(1) the above-mentioned substituent group A,
(2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably, C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)
and the like, and substituents in a substitutable number may be present at substitutable position(s).

In addition, as to the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have, two substituents are optionally bonded to each other to form a ring. As the ring formed by such "substituents" bonded to each other,
(1) 5- to 7-membered homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, cycloheptane, benzene), and
(2) 5- to 7-membered heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran, 1,3-dioxole)
can be mentioned.

The ring formed by the substituents of ring A, which are bonded to each other, may have substituent(s) and examples of

the substituent include

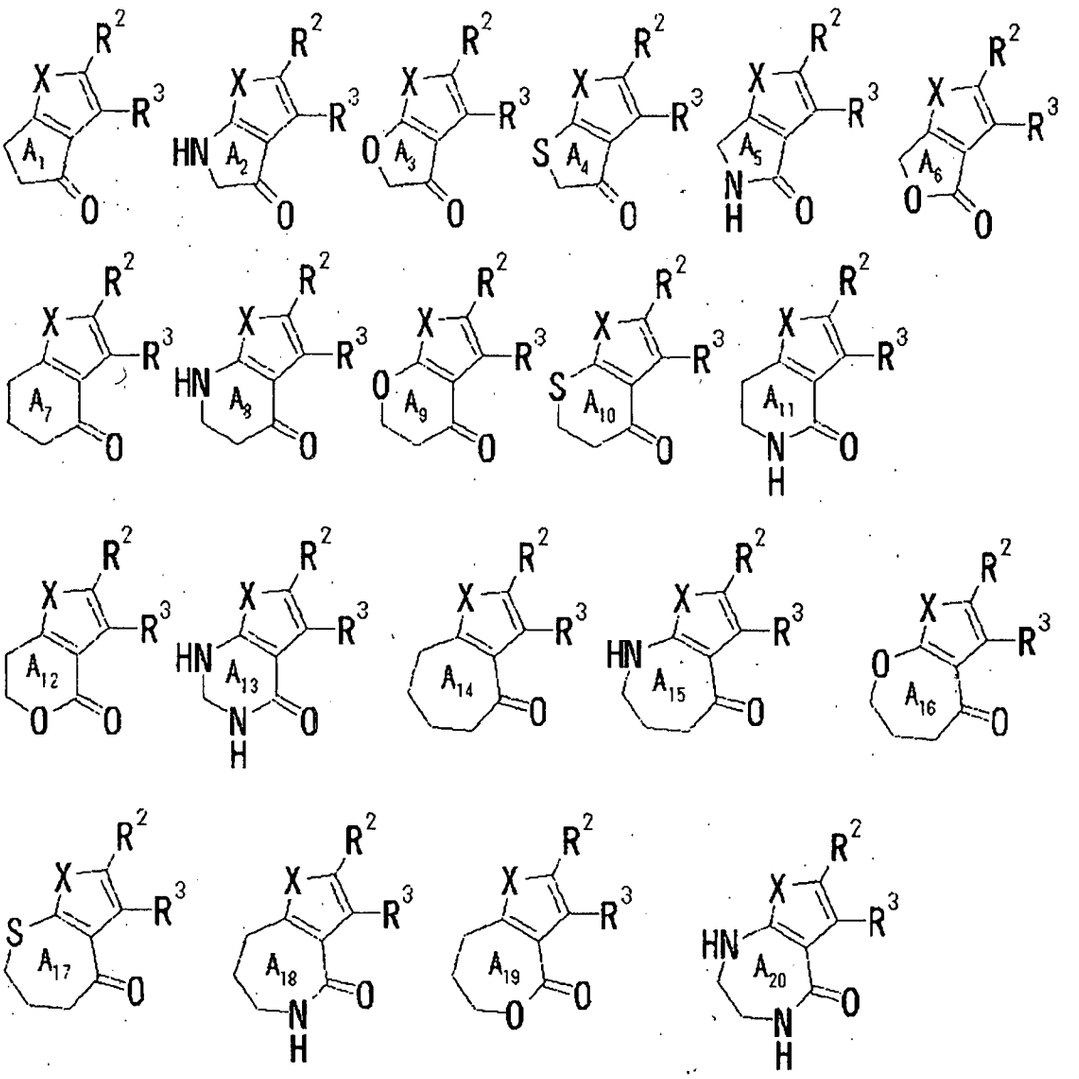
(1) the above-mentioned substituent group A,

(2) those similar to the above-mentioned "hydrocarbon group optionally having substituent(s)" (preferably C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A)

and the like, and substituents in a substitutable number may be present at substitutable position(s).

Compound (I) specifically has a structure represented by the following formula.

[0033]



[0034]

wherein ring A_1 - ring A_{20} optionally further have

substituent(s), the substituents are optionally bonded to each other to form a ring, $-CH_2-CH_2-$ part constituting the ring in ring A_1, ring A_7, ring A_8, ring A_9, ring A_{10}, ring A_{11}, ring A_{12}, ring A_{14}, ring A_{15}, ring A_{16}, ring A_{17}, ring A_{18}, ring A_{19} and ring A_{20} is optionally converted to $-CH=CH-$, $-NH-CH_2-$ part constituting the ring in ring A_2, ring A_5, ring A_8, ring A_{11}, ring A_{13}, ring A_{15}, ring A_{18} and ring A_{20} is optionally converted to $-N=CH-$, and other symbols are as defined above.

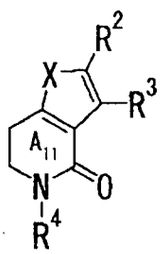
[0035]

As the substituent that ring A_1 - ring A_{20} may have, those similar to the "substituent" that the "5- to 7-membered ring" of the "5- to 7-membered ring optionally having substituent(s)" for ring A may have can be mentioned.

[0036]

As compound (I), a compound represented by the formula

[0037]



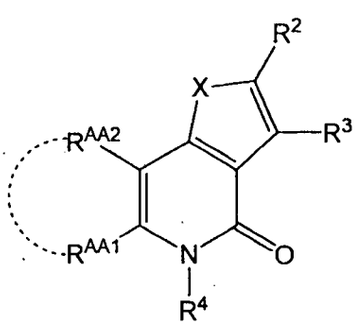
[0038]

wherein each symbol is as defined above, is preferable.

[0039]

Of the above-mentioned compounds, compound (I"') represented by the formula

[0040]



(I"')

[0041]

wherein X, R^2 and R^3 are as defined above, R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent, or R^{AA1} and R^{AA2} are optionally bonded to each other to form a 5- to 7-membered ring optionally having substituent(s), and R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s), is preferable.

[0042]

Compound (I"') is explained in detail in the following.

X, R^2 and R^3 are as defined above.

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s). As the "hydrocarbon group optionally having substituent(s)" for R^4, those similar to the aforementioned "hydrocarbon group optionally having substituent(s)" for R^1 can be mentioned.

As R^4, a hydrogen atom or alkyl optionally having substituent(s) is preferable. Particularly,

(1) hydrogen atom,

(2) C_{1-6} alkyl optionally having one substituent selected from

(1') C_{3-6} cycloalkyl,

(2') C_{6-10} aryl optionally having (i) 1 or 2 C_{1-6} alkoxy optionally having 1 to 3 halogen atoms or (ii) 1 to 3 halogen atoms,

(3') C_{1-6} alkyl-carbonyl,

(4') C_{6-10} aryl-carbonyl optionally having one halogen atom or C_{1-6} alkoxy,

(5') C_{1-6} alkoxy-carbonyl,

(6') C_{6-10} aryl-carbamoyl,

(7') heterocyclic group optionally having 1 or 2 C_{1-6} alkyl optionally having 1 to 3 halogen atoms,

(8') C_{6-10} aryloxy,

(9') carboxy,

(10') cyano, and

(11') C_{1-6} alkoxy optionally having one C_{6-10} aryl,

(3) C_{1-6} alkyl optionally having 1 to 3 halogen atoms

and the like are preferable.

[0043]

(1) R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent. As the substituent, those similar to the aforementioned substituent for ring A can be mentioned.

As R^{AA1}, a hydrogen atom or C_{1-6} alkyl group is preferable.

As R^{AA2}, a hydrogen atom or C_{1-6} alkyl group is preferable.

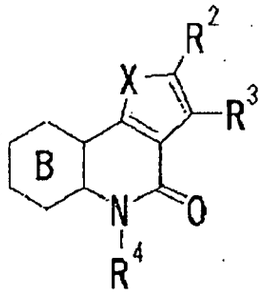
Alternatively,

(2) R^{AA1} and R^{AA2} are bonded to each other to form a 5- to 7-membered ring optionally having substituent(s). As the "5- to 7-membered ring optionally having substituent(s)", those similar to the above-mentioned "5- to 7-membered ring optionally having substituent(s)" for ring A can be mentioned. The 5- to 7-membered ring optionally has a substitutable number of substituents at substitutable positions.

[0044]

In one embodiment, compound (I') represented by the formula

[0045]



(I')

[0046]

wherein X, R^2 and R^3 are as defined above, ring B is a 6-membered ring optionally having substituent(s), and R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s), in which R^{AA1} and R^{AA2} are bonded to each other to form a 6-membered ring optionally having substituent(s), is preferable from among the above-mentioned compounds (I"').

[0047]

Compound (I') is explained in detail in the following.

[0048]

X, R^2, R^3 and R^4 are as defined above.

[0049]

In the formula (I'), preferable examples of R^2 include (A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl, 1-ethylpropyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, di-i-propylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, morpholino, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-furyl, 2-tetrahydrofuryl, 1,3-benzodioxol-5-yl) optionally having one

(a) hydroxy,

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(c) oxo,

(d) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), or

(e) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from C_{1-6} alkyl-carbonyloxy

(e.g., methylcarbonyloxy) and hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(12') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl) optionally having one hydroxy,

(13') C_{1-6} alkoxy (e.g., methoxy, i-propoxy),

(14') C_{2-6} alkynyl (e.g., ethynyl),

(15') C_{6-10} aryl (e.g., phenyl) optionally having 1 or 2 C_{1-6} alkoxy (e.g., methoxy),

(16') carbamoyl, and

(17') C_{1-6} alkyl-carbonyl-amino (e.g., methylcarbonylamino) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),

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

(c) hydroxy,

(2) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl) or 1,2,3,4-tetrahydronaphthalenyl (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl) optionally having 1 or 2 substituents selected from

(1') amino optionally having one substituent selected from

(a) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(b) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(2') hydroxy,

(3') carboxy,

(4') C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl),

(5') C_{1-6} alkyl-carbamoyl (e.g., ethylcarbamoyl) optionally having one hydroxy,

(6') C_{1-6} alkyl (e.g., methyl) optionally having one hydroxy, and

(7') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-azetidinyl, 3-pyrrolidinyl, 4-piperidyl, 2-tetrahydrofuryl, 3-azepanyl, 4-azepanyl, tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl) optionally

having 1 to 4 substituents selected from

(1') C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl) optionally having 1 to 5 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl),

(b) hydroxy, and

(c) halogen atom,

(2') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, i-propylcarbonyl, i-butylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(b) hydroxy,

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

(d) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl), and

(e) amino,

(3') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl),

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-pyrimidinyl) optionally having one substituent selected from

(a) C_{1-6} alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

(b) cyano,

(c) carbamoyl,

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

(e) C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl),

(5') oxo,

(6') C_{1-6} alkyl-carbamoyl (e.g., ethylcarbamoyl),

(7') C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl),

(8') C_{6-10} aryl (e.g., phenyl) optionally having one substituent selected from

(a) hydroxy,

(b) cyano, and

(c) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl),

(9') heterocyclyl-carbonyl (e.g., 2-pyrrolidinylcarbonyl, 2-tetrahydrofurylcarbonyl), and

(10') C_{6-10} aryloxy-carbonyl (e.g., phenoxycarbonyl),

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-piperazinylcarbonyl, 1-homopiperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl) optionally having one substituent selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl),

(b) amino,

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

(d) C_{6-10} aryl (e.g., phenyl),

(2) amino optionally having one C_{1-6} alkyl-carbonyl (e.g., acetyl),

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyridyl),

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy, ethoxy),

(c) amino,

(d) C_{1-6} alkylamino (e.g., isopropylamino),

(e) di-C_{1-6} alkylamino (e.g., dimethylamino), and

(f) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(6) C_{6-10} aryl (e.g., phenyl), and

(7) oxo, and

(C) 5- to 7-membered cyclic carbamoyl fused with 5- to 7-membered ring (e.g., cyclohexane ring, benzene ring, 1,3-dioxolering) (e.g., 1-piperidylcarbonyl).

[0050]

In the formula (I'), preferable examples of R^3 include hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-butyl) optionally having one

(a) C_{1-6} alkoxy (e.g., ethoxy),

(b) C_{6-10} aryl (e.g., phenyl), or

(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

[preferably, hydroxy substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-butyl) optionally having one

(a) C_{1-6} alkoxy (e.g., ethoxy),

(b) C_{6-10} aryl (e.g., phenyl), or

(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)].

[0051]

In the formula (I'), preferable examples of R^4 include

(1) hydrogen atom,

(2) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, n-butyl, n-pentyl, i-pentyl, 2-ethylbutyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having (i) one C_{1-6} alkoxy (e.g., methoxy) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) or (ii) 1 to 3 halogen atoms (e.g., fluorine atom, chlorine atom),

(3') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl),

(5') C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-imidazolyl, 2-furyl, 2-tetrahydrofuryl) optionally having 1 or 2 C_{1-6} alkyl (e.g., methyl) optionally

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

(8') C_{6-10} aryloxy (e.g., phenoxy),

(9') carboxy,

(10') cyano, and

(11') C_{1-6} alkoxy (e.g., methoxy) optionally having one C_{6-10} aryl (e.g., phenyl), and

(3) C_{1-6} alkyl (e.g., ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom).

[0052]

Ring B is a 6-membered ring optionally having substituent(s). As the "6-membered ring" of the "6-membered ring optionally having substituent(s)",

(1) homocyclic ring (e.g., cyclohexane, cyclohexene, cyclohexanediene, benzene), and

(2) heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, pyridine, pyrazine, pyrimidine, pyridazine, triazine, pyran, dihydropyran, tetrahydropyran)

can be mentioned.

Examples of the substituent that the ring B may have include

(1) the above-mentioned substituent group A,

(2) C_{1-6} alkyl optionally having 1 to 3 substituents selected from the above-mentioned substituent group A

and the like, and substituents in a substitutable number may be present at substitutable position(s).

As ring B, cyclohexene ring optionally having substituent(s), benzene ring optionally having substituent(s), or pyridine ring optionally having substituent(s) is preferable, and cyclohexene ring, benzene ring optionally having one halogen atom (e.g., fluorine atom), or pyridine ring is more preferable. Particularly, benzene ring and pyridine ring are preferable.

[0053]

Of compounds (I'), a compound wherein

ring B is a 6-membered ring optionally having

substituent(s),

X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s), and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s)

is preferable.

[0054]

Specific examples of preferable compound (I') include the following.

[Compound (I'-1)]

Compound (I') wherein

X is O, S or N(C_{1-6} alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having one substituent selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-

piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally having one

(a) hydroxy, or

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy, and

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(2) C_{3-6} cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

(2') hydroxy,

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl) optionally having one C_{1-6} alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl), and

(b) hydroxy, or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy),

(c) amino, and

(d) C_{1-6} alkylamino (e.g., isopropylamino);

R^3 is hydroxy optionally having C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy);

R^4 is

(1) hydrogen atom, or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having one C_{1-6} alkoxy (e.g., methoxy),

(3') C_{1-6} alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl),

(5') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

(8') C_{6-10} aryloxy (e.g., phenoxy), and

(9') carboxy; and

ring B is benzene ring.

[0055]

[Compound (I'-2)]

Compound (I') wherein

X is O, S or N(C_{1-6} alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally having one (a) hydroxy, or (b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl), and

(12') C_{3-6} cycloalkyl (e.g., cyclohexyl),

(2) C_{3-6} cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

(2') hydroxy,

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl) optionally having one substituent selected from

(1') C_{1-6} alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl), and

(b) hydroxy,

(2') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy), and

(b) hydroxy,

(3') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy),

(c) amino, and

(d) C_{1-6} alkylamino (e.g., isopropylamino);

R^3 is hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

[preferably, hydroxyl substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

R^4 is

(1) hydrogen atom, or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having one C_{1-6} alkoxy (e.g., methoxy),

(3') C_{1-6} alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl),

(5') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

(8') C_{6-10} aryloxy (e.g., phenoxy), and

(9') carboxy; and

ring B is cyclohexene ring or benzene ring (particularly, benzene ring).

[0056]

[Compound (I'-3)]

Compound (I') wherein

X is O, S or N(C_{1-6} alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl, 1-ethylpropyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, di-i-propylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, morpholino, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-furyl, 2-tetrahydrofuryl, 1,3-benzodioxol-5-yl) optionally having one

(a) hydroxy,

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(c) oxo,

(d) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), or

(e) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy) and hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(12') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl) optionally having one hydroxy,

(13') C_{1-6} alkoxy (e.g., methoxy, i-propoxy),

(14') C_{2-6} alkynyl (e.g., ethynyl),

(15') C_{6-10} aryl (e.g., phenyl) optionally having 1 or 2 C_{1-6} alkoxy (e.g., methoxy),

(16') carbamoyl, and

(17') C_{1-6} alkyl-carbonyl-amino (e.g., methylcarbonylamino) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyl-oxy (e.g., methylcarbonyloxy),

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

(c) hydroxy,

(2) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl) or 1,2,3,4-tetrahydronaphthalenyl (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl) optionally having 1 or 2 substituents selected from

(1') amino optionally having one substituent selected from

(a) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(b) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one hydroxy or C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(2') hydroxy,

(3') carboxy,

(4') C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl),

(5') C_{1-6} alkyl-carbamoyl (e.g., ethylcarbamoyl) optionally having one hydroxy,

(6') C_{1-6} alkyl (e.g., methyl) optionally having one hydroxy, and

(7′) C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-azetidinyl, 3-pyrrolidinyl, 4-piperidyl, 2-tetrahydrofuryl, 3-azepanyl, 4-azepanyl, tetrahydrothiopyran-4-yl, tetrahydropyran-4-yl) optionally having 1 to 4 substituents selected from

(1′) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl) optionally having 1 to 5 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl),

(b) hydroxy, and

(c) halogen atom,

(2′) C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, ethylcarbonyl, i-propylcarbonyl, i-butylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(b) hydroxy,

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

(d) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl), and

(e) amino,

(3′) C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl),

(4′) 5- or 6-membered aromatic heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thiazolyl, 4-pyrimidinyl) optionally having one substituent selected from

(a) C_{1-6} alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

(b) cyano,

(c) carbamoyl,

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

(e) C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl),

(5′) oxo,

(6′) C_{1-6} alkyl-carbamoyl (e.g., ethylcarbamoyl),

(7′) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl),

(8′) C_{6-10} aryl (e.g., phenyl) optionally having one substituent selected from

(a) hydroxy,

(b) cyano, and

(c) C_{1-6} alkyl-sulfonyl (e.g., methylsulfonyl),

(9') heterocyclyl-carbonyl (e.g., 2-pyrrolidinylcarbonyl, 2-tetrahydrofurylcarbonyl), and

(10') C_{6-10} aryloxy-carbonyl (e.g., phenoxycarbonyl),

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-piperazinylcarbonyl, 1-homopiperazinylcarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl) optionally having one group selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl),

(b) amino,

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

(d) C_{6-10} aryl (e.g., phenyl),

(2) amino optionally having one C_{1-6} alkyl-carbonyl (e.g., acetyl),

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyridyl),

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy, ethoxy),

(c) amino,

(d) C_{1-6} alkylamino (e.g., isopropylamino),

(e) di-C_{1-6} alkylamino (e.g., dimethylamino), and

(f) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy),

(6) C_{6-10} aryl (e.g., phenyl), and

(7) oxo, or

(C) 5- to 7-membered cyclic carbamoyl (e.g., 1-piperidylcarbonyl) fused with 5- to 7-membered ring (e.g.,

cyclohexane ring, benzene ring, 1,3-dioxole ring);

R^3 is hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-butyl) optionally having one

(a) C_{1-6} alkoxy (e.g., ethoxy),

(b) C_{6-10} aryl (e.g., phenyl), or

(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

[preferably, hydroxy substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-butyl) optionally having one

(a) C_{1-6} alkoxy (e.g., ethoxy),

(b) C_{6-10} aryl (e.g., phenyl), or

(c) heterocyclic group (e.g., 4-pyridyl, morpholino, 2-tetrahydrofuryl), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

R^4 is

(1) hydrogen atom,

(2) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, n-butyl, n-pentyl, i-pentyl, 2-ethylbutyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having (i) one C_{1-6} alkoxy (e.g., methoxy) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) or (ii) 1 to 3 halogen atoms (e.g., fluorine atom, chlorine atom),

(3') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl),

(5') C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-imidazolyl, 2-furyl, 2-tetrahydrofuryl) optionally having 1 or 2 C_{1-6} alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom),

(8') C_{6-10} aryloxy (e.g., phenoxy),

(9') carboxy,

(10') cyano, and

(11') C_{1-6} alkoxy (e.g., methoxy) optionally having one C_{6-10} aryl (e.g., phenyl), or

(3) C_{1-6} alkyl (e.g., ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom); and

ring B is cyclohexene ring, benzene ring optionally having one halogen atom (e.g., fluorine atom), or pyridine ring (particularly, benzene ring and pyridine ring).

[0057]

[Compound (I'-4)]

N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide;

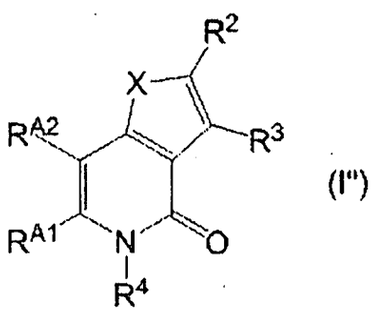
N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide;

or a salt thereof.

[0058]

In another embodiment, of the above-mentioned compounds (I"'), a compound (I") represented by the formula

[0059]



(I")

[0060]

wherein X, R^2, R^3 and R^4 are as defined above, and R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent, is preferable.

[0061]

In the following, compound (I") is described in detail.

[0062]

X, R^2, R^3 and R^4 are as defined above.

[0063]

In the formula (I"), preferable examples of R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl, 2-tetrahydrofuryl) optionally having one

(a) hydroxy, or

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl), and

(12') C_{3-6} cycloalkyl (e.g., cyclohexyl),

(2) C_{3-6} cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

(2') hydroxy,

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl, S-oxido-tetrahydrothiopyran-4-yl) optionally having one substituent selected from

(1') C_{1-6} alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl), and

(b) hydroxy,

(2') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy), and

(b) hydroxy,

(3') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy),

(c) amino, and

(d) C_{1-6} alkylamino (e.g., isopropylamino).

[0064]

In the formula (I"), preferable examples of R^3 is hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom) [preferably, hydroxyl substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)].

[0065]

In the formula (I"), preferable examples of R^4 is

(1) hydrogen atom, or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having (i) 1 or 2 C_{1-6} alkoxy (e.g., methoxy), or (ii) 1 to 3 halogen atoms (e.g., chlorine atom),

(3') C_{1-6} alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally having one halogen atom (e.g., chlorine atom) or C_{1-6} alkoxy (e.g., methoxy),

(5') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

(8') C_{6-10} aryloxy (e.g., phenoxy), and

(9') carboxy; and

R^{A1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl,

ethyl, n-propyl).

[0066]

R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent. As the substituent, those similar to the substituent of the aforementioned ring A can be mentioned.

As R^{A1}, a hydrogen atom or C_{1-6} alkyl group is preferable.

As R^{A2}, a hydrogen atom or C_{1-6} alkyl group is preferable.

[0067]

Of compounds (I"), a compound wherein

X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s),

R^{A1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl, n-propyl),

R^{A2} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl), and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s)

is preferable.

[0068]

Specific examples of preferable compound (I") include the following.

[Compound (I"-1)]

Compound (I") wherein

X is O, S or N(C_{1-6} alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl) optionally having one

(a) hydroxy, or

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl), and

(12') C_{3-6} cycloalkyl (e.g., cyclohexyl),

(2) C_{3-6} cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

(2') hydroxy,

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl) optionally having one substituent selected from

(1') C_{1-6} alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl), and

(b) hydroxy,

(2') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy), and

(b) hydroxy,

(3') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one group selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy),

(c) amino, and

(d) C_{1-6} alkylamino (e.g., isopropylamino);

R^3 is hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

[preferably, hydroxy substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

R^4 is

(1) hydrogen atom, or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having one C_{1-6} alkoxy (e.g., methoxy),

(3') C_{1-6} alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl),

(5') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

(8') C_{6-10} aryloxy (e.g., phenoxy), and

(9') carboxy;

R^{A1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl, n-propyl); and

R^{A2} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl).

[0069]

[Compound (I"-2)]

Compound (I") wherein

X is O, S or N(C_{1-6} alkyl) (particularly N(methyl));

R^2 is

(A) carbamoyl optionally having 1 or 2 substituents selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-methylbutyl) optionally having 1 or 2 substituents selected from

(1') halogen atom (e.g., fluorine atom),

(2') cyano,

(3') amino,

(4') C_{1-6} alkylamino (e.g., isopropylamino),

(5') di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino) optionally having one hydroxy,

(6') C_{1-6} alkoxy-carbonylamino (e.g., tert-butoxycarbonylamino),

(7') hydroxy,

(8') di-C_{1-6} alkyl-carbamoyl (e.g., diethylcarbamoyl),

(9') 5- to 7-membered cyclic carbamoyl (e.g., 1-

pyrrolidinylcarbonyl),

(10') heterocyclic group (e.g., 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-pyrazolyl, 1-imidazolyl, 1-piperidyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperazinyl, 1-morpholinyl, 2-pyridyl, 3-pyridyl, 2-tetrahydrofuryl) optionally having one

(a) hydroxy, or

(b) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one hydroxy,

(11') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl), and

(12') C_{3-6} cycloalkyl (e.g., cyclohexyl),

(2) C_{3-6} cycloalkyl (e.g., cyclohexyl) optionally having 1 or 2 substituents selected from

(1') amino, and

(2') hydroxy,

(3) C_{6-10} aryl (e.g., phenyl), and

(4) heterocyclic group (e.g., 3-pyrrolidinyl, 4-piperidyl, S-oxido-tetrahydrothiopyran-4-yl) optionally having one substituent selected from

(1') C_{1-6} alkyl (e.g., methyl) optionally having 1 or 2 substituents selected from

(a) C_{6-10} aryl (e.g., phenyl), and

(b) hydroxy,

(2') C_{1-6} alkyl-carbonyl (e.g., methylcarbonyl) optionally having one substituent selected from

(a) C_{1-6} alkyl-carbonyloxy (e.g., methylcarbonyloxy), and

(b) hydroxy,

(3') C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), and

(4') 5- or 6-membered aromatic heterocyclic group (e.g., 4-pyridyl), or

(B) 5- to 7-membered cyclic carbamoyl (e.g., 1-pyrrolidinylcarbonyl, 1-piperidylcarbonyl, 1-homopiperazinylcarbonyl) optionally having one substituent selected from

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one

substituent selected from

(a) heterocyclic group (e.g., 1-pyrrolidinyl, benzodioxol-5-yl), and

(b) amino,

(2) amino,

(3) N-C_{1-6} alkyl-N-(C_{1-6} alkyl-carbonyl)amino (e.g., N-acetyl-N-ethylamino),

(4) heterocyclic group (e.g., 1-pyrrolidinyl), and

(5) C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl) optionally having one substituent selected from

(a) hydroxy,

(b) C_{1-6} alkoxy (e.g., methoxy),

(c) amino, and

(d) C_{1-6} alkylamino (e.g., isopropylamino);

R^3 is hydroxy optionally having

(1) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl, n-propyl, i-propyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)

[preferably, hydroxyl substituted by

(1) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one C_{1-6} alkoxy (e.g., ethoxy), or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having 1 to 3 halogen atoms (e.g., fluorine atom)];

R^4 is

(1) hydrogen atom, or

(2) C_{1-6} alkyl (e.g., methyl, ethyl) optionally having one substituent selected from

(1') C_{3-6} cycloalkyl (e.g., cyclopropyl),

(2') C_{6-10} aryl (e.g., phenyl) optionally having (i) 1 or 2 C_{1-6} alkoxy (e.g., methoxy) or (ii) 1 to 3 halogen atoms (e.g., chlorine atom),

(3') C_{1-6} alkyl-carbonyl (e.g., tert-butylcarbonyl),

(4') C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally having one halogen atom (e.g., chlorine atom) or C_{1-6} alkoxy (e.g.,

methoxy),

(5') C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),

(6') C_{6-10} aryl-carbamoyl (e.g., phenylcarbamoyl),

(7') heterocyclic group (e.g., 2-pyridyl),

(8') C_{6-10} aryloxy (e.g., phenoxy), and

(9') carboxy;

R^{A1} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl, ethyl, n-propyl); and

R^{A2} is a hydrogen atom or a C_{1-6} alkyl group (e.g., methyl).

[0070]

[Compound (I"-3)]

3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

or a salt thereof.

[0071]

When compound (I) is a salt, examples of such salt include metal salt, ammonium salt, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like. Preferable examples of the metal salt include alkali metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like. Preferable examples of the salt with organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with inorganic acid include a

salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like. Preferable examples of the salt with basic amino acid include a salt with arginine, lysine, ornithine and the like, and preferable examples of the salt with acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, an inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt etc., and when a compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or a salt 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.

[0072]

The production method of the compound of the present invention is described in the following.

In each of the following production methods, when alkylation reaction, amidation reaction (condensation reaction), esterification reaction, reduction reaction, reductive amination reaction, amination reaction, halogenation reaction, oxidation reaction and the like are performed, these reactions are performed according to known methods. Examples of such methods include the methods described in Organic Functional Group Preparations, 2nd edition, Academic Press,

Inc. (1989), Comprehensive Organic Transformations, VCH Publishers Inc. (1989) and the like, and the like. Protection and deprotection reactions are performed according to known methods, for example, the methods described in Protective Groups in Organic Synthesis, 3rd edition, John Wiley and Sons, Inc. (1999) or a method analogous thereto.

[0073]

The solvents indicated in generic terms, which are used in the following reactions are explained in the following.

Examples of the "alcohols" include methanol, ethanol, 1-propanol, 2-propanol, tert-butyl alcohol and the like.

Examples of the "ethers" include diethyl ether, diisopropyl ether, diphenyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like.

Examples of the "esters" include ethyl acetate, methyl acetate, tert-butyl acetate and the like.

Examples of the "hydrocarbons" include benzene, toluene, xylene, cyclohexane, hexane, pentane and the like.

Examples of the "amides" include N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide and the like.

Examples of the "halogenated hydrocarbons" include dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, tetrachloroethylene, chlorobenzene and the like.

Examples of the "nitriles" include acetonitrile, propionitrile and the like.

Examples of the "ketones" include acetone, 2-butanone and the like.

Examples of the "organic acids" include formic acid, acetic acid, propionic acid, trifluoroacetic acid, methanesulfonic acid and the like.

Examples of the "aromatic amines" include pyridine, 2,6-lutidine, quinoline and the like.

Examples of the "sulfoxides" include dimethyl sulfoxide

and the like.

In the present production methods, a starting material compound and a production intermediate may be salts. As such salt, those similar to the salts of the aforementioned compound (I) can be mentioned.

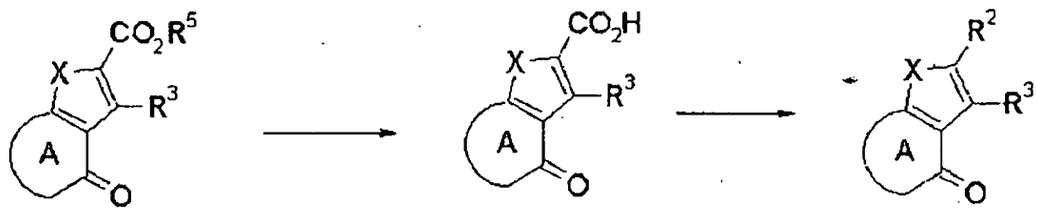
[0074]

Compound (I) can be produced, for example, by [Method A] shown below or a method analogous thereto.

[Method A]

Compound (III) is hydrolyzed and the obtained compound (II) is condensed with amine, whereby compound (I) can be produced.

[0075]



(III) (II) (I)

[0076]

wherein R^5 is C_{1-6} alkyl or benzyl, and other symbols are as defined above.

Examples of C_{1-6} alkyl for R^5 include methyl, ethyl and the like, preferably ethyl.

Compound (III) can be produced according to the production methods of compound (IIIa) and compound (IIIb) shown below.

Compound (III) can be converted to compound (II) by hydrolysis under acidic or basic conditions in a solvent that does not adversely influence the reaction. Particularly, when R^5 is benzyl, a catalytic hydrogenation reaction in a solvent that does not adversely influence the reaction can be used.

As the acid used for hydrolysis, hydrochloric acid, sulfuric acid and the like can be mentioned, and as the base, sodium hydroxide, potassium hydroxide, lithium hydroxide and

the like can be mentioned. The amount thereof is generally 1 to 20 molar equivalent, preferably 1 to 10 molar equivalents, per 1 mol of compound (III).

Examples of the catalyst used for the catalytic hydrogenation reaction include Raney-nickel, platinum oxide, or palladium, ruthenium, rhodium, iridium and the like on activated carbon, barium sulfate, calcium carbonate and the like. The amount thereof is generally 0.01 to 1 molar equivalent, preferably 0.05 to 0.5 molar equivalent, per 1 mol of compound (III).

As the hydrogen source, hydrogen, cyclohexene, hydrazine, ammonium formate and the like are used.

Examples of the solvent that does not adversely influence the reaction include ethers, alcohols, hydrocarbons, ketones, nitriles, amides, esters, water and the like, with preference given to alcohols, ethers and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0077]

The condensation reaction of compound (II) and amine can be performed in a solvent that does not adversely influence the reaction and using, for example, a condensation agent.

The amine to be used in this reaction can be condensed with carboxy group of compound (II) to form a "carbamoyl optionally having substituent(s)" for R^2. Such amine may be a commercially available one, or can be produced from the corresponding starting material compound by a method known *per se*.

Examples of the condensation agent include carbodiimide (e.g., dicyclohexylcarbodiimide (DCCD), water-soluble carbodiimide (WSCD) and the like), phosphate ester (e.g.,

diethyl cyanophosphonate, diethyl chlorophosphonate, diphenyl phosphoroazide and the like), BOP reagent (1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbonyldiimidazole and the like, with preference given to WSCD.

The amount of each of the amine and condensation agent to be used is generally 1 to 10 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (II).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, ketones, nitriles, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

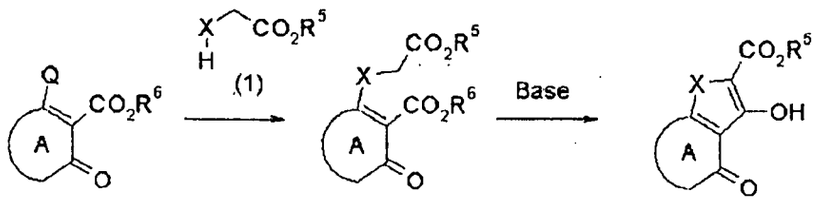
[0078]

In compounds (III), compound (IIIa) wherein R^3 is hydroxy can be produced, for example, [Method B] shown below or a method analogous thereto.

[Method B]

Compound (V) is reacted with compound (1) and the obtained compound (IV) is treated with a base to give compound (IIIa).

[0079]



(V) (IV) (IIIa)

[0080]

wherein Q is a leaving group, R^6 is C_{1-6} alkyl, and other symbols are as defined above.

Examples of the leaving group for Q include halogen atom (e.g., chlorine, bromine, iodine), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), C_{6-10} arylsulfonyloxy optionally having C_{1-6} alkyl (e.g., benzenesulfonyloxy, 4-toluenesulfonyloxy), methylmercapto, methanesulfonyl and the like, with preference given to halogen atom.

Examples of the C_{1-6} alkyl for R^6 include methyl, ethyl and the like.

Compound (V) can be produced according to the production methods of compound (Va) and compound (Va-2) shown below.

The reaction of compound (V) and compound (1) can be performed in the presence of a base as necessary and in a solvent that does not adversely influence the reaction.

Compound (1) may be a commercially available one, or can be produced from the corresponding starting material compound by a method known *per se*.

The amount of compound (1) to be used is generally 1 to 20 molar equivalents, preferably 1 to 10 molar equivalents, per 1 mol of compound (V). Examples of the base to be used as necessary include sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like. The amount thereof to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (V).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0081]

Compound (IV) can be converted to compound (IIIa) using a base in a solvent that does not adversely influence the reaction.

Examples of the base include sodium methoxide, sodium ethoxide, sodium hydroxide, triethylamine and the like and the amount thereof to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (IV).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (V) can be directly converted to compound (IIIa) without isolating compound (IV).

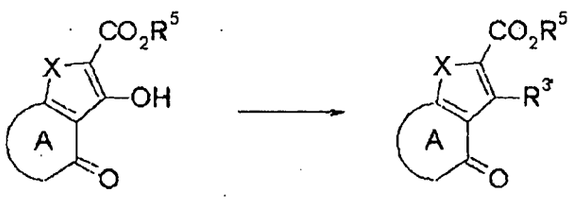
[0082]

In compound (III), compound (IIIb) wherein R^3 is alkoxy optionally having substituent(s) can be produced, for example, by [Method C] shown below or a method analogous thereto.

[Method C]

Compound (IIIa) is reacted with halogenated alkyl, sulfate ester, methanesulfonate ester optionally substituted by halogen atom(s) and the like to give compound (IIIb).

[0083]



(IIIa) (IIIb)

[0084]

wherein $R^{3'}$ is alkoxy optionally having substituent(s), and other symbols are as defined above.

The "alkoxy optionally having substituent(s)" for $R^{3'}$ means "hydroxy substituted by alkyl optionally having substituent(s)" encompassed in the "hydroxy optionally having substituent(s)" for R^3.

The reaction between compound (IIIa) and halogenated alkyl, sulfate ester, methanesulfonate ester optionally substituted by halogen atom(s) and the like can be performed in the presence of a base in a solvent that does not adversely influence the reaction.

The halogenated alkyl, sulfate ester and methanesulfonate ester optionally substituted by halogen atom(s) used in this reaction can alkylate the hydroxyl group of compound (IIIa) to form "alkoxy optionally having substituent(s)" for $R^{3'}$. Such halogenated alkyl, sulfate ester, sulfate ester and methanesulfonate ester optionally substituted by halogen atom(s) may be commercially available ones, or can be produced from the corresponding starting material compound by a method known *per se*.

The amount of halogenated alkyl and the like to be used is generally 1 to 3 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (IIIa). Examples of the base to be used include sodium methoxide, sodium ethoxide, cesium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like, and the amount thereof to be used is generally 1 to 5 molar equivalents, preferably 1 to 3 molar equivalents, per 1 mol of compound (IIIa).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned

solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 20 to 90°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

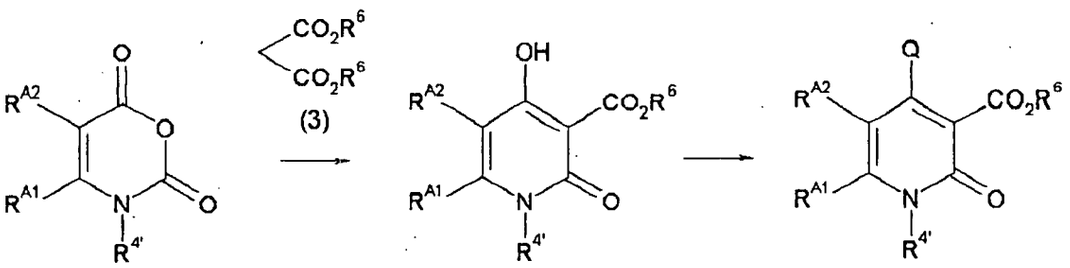
[0085]

Of compounds (V), 2-oxonicotinate ester (Va) wherein ring A is pyridine ring or fused pyridine ring can be produced, for example, by [Method D] shown below or a method analogous thereto.

[Method D]

Compound (VII) is reacted with malonate ester (3) and hydroxy of the obtained compound (VI) is converted to a leaving group Q to give compound (Va).

[0086]



(VII) (VI) (Va)

[0087]

wherein $R^{4'}$ is hydrocarbon group optionally having substituent(s), and other symbols are as defined above.

As the "hydrocarbon group optionally having substituent(s)" for $R^{4'}$, those similar to the "hydrocarbon group optionally having substituent(s)" for R^4 can be mentioned.

[0088]

The reaction of compound (VII) and malonate ester (3) can be performed in the presence of a base in a solvent that does not adversely influence the reaction.

Malonate ester (3) may be a commercially available one, or can be produced from the corresponding starting material compound by a method known *per se*.

The amount of malonate ester (3) to be used is generally 1 to 2 molar equivalents, preferably 1 to 1.5 molar equivalents, per 1 mol of compound (VII). Examples of the base to be used include sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, DBU and the like and the amount thereof to be used is generally 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (VII).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, ketones, nitriles, amides and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 100°C, preferably 0 to 80°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0089]

Conversion of hydroxy of compound (VI) to leaving group Q can be performed by, for example, using a halogenating reagent and a sulfonylation reagent in a solvent that does not adversely influence the reaction or without solvent and in the presence of a base as necessary.

Examples of the halogenating reagent include thionyl chloride, phosphoryl chloride, phosphorus pentachloride, phosphorus tribromide and the like.

The amount of the halogenating reagent to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (VI).

The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Examples of the sulfonylation reagent include

trifluoromethanesulfonic acid anhydride, methanesulfonyl halide, benzenesulfonyl halide and the like and the amount thereof to be used is generally 1 to 2 molar equivalents, preferably 1 to 1.5 molar equivalents, per 1 mol of compound (VI). Examples of the base to be used as necessary include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (VI).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides, esters and the like, with preference given to ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -10 to 100°C, preferably 0 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

Compound (VII) to be the starting material in [Method D] can be synthesized by a known method, for example, the method described in Journal of Heterocyclic Chemistry, vol. 12, pages 565-572 (1975).

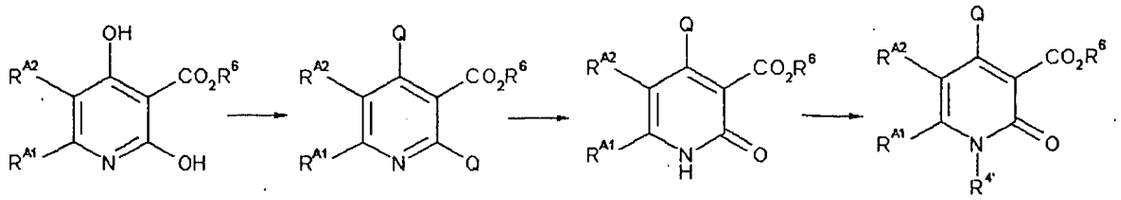
[0090]

Also, compound (Va) can be produced, for example, by [Method E] shown below or a method analogous thereto.

[Method E]

The hydroxy of compound (VIII-2) is converted to leaving group Q, and the obtained compound (VIII) is hydrolyzed to give compound (Va-2). This compound (Va-2) is reacted with halogenated hydrocarbon and the like to give compound (Va).

[0091]



(VIII-2) (VIII) (Va-2) (Va)

[0092]

wherein each symbol is as defined above.

Compound (VIII) can be produced according to the synthesis method of compound (Va) in the aforementioned [Method D]. The amount of the halogenating reagent and the sulfonylation reagent to be used can be increased as necessary.

[0093]

Hydrolysis of compound (VIII) can be performed, for example, after once substituting leaving group Q with acetoxy or alkoxy or directly under alkaline conditions or acidic conditions, in a solvent that does not adversely influence the reaction.

When the leaving group Q is once substituted with acetoxy or alkoxy, for example, sodium acetate, sodium methoxide, sodium ethoxide and the like can be used and the amount thereof to be used is generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (VIII).

For direct hydrolysis under acidic conditions, for example, acetic acid, hydrochloric acid, sulfuric acid, methanesulfonic acid and the like can be used as an acid.

For direct hydrolysis under alkaline conditions, for example, aqueous sodium hydroxide solution, aqueous potassium hydroxide solution, aqueous lithium hydroxide solution and the like can be used as a base.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate

ratio.

The reaction temperature is generally 0 to 130°C, preferably 20 to 130°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0094]

Compound (Va-2) can be converted to compound (Va) by reacting compound (Va-2) with a compound represented by the formula $R^{4'}$-Q' wherein $R^{4'}$ is as defined above and Q' is a leaving group, in a solvent that does not adversely influence the reaction or without solvent in the presence of a base as necessary.

Examples of the leaving group for Q' include halogen atom (e.g., chlorine, bromine, iodine), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, trifluoromethylsulfonyloxy), C_{6-10} arylsulfonyloxy optionally having C_{1-6} alkyl (e.g., benzenesulfonyloxy, 4-toluenesulfonyloxy), methylmercapto, methanesulfonyl and the like, with preference given to halogen atom.

The amount of the compound represented by the formula $R^{4'}$-Q' to be used is generally 1 to 20 molar equivalents, preferably 2 to 10 molar equivalents, per 1 mol of compound (Va-2).

Examples of the base to be used as necessary include triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, sodium hydride, potassium carbonate, cesium carbonate, potassium tert-butoxide, sodium tert-butoxide and the like, with preference given to sodium tert-butoxide, and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (Va-2).

Preferably, tetrabutylammonium bromide or the like is added to the reaction.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, amides,

esters and the like, preferably ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -10 to 100°C, preferably 0 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 48 hr.

[0095]

Compound (VIII-2) to be the starting material in [Method E] can be synthesized by a known method, for example, the method described in Journal of Organic Chemistry, vol. 46, pages 3040-3048 (1981).

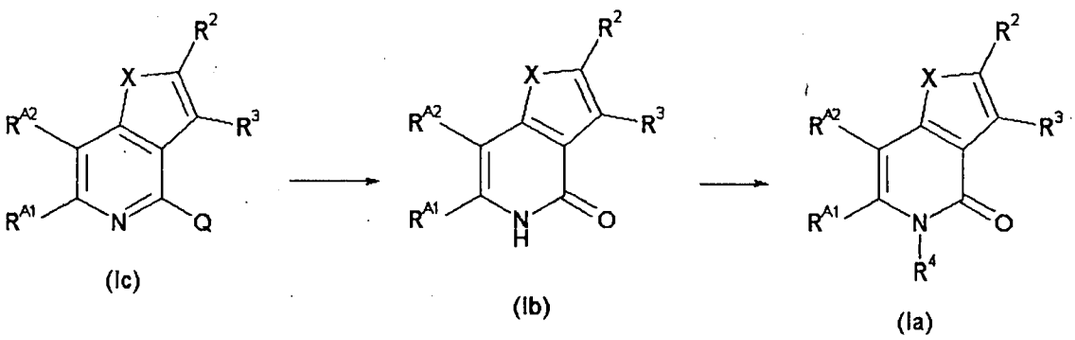
[0096]

In compounds (I), compound (Ia) and compound (Ib) can be produced, for example, [Method F] shown below or a method analogous thereto.

[Method F]

Compound (Ib) and compound (Ia) can be produced from compound (Ic) by reactions according to [Method E].

[0097]



[0098]

wherein each symbol is as defined above.

The reaction from compound (Ic) to compound (Ib) can be performed according to the reaction from compound (VIII) to compound (Va-2) in [Method E].

The reaction from compound (Ib) to compound (Ia) can be performed according to the reaction from compound (Va-2) to compound (Va) in [Method E].

Compound (Ic) can be produced according to the production method of compound (Ica) and compound (Icb) shown below.

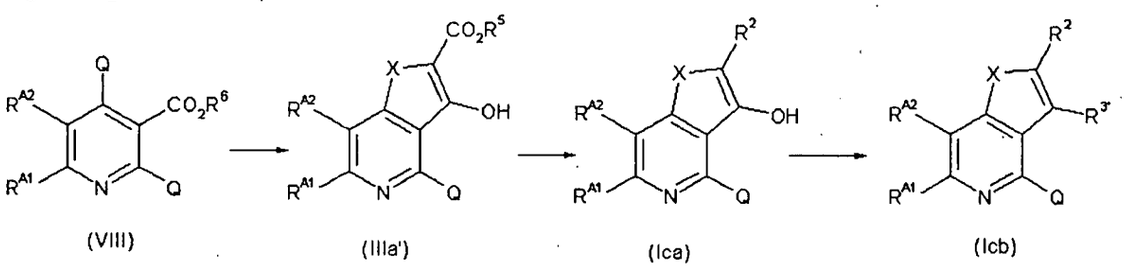
[0099]

In compounds (Ic), compound (Ica) wherein R^3 is hydroxy and compound (Icb) wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Icb)) can be produced, for example, by [Method G] shown below or a method analogous thereto.

[Method G]

Compound (Ica) and compound (Icb) can be produced from compound (VIII) by reactions according to [Method A], [Method B] and [Method C].

[0100]



[0101]

wherein each symbol is as defined above.

The reaction from compound (VIII) to compound (IIIa') can be performed according to [Method B].

The reaction from compound (IIIa') to compound (Ica) can be performed according to [Method A].

The reaction from compound (Ica) to compound (Icb) can be performed according to [Method C].

[0102]

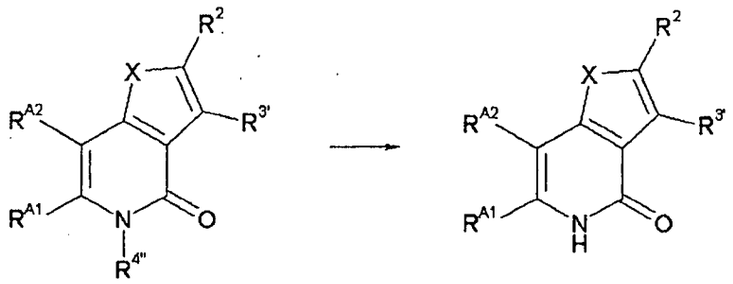
Also, compound (Ib) can be produced, for example, [Method H] shown below or a method analogous thereto.

[Method H]

Of compounds (Ib), compound (Ib') wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Ib')) can be produced by removing $R^{4''}$ from compound (Id) wherein R^3 is alkoxy optionally having substituent(s) (shown by $R^{3'}$ in the following formula (Id)) and R^4 is phenacyl

optionally having substituent(s), methoxymethyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl (shown by $R^{4''}$ in the following formula (Id)) from among compounds (Ia).

[0103]



(Id) (Ib')

[0104]

wherein $R^{4''}$ is phenacyl optionally having substituent(s), methoxymethyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, and other symbols are as defined above.

[0105]

When $R^{4''}$ is phenacyl optionally having substituent(s), conversion of compound (Id) to compound (Ib') can be performed, for example, in the presence of metal such as zinc and the like under acidic conditions in a solvent that does not adversely influence the reaction. The amount of zinc to be used is generally 1 to 20 molar equivalents, preferably 1 to 10 molar equivalents, per 1 mol of compound (Id). As acid, hydrochloric acid, sulfuric acid and the like are used.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 20 to 120°C, preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0106]

When $R^{4''}$ is methoxymethyl, conversion of compound (Id) to compound (Ib') can be performed under acidic conditions in a solvent that does not adversely influence the reaction. As acid, hydrochloric acid, sulfuric acid and the like can be used.

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0107]

When $R^{4''}$ is 4-methoxybenzyl, conversion of compound (Id) to compound (Ib') can be performed under strong acidic conditions in a solvent that does not adversely influence the reaction. As acid, trifluoroacetic acid, trifluoromethanesulfonic acid and the like can be used. In this case, anisole can be used as a cation scavenger in an amount of generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (Id).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, and the like, preferably ethers and amides. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0108]

When $R^{4''}$ is 2,4-dimethoxybenzyl, conversion of compound

(Id) to compound (Ib') can be performed in the presence of an oxidant such as cerium (IV) diammonium nitrate (CAN), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the like in a solvent that does not adversely influence the reaction.

The amount of the oxidant to be used is generally 1 to 20 molar equivalents, preferably 1 to 5 molar equivalents, per 1 mol of compound (Id).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, nitriles, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 20 to 60°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

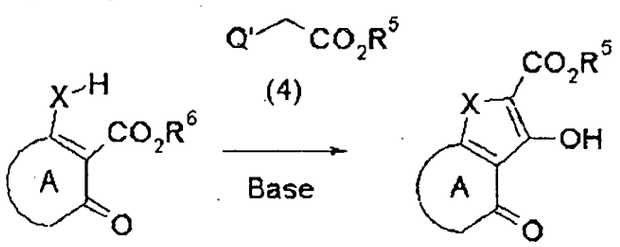
[0109]

Also, compound (IIIa) can be produced, for example, by [Method I] shown below or a method analogous thereto.

[Method I]

Compound (Vb) is reacted with compound (4) to give compound (IIIa).

[0110]



(Vb) (IIIa)

[0111]

wherein Q' is a leaving group, and other symbols are as defined above.

Examples of the leaving group for Q' include those similar to the leaving group for the aforementioned Q, with

preference given to halogen atom.

Compound (4) may be a commercially available reagent, or can be synthesized by a method known *per se*.

Compound (Vb), for example, 6-amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivative and the like, to be the starting material in [Method I] can be synthesized by a known method, for example, the method described in Journal of Chemical Society of Japan, vol. 46, pages 3849-3853 (1973). For example, 2-mercapto-4-oxo-1,4-dihydroquinoline-3-carboxylate derivative and the like can be synthesized by a known method, for example, the method described in Journal of Heterocyclic Chemistry, vol. 27, pages 839-843 (1990).

The reaction between compound (Vb) and compound (4) can be performed in the presence of a base in a solvent that does not adversely influence the reaction.

The amount of compound (4) to be used is generally 1 to 3 molar equivalents, preferably 1 to 2 molar equivalents, per 1 mol of compound (Vb). Examples of the base include sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine and the like and the amount thereof to be used is generally 2 to 5 molar equivalents, preferably 2 to 3 molar equivalents, per 1 mol of compound (Vb).

Examples of the solvent that does not adversely influence the reaction include ethers, hydrocarbons, alcohols, ketones, nitriles, amides, water and the like, with preference given to ethers, amides and water. Two or more kinds of the above-mentioned solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 20 to 120°C, preferably 20 to 100°C.

The reaction time is generally 0.5 to 100 hr, preferably 1 to 24 hr.

[0112]

A compound within the scope of the present invention can also be produced by applying a means known *per se* to compound (I) 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 by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination of nitro by reduction, alkylation of hydroxy, substitution and amination of hydroxy 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 also be produced.

In the above-mentioned production method, when the starting compound or the compound of the present invention has an amino group, a carboxyl group, a hydroxy group or a mercapto group as a substituent, a protecting group generally used in peptide chemistry and the like may be introduced into these groups. The protecting group can be removed according to a conventional method in any step in each scheme.

[0113]

Compound (I) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compound (I) is obtained as a free compound, it can be converted to a desired salt by a method known *per se* or a method analogous

thereto. Conversely, when the compound is obtained as a salt, it can be converted to a free form or other desired salt by a method known *per se* or a method analogous thereto.

[0114]

Compound (I) may be used as a prodrug. A prodrug of compound (I) means a compound converted to compound (I) by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound converted to compound (I) by oxidation, reduction, hydrolysis, etc. due to an enzyme, a compound converted to compound (I) by hydrolysis etc. due to gastric acid, and the like.

[0115]

A prodrug of compound (I) may be a compound obtained by subjecting an amino in compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino in compound (I) to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting hydroxy in compound (I) to acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting hydroxy in the compound (I) of the present invention to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound obtained by subjecting carboxy in compound (I) to esterification or amidation (e.g., a compound obtained by subjecting carboxy in compound (I) to 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 compound (I) by a method known *per se*.

[0116]

A prodrug of compound (I) may also be a compound converted into compound (I) under physiological conditions, such as those described in IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

[0117]

When compound (I) has an isomer such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, any isomer and a mixture thereof are encompassed in compound (I). For example, when compound (I) has an optical isomer, an optical isomer resolved from a racemate is also encompassed in compound (I). Such 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*.

[0118]

Compound (I) may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I). Crystals can be produced by crystallization according to crystallization methods known *per se*.

Compound (I) may also be a cocrystal.

Compound (I) may be a hydrate, a non-hydrate, a solvate or a non-solvate, both of which are encompassed in compound (I) and the like.

A compound labeled with an isotope (e.g., ^{2}H, ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.) is also encompassed in compound (I).

[0119]

Compound (I) of the present invention, or a salt thereof, or a prodrug thereof (sometimes to be abbreviated as "the compound of the present invention" in the present specification) interacts, for example, with human Smo protein and changes the steric structure thereof, whereby formation of

a complex with a protein involved in the signal transduction in the cytoplasm is inhibited and the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with human Smo protein and directly inhibits formation of a complex of human Smo protein with a protein involved in the Hedgehog signal transduction system in the cytoplasm, whereby the Hedgehog signal transduction system is inhibited. Alternatively, the compound of the present invention interacts with a site of an Smo protein, for example, phosphorylation site and the like, which is modified by a protein involved in the Hedgehog signal transduction system, whereby modification such as phosphorylation of Smo and the like is inhibited and the Hedgehog signal transduction system is inhibited.

Inhibition of the Hedgehog signal transduction system can be measured, for example, by quantifying a decrease in the expression level of a reporter gene connected to the downstream of the Gli binding site based on the fluorescence intensity according to Experimental Example 1. Alternatively, it can be measured by quantifying the expression of Gli-1 mRNA in a cell extract by quantitative PCR method and the like. A compound that inhibits Hedgehog signal targets Smo, which can be confirmed, for example, by binding fluorescence-labeled Cyclopamine and a test compound to cells expressing Smo, measuring the fluorescence level of the cell, and comparing the value with that without addition of a test compound to find a decrease.

[0120]

Accordingly, the compound of the present invention is useful as an Smo inhibitor for mammals (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human, etc.). The compound of the present invention is used as a pharmaceutical agent such as an agent for the prophylaxis or treatment of diseases possibly influenced by Smo, for example, cancer [e.g., colorectal cancer (e.g., colon cancer, rectal

cancer, anal cancer, familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor, etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, pancreatic endocrine tumor, etc.), pharyngeal cancer, laryngeal cancer, esophageal cancer, gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous cancer, etc.), duodenal cancer, small intestinal cancer, breast cancer (e.g., invasive ductal breast carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), ovarian cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor, etc.), testicular tumor, prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, etc.), liver cancer (e.g., hepatocellular carcinoma, primary liver cancer, extrahepatic bile duct cancer, etc.), thyroid cancer (e.g., medullary thyroid cancer, etc.), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter transitional cell cancer, etc.), uterus cancer (e.g., cervical cancer, cancer of uterine body, uterine sarcoma, etc.), brain tumor (e.g., medulloblastoma, glioma, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, pituitary adenoma, etc.), retinoblastoma, skin cancer (e.g., basal cell carcinoma, malignant melanoma, etc.), sarcoma (e.g., rhabdomyosarcoma, leiomyosarcoma, soft tissue sarcoma, etc.), malignant bone tumor, urinary bladder cancer, blood cancer (e.g., multiple myeloma, leukemia, malignant lymphoma, Hodgkin's disease, chronic myeloproliferative disorder, etc.), cancer unknown primary etc.], a cancer growth inhibitor, a cancer metastasis inhibitor, an apoptosis promoter and the like. Among these, the compound of the present invention is effective, for example, for brain tumor, skin cancer, lung cancer, pancreatic cancer, cancer of the bile duct, prostate cancer, esophagus cancer, gastric cancer, colorectal cancer,

sarcoma and breast cancer. Especially, the compound of the present invention is effective for glioma, medulloblastoma, basal cell tumor, small cell lung cancer, pancreatic cancer, cancer of the bile duct, prostate cancer, esophagus cancer, gastric cancer, colorectal cancer, rhabdomyosarcoma and breast cancer.

[0121]

The compound of the present invention can be administered orally or parenterally as it is or in a mixture with a pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining the compound with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

[0122]

As a method for producing the compound of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier and the like, generally used in the pharmaceutical field, are appropriately added as necessary for production.

[0123]

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like,

and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

[0124]

Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, microcrystalline cellulose, powdered glycyrrhiza, mannitol, sodium hydrogen carbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

[0125]

Furthermore, when the compound of the present invention is produced in the above-mentioned dosage form, a suitable amount

of a colorant, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

[0126]

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

[0127]

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable solubilizing agents, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with solubilizing agents such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like can be blended. A prepared injection is generally filled in an ampoule.

[0128]

While the content of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire

preparation.

[0129]

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

[0130]

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 1 to 1000 mg, preferably about 3 to 300 mg, more preferably about 10 to 200 mg, as an active ingredient (the compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

[0131]

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

[0132]

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors

and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

[0133]

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), 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, epristeride, and the like), aderenal cortex hormone 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), thyroid hormone, and DDS (Drug Delivery System) preparations thereof, and the like.

[0134]

Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

[0135]

Examples of the "alkylating agents" include 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, DDS (Drug Delivery System) preparations thereof, and the like.

[0136]

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emitefur, capecitabine, and the like), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, calcium folinate, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine, DDS preparations thereof, and the like.

[0137]

Examples of the "anticancer antibiotics" include 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, DDS preparations thereof, and the like.

[0138]

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, DDS preparations thereof, and the like.

[0139]

Examples of the "immunotherapeutic agents (BRM)" include 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, anti-CTLA4 antibody, and the like.

[0140]

Example of the "cell growth factors" in the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight 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 EGF [e.g., TGFα, and the like], (2) insulin or substances possessing substantially the same activity as insulin [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 FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], and (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), heregulin, angiopoietin, and the like].

[0141]

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned cell growth factors, including EGF receptor, heregulin receptor (HER3, etc.), insulin receptor, IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin

receptor (Tie2 etc.), PDGF receptor, and the like.

[0142]

As the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGFα inhibitor, heregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor inhibitor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK(MEK1/2) inhibitor, MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor and the like are used. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, anti-HGF antibody, Imatinib mesylate, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide

(VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901), Everolimus (RAD001) and the like are used.

[0143]

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), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor, and the like), α-blockers (e.g., tamsulosin hydrochloride, and the like), bisphosphonic acids (e.g., pamidronate, zoledronate, and the like), thalidomide, 5-azacytidine, decitabine, proteasome inhibitor (e.g., bortezomib, and the like), antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

[0144]

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration of the compound of the present invention or a concomitant drug,

(2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like),

(3) the period of treatment can be set longer,

(4) a sustained treatment effect can be designed,

(5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

[0145]

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

For use of the combination agent of the present invention, 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 an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the dose clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

[0146]

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug 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 then 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 at 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 (e.g., the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is appropriately determined in accordance with its clinical dose, and the ratio of the compound of the present invention and the concomitant drug is appropriately determined depending on the administration subject, administration route, target disease, symptom, combination, and the like. For example, when the administration subject is human, the concomitant drug is used in 0.01 to 100 (parts by weight), relative to 1 part by weight of the compound of the present invention.

[0147]

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous, and the like). An injection can be administered by intravenous, intramuscular, subcutaneous or intra-organ administration, or directly to the lesion.

[0148]

As a pharmacologically acceptable carrier which may be used for preparing the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present

invention, such as preservatives, antioxidants, colorants, sweetening agents, adsorbents, wetting agents and the like can also be appropriately used in appropriate amounts.

[0149]

The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the entire preparation.

The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the entire preparation.

The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the entire preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

[0150]

These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate,

hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH adjuster (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl paraoxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a solubilizing agent such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

[0151]

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like may be added to the compound of the present invention or the concomitant drug, and the mixture can be compression-molded, according to a method known *per se* then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate,

hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

[0152]

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acid [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

[0153]

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known *per se*, for example, a method shown in the following [2].

[0154]

The compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned

drug form depending on the kind of the drug.

[0155]

[1] An injection of the compound of the present invention or the concomitant drug, and preparation thereof, [2] a sustained release preparation or immediate-release preparation of the compound of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual, buccal or intraoral quick integrating agent of the compound of the present invention or the concomitant drug, and preparation thereof, will be described below specifically.

[0156]

[1] Injection and preparation thereof

An injection prepared by dissolving the compound of the present invention or the concomitant drug into water is preferable. This injection may be allowed to contain a benzoate and/or salicylate.

The injection is obtained by dissolving the compound of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, into water.

[0157]

As the above-mentioned salts of benzoic acid and salicylic acid, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, meglumine salts, salts with organic bases such as tromethamol and the like, etc. are listed.

[0158]

The concentration of the compound of the present invention or the concomitant drug in an injection is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%. The concentration of a benzoate or/and salicylate is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%.

[0159]

The injection of the present invention appropriately contains additives usually used in an injection, for example,

a stabilizer (e.g., ascorbic acid, sodium pyrosulfite and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride and the like), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin), a pH regulator (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl parahydroxybenzoate, benzoic acid and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a solubilizing agent (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like. These additives are generally blended in a proportion usually used in an injection.

[0160]

It is advantageous that pH of an injection be controlled from pH 2 to 12, preferably from pH 2.5 to 8.0, by addition of a pH regulator.

An injection is obtained by dissolving the compound of the present invention or the concomitant drug and if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives into water. These may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional method of producing an injection.

[0161]

An aqueous solution for injection may be advantageously heated, alternatively, for example, filter sterilization, high pressure heat sterilization and the like can be conducted in the same manner as for a usual injection, to provide an injection.

It may be advantageous that an aqueous solution for injection is subjected to high pressure heat sterilization at 100 to 121°C for 5 to 30 min.

Further, a preparation endowed with an antibacterial property of a solution may also be produced so that it can be used as a preparation which is divided and administered multiple-times.

[0162]

[2] Sustained release preparation or immediate-release preparation, and preparation thereof

A sustained release preparation is preferable which is obtained, if desirable, by coating a nucleus containing the compound of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, swellable polymer and the like. For example, a sustained release preparation for oral administration of once administration per day type is preferable.

[0163]

As the water-insoluble substance used in a film agent, there are listed, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like, polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudoragit (manufactured by Rohm Pharma) such as Eudoragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/trimethylchloride methacrylate/ethyl ammonium copolymer), Eudoragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), and the like, hydrogenated oils such as hydrogenated castor oil (e.g., Lubri wax (manufactured by Freund Corporation) and the like), waxes such as carnauba wax,

fatty acid glycerin ester, paraffin and the like, polyglycerin fatty acid esters, and the like.

[0164]

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swell are preferable, and polymers having an acidic dissociating group, which manifest small swelling in acidic regions such as in stomach and large swelling in neutral regions such as in small intestine and large intestine, are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swell, cross-linkable polyacrylic acid polymers such as, for example, Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all of which are manufactured by BF Goodrich), Hiviswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Industries, Ltd.), and the like, are listed.

[0165]

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having a hydroxyalkyl or carboxyalkyl such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like can be mentioned.

[0166]

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to about 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in

which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to about 40% (w/w), further preferably from about 5 to about 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like) from a film agent solution.

[0167]

The sustained release preparation is produced by preparing a nucleus containing a drugs as exemplified below, then, coating the resulted nucleus with a film agent solution prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

[0168]

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably, the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to about 2000 μm, further preferably, from about 500 to about 1400 μm.

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binding agent, disintegrating agent, lubricant, stabilizer and the like are mixed with a drug, and the mixture is subjected to a wet extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

[0169]

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline cellulose, corn starch are preferable.

[0170]

As the binding agent, for example, polyvinyl alcohol, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the like are used. As the disintegrating agent, for example, carboxymethylcellulose calcium (ECG505), croscarmelose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low substituted hydroxypropylcellulose (L-HPC) and the like are used. Among them, hydroxypropylcellulose, polyvinylpyrrolidone, lower substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

[0171]

A nucleus can also be prepared by, in addition to the above-mentioned productions method, for example, a rolling granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like) and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size thereof is preferably from about 100 μm to about 1500 μm.

[0172]

For separating a drug contained in a nucleus and a film agent, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent, preferably polyethylene glycol, and polysaccharides having a hydroxyalkyl or carboxyalkyl are used, more preferably, hydroxypropylmethylcellulose and hydroxypropylcellulose are used. The protective agent may contain, as stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

[0173]

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be coated by spray-coating the nucleus, for example, by a fluidized bed coating method, pan coating method and the like.

[0174]

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are listed.

The composition ratio of a water-insoluble substance, swellable polymer or hydrophilic substance in a film agent solution is appropriately selected so that the contents of

these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w), further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

[0175]

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform, methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into a film agent solution for stabilizing the film agent solution.

[0176]

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by coating a film agent solution onto a nucleus by a fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hydrogenated castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol and the like may also be added as a

plasticizer.

[0177]

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

The immediate-release preparation may be liquid (solution, suspension, emulsion and the like) or solid (particle, pill, tablet and the like). As the immediate-release preparation, oral administration agents and parenteral administration agents such as an injection and the like are used, and oral administration agents are preferable.

[0178]

The immediate-release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the pharmaceutical field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, and the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are listed, and preferably, corn starch and mannitol and the like are listed. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4 w/w%, preferably from about 20 to about 98.5 w/w%, further preferably from about 30 to about 97 w/w%, based on the total amount of the immediate-release preparation.

[0179]

The content of a drug in the immediate-release preparation can be appropriately selected in the range from about 0.5 to about 95w/w%, preferably from about 1 to about 60w/w% based on the total amount of the immediate-release preparation.

[0180]

When the immediate-release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also an integrating agent. As this integrating agent, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), croscarmelose sodium (e.g., Actisol, manufactured by Asahi Kasei Corporation), crospovidone (e.g., Kollidon CL, manufactured by BASF), low substituted hydroxypropylcellulose (manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (manufactured by Matsutani Kagaku K.K.), carboxymethylstarch sodium (Exprotab, manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Kasei Corporation), and the like are used, and for example, those which disintegrate a granule by absorbing water in contact with water, causing swelling, or making a channel between an effective ingredient and an excipient constituting the nucleus, can be used. These disintegrating agents can be used alone or in combination of two or more. The amount of the disintegrating agent used is appropriately selected depending on the kind and blending amount of a drug used, design of releasing property, and the like, and for example, from about 0.05 to about 30 w/w%, preferably from about 0.5 to about 15 w/w%, based on the total amount of the immediate-release preparation.

[0181]

When the immediate-release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a lubricant (e.g., polyethylene glycol, magnesium stearate, talc,

light anhydrous silicic acid (e.g., Aerosil (manufactured by Nippon Aerosil))), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a colorant (e.g., tar coloring matter, caramel, iron oxide red, titanium oxide, riboflavins), if necessary, an appetizing agent (e.g., sweetening agent, flavoring agent and the like), an adsorbent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

[0182]

As the above-mentioned binder, hydroxypropylcellulose, polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

[0183]

The immediate-release preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a immediate-release preparation is formed, for example, into a particle, it can be prepared, according to the same means as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex Corporation), and the like, and then, granulating the mixture by a wet extrusion granulation method, fluidized bed granulation method and the like.

[0184]

Thus obtained immediate-release preparation and sustained release preparation may be themselves made into products or

made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or they may be themselves made into one preparation for oral administration (e.g., granule, fine particle, tablet, capsule and the like) or made into one preparation for oral administration appropriately together with preparation excipients and the like. It may also be permissible that they are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[0185]

[3] Sublingual, buccal or intraoral quick disintegrating agent and preparation thereof

Sublingual, buccal or intraoral quick disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral quick disintegrating agent, a preparation containing the compound of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for easy absorption and increased *in vivo* use efficiency, β-cyclodextrin or β-cyclodextrin derivatives (e.g., hydroxypropyl-β-cyclodextrin and the like) and the like may also be contained.

[0186]

As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are listed. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are listed, and particularly, magnesium stearate and colloidal silica are preferable. As the isotonizing agent,

sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are listed, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are listed, and particularly, crystalline cellulose (e.g., microcrystalline cellulose and the like) is preferable. As the water-dispersible polymer, gums (e.g., gum tragacanth, acacia gum, cyamoposis gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, water-soluble starch, polyacrylic acids (e.g., Carbomer), polymethacylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, ascorbic acid, palmitates and the like are listed, and hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are listed, and particularly, citric acid and ascorbic acid are preferable.

[0187]

The sublingual, buccal or intraoral quick disintegrating agent can be produced by mixing the compound of the present invention or the concomitant drug and an excipient by a method known *per se*. Further, if desired, the above-mentioned auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, colorant, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral quick disintegrating agent is obtained by mixing the above-mentioned

components simultaneously or at a time interval, then subjecting the mixture to tablet-making molding under pressure. For obtaining suitable hardness, it may also be permissible that the materials are moistened by using a solvent such as water, alcohol and the like if desired before and after the tablet making process, and after the molding, the materials are dried, to obtain a product.

[0188]

In the case of molding into a mucosa membrane patch (film), the compound of the present invention or the concomitant drug and the above-mentioned water-dispersible polymer (preferably, hydroxypropylcellulose, hydroxypropylmethylcellulose), excipient and the like are dissolved in a solvent such as water and the like, and the resulted solution is cast to give a film. Further, additives such as a plasticizer, stabilizer, antioxidant, preservative, colorant, buffer, sweetening agent and the like may also be added. For imparting suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be contained, or for enhancing adhesion of the film to an intraoral mucosa membrane lining, a bio-adhesive polymer (e.g., polycarbophil, carbopol) may also be contained. In the casting, a solution is poured on the non-adhesive surface, spread to uniform thickness (preferably, about 10 to 1000 micron) by an application tool such as a doctor blade and the like, then, the solution is dried to form a film. It may be advantageous that thus formed film is dried at room temperature or under heat, and cut into a desired area.

[0189]

As the preferable intraoral quick disintegrating agent, there are listed solid quick scattering dose agents composed of a network body comprising the compound of the present invention or the concomitant drug, and a water-soluble or water-diffusible carrier which is inert to the compound of the present invention or concomitant drug, are listed. This

network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the compound of the present invention or the concomitant drug in a suitable solvent.

[0190]

It is preferable that the composition of an intraoral quick disintegrating agent contains a matrix forming agent and a secondary component, in addition to the compound of the present invention or the concomitant drug.

[0191]

Examples of the matrix forming agent include gelatins, dextrins, animal proteins or vegetable proteins such as soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, guar gum, agar, xanthan and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectines; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

[0192]

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such as matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agents aid to maintain the compound of the present invention or the concomitant drug in the solution or suspension in diffused condition, in addition to formation of the matrix.

[0193]

The composition may contain secondary components such as a preservative, antioxidant, surfactant, thickening agent, colorant, pH controlling agent, flavoring agent, sweetening agent, food taste masking agent and the like. As the suitable colorant, there are listed red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Ellis and Everard. Examples of the suitable flavoring agent include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry, grape flavor and combinations thereof. Examples of the suitable pH controlling agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetening agent include aspartame, acesulfame K and thaumatin and the like. Examples of the suitable food taste masking agent include sodium bicarbonate, ion exchange resin, cyclodextrin-inclusion compounds, adsorbent substances and microcapsulated apomorphine.

[0194]

The preparation contains the compound of the present invention or the concomitant drug in an amount usually from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferable are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the compound of the present invention or the concomitant drug (into water) within the time range of about 1 to about 60 min, preferably of about 1 to about 15 min, more preferably of about 2 to about 5 min, and intraoral quick disintegrating preparations which are disintegrated within the range of 1 to 60 sec, preferably of 1 to 30 sec, further preferably of 1 to 10 sec, after placed in an oral cavity.

[0195]

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight, preferably from about 30 to about 90% by weight. The content

of β-cyclodextrin or β-cyclodextrin derivative in the whole preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably, from about 10 to about 70% by weight. The content of the hydrophilic carrier in the whole preparation is from about 0.1 to about 50% by weight, preferably, from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably, from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation is from about 0.1 to about 10% by weight, preferably, from about 1 to 5% by weight. The above-mentioned preparation may further contain additives such as a colorant, sweetening agent, preservative and the like, if necessary.

[0196]

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

[0197]

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the symptom, age, sex, body weight, sensitivity difference of the administration subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg body weight of a mammal, which is usually administered once to 4-times in division a day.

[0198]

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

[0199]

In a preferable administration method, for example, the concomitant drug which has been molded into an oral

administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

[0200]

Furthermore, the compound of the present invention or the combination agent of the present invention can be used concurrently with a non-drug therapy. To be precise, the compound of the present invention or the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

[0201]

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

[0202]

In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β-lactam type such as pansporin and the like, macrolide type such as clarithromycin and the like etc.) for the complication with various infectious diseases, (ii) administration of high-calorie transfusion, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent for ameliorating side effects such as nausea, vomiting,

anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the like].

[0203]

Preferably, the compound of the present invention or the combination agent of the present invention is administered orally (including sustained-release preparations), intravenously (including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

[0204]

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because, for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

[0205]

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

Examples

[0206]

The present invention is explained in detail in the following by referring to Reference Examples, Examples, Formulation Examples and Experimental Examples, which are not to be construed as limitative.

[0207]

In the Reference Examples and Examples, the purity of the compounds was measured under the following HPLC conditions.

measurement device: SHIMADZU Corporation LC-10 Avp system

column: CAPSEL PAK C18UG120 S-3 μm, 2.0 X 50 mm

solvent: Solution A; 0.1% trifluoroacetic acid-containing water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle: 0.00 min (Solution A/Solution B=90/10), 4.00 min (Solution A/Solution B=5/95), 5.50 min (Solution A/Solution B=5/95), 5.51 min (Solution A/Solution B=90/10), 8.00 min (Solution A/Solution B=90/10)

injection volume: 2 μl

flow rate: 0.5 ml/min

detection method: UV 220 nm

In the Reference Examples and Examples, the purification of the compounds by preparative HPLC was performed under the following conditions.

1) measurement device: Gilson Company Inc., High Throughput Purification System

column: YMC CombiPrep ODS-A, S-5 μm, 50 X 20 mm

detection method: UV 220 nm

solvent: Solution A; 0.1% trifluoroacetic acid-containing water,

Solution B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle: representative example 0.00 min (Solution A/Solution B=98/2), 1.00 min (Solution A/Solution B=98/2), 5.20 min (Solution A/Solution B=0/100), 6.40 min (Solution

A/Solution B=0/100), 6.50 min (Solution A/Solution B=98/2), 6.60 min (Solution A/Solution B=98/2), flow rate: 25 mL/min, or 0.00 min (Solution A/Solution B= 90/10), 1.00 min (Solution A/Solution B= 90/10), 4.00 min (Solution A/Solution B= 10/95), 8.50 min (Solution A/Solution B= 10/95), 8.60 min (Solution A/Solution B= 90/10), 8.70 min (Solution A/Solution B= 90/10) flow rate: 20 ml/min

2) measurement device: Gilson Company Inc., High Throughput Purification System

column: YMC CombiPrep, ProC18 RS, S-5 μm, 20 X 50 mm (YMC)

solvent: SOLUTION A; 10 mM ammonium carbonate-containing water,

SOLUTION B; acetonitrile

gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=95/5), 2.00 min (SOLUTION A/SOLUTION B=95/5), 4.02 min (SOLUTION A/SOLUTION B=5/95), 6.40 min (SOLUTION A/SOLUTION B=5/95), 6.50 min (SOLUTION A/SOLUTION B=95/5), 8.00 min (SOLUTION A/SOLUTION B=95/5)

3) measurement device: Gilson Company Inc., High Throughput Purification System

column: YMC CombiPrep, ProC18 RS, S-5 μm, 20 X 50 mm (YMC)

solvent: SOLUTION A; 0.1% trifluoroacetic acid-containing water,

SOLUTION B; 0.1% trifluoroacetic acid-containing acetonitrile

gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=98/2), 1.00 min (SOLUTION A/SOLUTION B=98/2), 5.20 min (SOLUTION A/SOLUTION B=60/40), 5.40 min (SOLUTION A/SOLUTION B=5/95), 6.40 min (SOLUTION A/SOLUTION B=5/95), 6.50 min (SOLUTION A/SOLUTION B=98/2), 6.60 min (SOLUTION A/SOLUTION B=98/2)

injection volume: 500 μl, flow rate: 20 ml/min, detection method: UV 220 nm, 254 nm

In the Reference Examples and Examples, mass spectrum (MS) was measured under the following conditions.

measurement device: Micromass platform II or Waters ZMD

ionization method: Atmospheric Pressure Chemical Ionization:

APCI or electron impact ionization method (Electron Spray Ionization: ESI)

In the Reference Examples and Examples, HPLC-mass spectrum (LC-MS) was measured under the following conditions.

1) measurement device: Micromass ZMD, Agilent Technologies HP1100 and 1200 LC/MSD

column: CAPCELL PAK C18UG120, S-3 μm, 1.5 X 35 mm

solvent: SOLUTION A; 0.05% trifluoroacetic acid-containing water,

SOLUTION B; 0.04% trifluoroacetic acid-containing acetonitrile

gradient cycle: 0.00 min (Solution A/Solution B=90/10), 2.00 min (Solution A/Solution B=5/95), 2.75 min (Solution A/Solution B=5/95), 2.76 min (Solution A/Solution B=90/10), 3.45 min (Solution A/Solution B=90/10)

injection volume: 2 μl

flow rate: 0.5 ml/min

detection method: UV 220 nm

ionization method: electron impact ionization method (Electron Spray Ionization: ESI)

2) measurement device: Waters, 4-ch LC/MS system with MUX

column: CAPCELL PAK C18 UG-120, S-3 μm, 1.5 X 35 mm (Shiseido Co., Ltd.)

solvent: SOLUTION A; 5 mM ammonium acetate-containing water,

SOLUTION B; 5 mM ammonium acetate-containing acetonitrile

gradient cycle: gradient: 0.00 min (SOLUTION A/SOLUTION B=100/0), 2.00 min (SOLUTION A/SOLUTION B=0/100), 3.00 min (SOLUTION A/SOLUTION B=0/100), 3.01 min (SOLUTION A/SOLUTION B=100/0), 3.30 min (SOLUTION A/SOLUTION B=100/0)

injection volume: 2 μL, flow rate: 0.5 mL/min, detection method: UV 220 nm

ionization method: electrospray ionization method (ESI)

measurement mode: full scan (positive+negative ions)

measured mass value range: m/z=150 - 750

^{1}H-NMR spectrum was measured using tetramethylsilane as the internal standard, using BRUKER AVANCE DPX-300 (300 MHz), AV300 (300MHz), AV400 (400 MHz) and VARIAN Mercury-300 (300 MHz), and all δ values are expressed in ppm.

As the Microwave reaction apparatus, Emrys Optimizer, Biotage Japan Ltd. was used.

Unless otherwise specified, the numerical value of mixed solvent shows a volume mixing ratio of each solvent. Unless otherwise specified, % means weight %. While the room temperature (ambient temperature) in the present specification means a temperature of from about 10°C to about 35°C, it is not particularly strictly limited.

[0208]

Other abbreviations used in the specification mean the following:

s: singlet

d: doublet

t: triplet

q: quartet

m: multiplet

sext: sextet

br: broad

J: coupling constant

Hz: Hertz

$CDCl_3$: deuterated chloroform

DMSO-d_6: dimethyl sulfoxide-d_6

CD_3OD: deuterated methanol

^{1}H-NMR: proton nuclear magnetic resonance

LC/MS: liquid chromatography-mass spectrometry spectrum

DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

THF: tetrahydrofuran

WSCD: water-soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) hydrochloride

HOBt: 1-hydroxybenzotriazole

Boc: tert-butoxycarbonyl

K_2CO_3: potassium carbonate

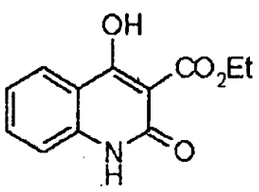
M: mol concentration

[0209]

Reference Example 1

Production of ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0210]



[0211]

To a solution of methyl anthranilate (121 g, 0.8 mol) and diethyl malonate (128 g, 0.8 mol) in ethanol (900 mL) was added a 20% solution (274 g) of sodium ethoxide in ethanol, and the mixture was stirred at room temperature for 30 min. Ethanol was evaporated, and the mixture was stirred at 140°C for 12 hr. After cooling, the obtained solid was washed with diethyl ether, and dissolved in water. Insoluble materials were filtered off, the filtrate was acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (161 g, 86%) as a pale-yellow powder.

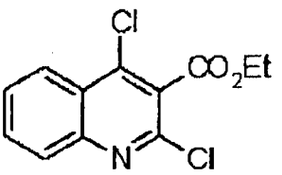
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.31 (3H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.1 Hz), 7.19-7.29 (2H, m), 7.63 (1H, td, J = 7.8, 1.2 Hz), 7.94 (1H, d, J = 8.1 Hz), 11.51 (1H, br s), 13.40 (1H, br s).

[0212]

Reference Example 2

Production of ethyl 2,4-dichloroquinoline-3-carboxylate

[0213]



[0214]

A mixture of the compound of Reference Example 1 (75 g, 0.32 mol) and phosphorus oxychloride (200 mL) was stirred at 110°C for 6 hr. After cooling, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in a small amount of ethyl acetate and the mixture was poured into ice water. The obtained mixture was extracted with ethyl acetate, and the extract was washed successively with 1N aqueous sodium hydroxide solution, water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/5) to give the title compound (68 g, 79%) as a white solid.

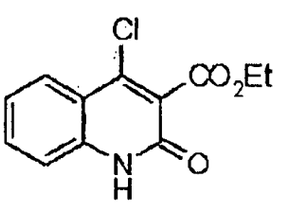
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.47 (3H, t, J = 7.2 Hz), 4.54 (2H, q, J = 7.2 Hz), 7.71 (1H, t, J = 7.5 Hz), 7.85 (1H, t, J = 7.5 Hz), 8.06 (1H, d, J = 8.2 Hz), 8.24 (1H, d, J = 8.2 Hz).

[0215]

Reference Example 3

Production of ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0216]



[0217]

A mixture of the compound of Reference Example 2 (68.0 g, 0.25 mol) and sodium acetate (21.7 g, 0.26 mol) in acetic acid (200 mL) was stirred at 120°C for 20 hr. After cooling, the reaction mixture was added to water, and the precipitated solid was collected by filtration. The obtained solid was

washed with water, and dried under reduced pressure to give the title compound (58.8 g, 94%) as a white solid.

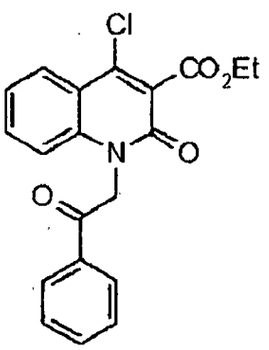
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.46 (3H, t, J = 7.2 Hz), 4.53 (2H, q, J = 7.2 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.8 Hz), 8.00 (1H, d, J = 8.1 Hz), 12.41 (1H, br s).

[0218]

Reference Example 4

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydroquinoline-3-carboxylate

[0219]



[0220]

To a solution of the compound of Reference Example 3 (10.0 g, 39.7 mmol) in DMF (160 mL) was added sodium hydride (60% in oil, 1.7 g, 41.7 mmol) under ice-cooling, and the mixture was stirred for 15 min. Phenacyl bromide (8.7 g, 43.7 mmol) was added to the obtained mixture under ice-cooling, and the mixture was stirred for 1 hr. The reaction mixture was added to water (1.5 L), and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=1/2 - 1/1) to give the title compound (10.5 g, 71%) as a pale-yellow solid.

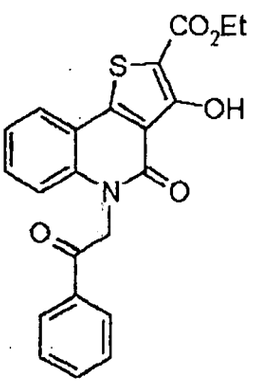
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.2 Hz), 4.47 (2H, q, J = 7.2 Hz), 5.80 (2H, s), 7.02 (1H, d, J = 8.1 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.53-7.60 (3H, m), 7.65-7.70 (1H, m), 8.06-8.13 (3H, m).

[0221]

Reference Example 5

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0222]



[0223]

A 20% solution (17.2 g, 50.5 mmol) of sodium ethoxide in ethanol was diluted with ethanol (50 mL), ethyl thioglycolate (6.1 g, 50.5 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 5 min. The compound of Reference Example 4 (9.3 g, 25.3 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with ice water (50 mL), 2N hydrochloric acid (30 mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water and diethyl ether, and dried under reduced pressure to give the title compound (10.0 g, 96%) as a white powder.

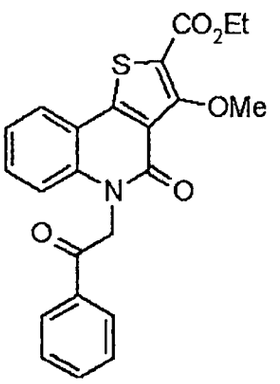
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (3H, t, J = 7.0 Hz), 4.25-4.35 (2H, m), 6.01 (2H, s), 7.40 (1H, t, J = 7.2 Hz), 7.55-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 8.00-8.07 (1H, m), 8.07-8.19 (2H, m), 10.40-10.65 (1H, br).

[0224]

Reference Example 6

Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0225]



[0226]

A mixture of the compound of Reference Example 5 (7.0 g, 17.1 mmol) and DBU (4.3 g, 18.3 mmol) in DMF (150 mL) was stirred at room temperature for 10 min, and iodomethane (4.0 g, 28.0 mmol) was added. The mixture was stirred at room temperature for 4 hr, and concentrated under reduced pressure. The residue was diluted with water, and extracted twice with ethyl acetate-THF mixed solution. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethyl acetate-diethyl ether mixed solution, and dried under reduced pressure to give the title compound (5.7 g, 79%) as a pale-green powder.

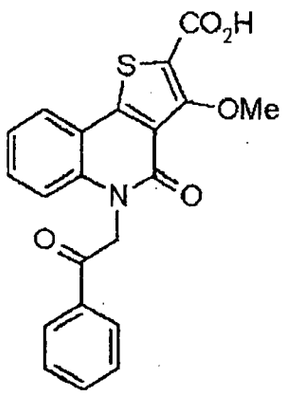
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (3H, t, J = 7.1 Hz), 3.95 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.98 (2H, s), 7.37 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.57-7.67 (3H, m), 7.76 (1H, t, J = 7.5 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.16-8.19 (2H, m).

[0227]

Reference Example 7

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0228]



[0229]

A mixed solution of the compound of Reference Example 6 (5.7 g, 13.5 mmol) and 2N aqueous sodium hydroxide solution (60 mL) in THF (200 mL)-ethanol (100 mL) was stirred at room temperature for 18 hr. The reaction mixture was neutralized with 2N hydrochloric acid (60 mL), and the precipitated solid was collected by filtration. The obtained solid was washed successively with water and diethyl ether, and dried under reduced pressure to give the title compound (4.2 g, 79%) as a pale-pink powder.

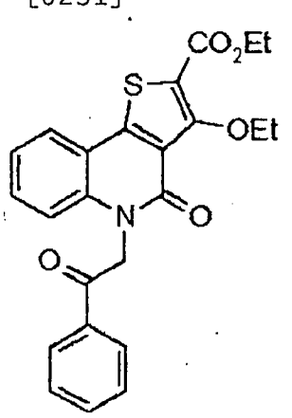
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.93 (3H, s), 5.98 (2H, s), 7.35 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 8.7 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.2 Hz), 8.04 (1H, dd, J = 8.1, 1.2 Hz), 8.16-8.19 (2H, m).

[0230]

Reference Example 8

Production of ethyl 3-ethoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0231]



[0232]

In the same manner as in Reference Example 6, the title compound (461 mg, 87%) was obtained as a white powder from the compound (500 mg, 1.22 mmol) of Reference Example 5, DBU (280 mg, 1.84 mmol) and iodoethane (302 mg, 1.84 mmol).

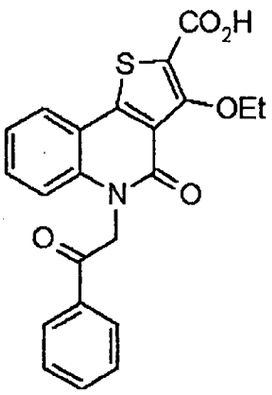
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (6H, t, J = 7.0 Hz), 4.21 (2H, q, J = 7.0 Hz), 4.34 (2H, q, J = 7.0 Hz), 5.98 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.76 (1H, t, J = 7.2 Hz), 8.06 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m).

[0233]

Reference Example 9

Production of 3-ethoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0234]



[0235]

In the same manner as in Reference Example 7, the title compound (392 mg, 95%) was obtained as a pale-pink powder from the compound (440 mg, 1.01 mmol) of Reference Example 8.

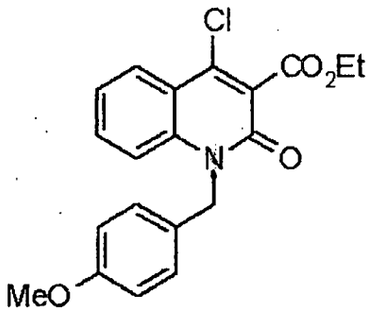
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.33 (3H, t, J = 7.0 Hz), 4.20 (2H, q, J = 7.0 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 8.4 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.04 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m).

[0236]

Reference Example 10

Production of ethyl 4-chloro-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0237]



[0238]

In the same manner as in Reference Example 4, the title compound (10.8 g, 79%) was obtained as a white powder from the compound (10.0 g, 39.8 mmol) of Reference Example 3 and 4-methoxybenzyl chloride (7.48 mL, 47.8 mmol).

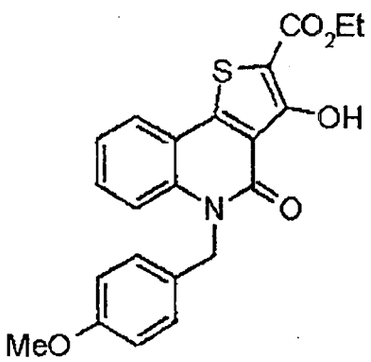
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (3H, t, J = 7.1 Hz), 3.70 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 5.48 (2H, s), 6.89 (2H, d, J = 8.7 Hz), 7.19 (2H, d, J = 8.7 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.61 (1H, d, J = 8.7 Hz), 7.69-7.75 (1H, m), 8.04 (1H, dd, J = 7.8, 1.2 Hz).

[0239]

Reference Example 11

Production of ethyl 3-hydroxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0240]



[0241]

In the same manner as in Reference Example 5, the title compound (10.4 g, 88%) was obtained as a white powder from the compound (10.6 g, 31.0 mmol) of Reference Example 10.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (3H, t, J = 7.0 Hz), 3.70 (3H, s), 4.32 (2H, q, J = 7.0 Hz), 5.53 (2H, s), 6.87 (2H, d, J =

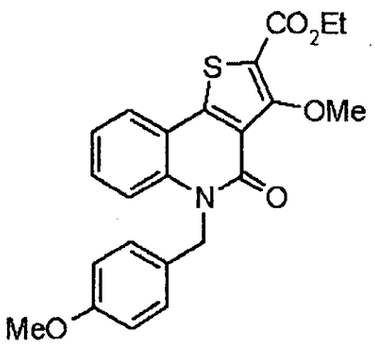
8.9 Hz), 7.23 (2H, d, J = 8.9 Hz), 7.34-7.39 (1H, m), 7.58-7.66 (2H, m), 8.00-8.03 (1H, m), 10.77 (1H, s).

[0242]

Reference Example 12

Production of ethyl 3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0243]



[0244]

In the same manner as in Reference Example 6, the title compound (5.2 g, 64%) was obtained as a white powder from the compound (7.5 g, 19.8 mmol) of Reference Example 11.

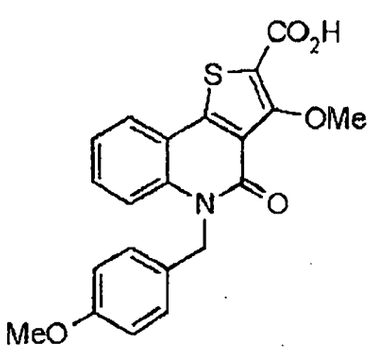
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (3H, t, J = 7.1 Hz), 3.70 (3H, s), 4.01 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.50 (2H, s), 6.87 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.27-7.32 (1H, m), 7.48-7.60 (2H, m), 8.01 (1H, dd, J = 7.7, 1.4 Hz).

[0245]

Reference Example 13

Production of 3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0246]



[0247]

In the same manner as in Reference Example 7, the title compound (4.75 g, 98%) was obtained as a white powder from the compound (5.0 g, 12.3 mmol) of Reference Example 12.

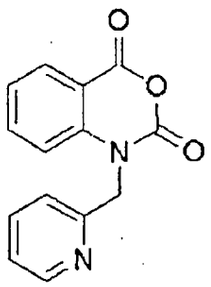
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.70 (3H, s), 3.93 (3H, s), 5.51 (2H, s), 6.87 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.27-7.32 (1H, m), 7.48-7.59 (2H, m), 7.99 (1H, dd, J = 7.8, 1.2 Hz), 13.40 (1H, s).

[0248]

Reference Example 14

Production of 1-(pyridin-2-ylmethyl)-2H-3,1-benzooxazine-2,4(1H)-dione

[0249]



[0250]

To a solution of isatoic anhydride (25.4 g, 0.156 mol) in DMF (300 mL) were added 2-(chloromethyl)pyridine hydrochloride (28.1 g, 0.171 mol) and sodium hydride (66% in oil, 12.5 g, 0.34 mol) under ice-cooling. The obtained mixture was stirred at room temperature for 42 hr. Water (750 mL) was added to the reaction mixture and the mixture was ice-cooled. The precipitated solid was collected by filtration, and recrystallized from acetone-diisopropyl ether to give the title compound (13.4 g, 34%).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:5.36 (2H, s), 7.24~7.34 (3H, m), 7.49 (1H, d, J = 8.1 Hz), 7.73 (1H, ddd, J = 8.6, 7.2, 1.5 Hz), 7.77 (1H, td, J = 7.7, 1.6 Hz), 8.03 (1H, dd, J = 7.8, 1.8 Hz), 8.50 (1H, ddd, J = 4.9, 1.7, 1.0 Hz).

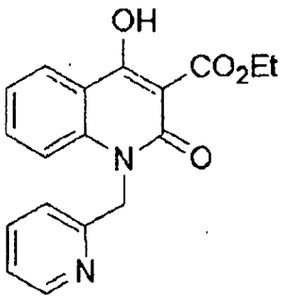
[0251]

Reference Example 15

Production of ethyl 4-hydroxy-2-oxo-1-(pyridin-2-ylmethyl)-

1,2-dihydroquinoline-3-carboxylate

[0252]



[0253]

To a solution of diethyl malonate (15.6 g, 97.4 mmol) in DMF (90 mL) was added sodium hydride (66% in oil, 2.60 g, 72 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. The compound of Reference Example 14 (16.5 g, 64.9 mmol) was added to the obtained mixture by small portions, and the mixture was stirred at 120°C for 6 hr. The reaction mixture was concentrated under reduced pressure, ice water was added to the residue and the mixture was washed with diethyl ether. The aqueous layer was weakly basified with 5N hydrochloric acid (8 mL) under ice-cooling. The precipitated crystals were collected by filtration, washed with water, and recrystallized from ethyl acetate-diisopropyl ether to give the title compound (12.8 g, 60%).

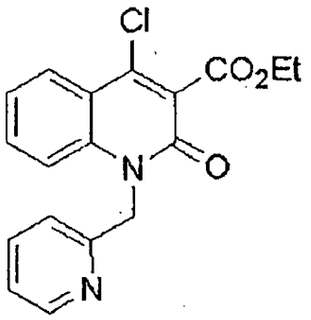
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.50 (3H, t, J = 7.1 Hz), 4.53 (2H, q, J = 7.1 Hz), 5.61 (2H, br s), 7.12-7.18 (2H, m), 7.18-7.25 (1H, m), 7.36 (1H, d, J = 8.7 Hz), 7.51-7.59 (2H, m), 8.18 (1H, dd, J = 8.3, 1.7 Hz), 8.56 (1H, dd, J = 5.3, 2.0 Hz), 14.53 (1H, s).

[0254]

Reference Example 16

Production of ethyl 4-chloro-2-oxo-1-(pyridin-2-ylmethyl)-1,2-dihydroquinoline-3-carboxylate

[0255]



[0256]

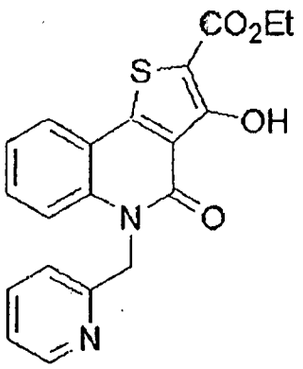
To a mixture of the compound of Reference Example 15 (16.1 g, 49.6 mmol) and toluene (50 mL) was added phosphorus oxychloride (12 mL, 0.13 mol), and the mixture was stirred at 110°C for 1 hr. The reaction mixture was allowed to cool, and the solvent was removed by decantation. Water was added to the residue and the mixture was washed with diethyl ether. The aqueous layer was neutralized with sodium carbonate and extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/1 - 3/1) and crystallized from ethyl acetate-hexane to give the title compound (2.54 g, 15%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.44 (3H, t, J = 7.2 Hz), 4.50 (2H, q, J = 7.2 Hz), 5.64 (2H, br s), 7.15-7.26 (2H, m), 7.31 (1H, ddd, J = 8.2, 5.9, 2.3 Hz), 7.52-7.63 (3H, m), 8.06 (1H, dt, J = 7.8, 0.8 Hz), 8.56 (1H, ddd, J = 4.7, 1.9, 0.8 Hz).

[0257]

Reference Example 17

Production of ethyl 3-hydroxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0258]



[0259]

A 20% solution (4.51 g, 13 mmol) of sodium ethoxide in ethanol was diluted with ethanol (15 mL), and ethyl thioglycolate (1.74 mL, 15.9 mmol) was added to the obtained solution. The mixture was stirred at room temperature for 10 min. The compound of Reference Example 16 (2.27 g, 6.62 mmol) was added to the mixture, and the mixture was stirred at room temperature for 5.5 hr. The reaction mixture was neutralized with ice water and 2N hydrochloric acid (3.2 mL) under ice-cooling, and extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained solid was washed with ethanol to give the title compound (2.50 g, 99%).

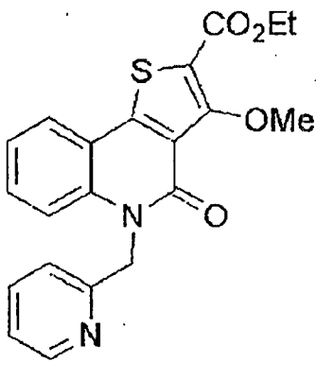
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43 (3H, t, J = 7.1 Hz), 4.43 (2H, q, J = 7.1 Hz), 5.69 (2H, br s), 7.16-7.24 (2H, m), 7.25-7.32 (1H, m), 7.49 (1H, ddd, J = 8.6, 7.1, 1.5 Hz), 7.57 (1H, d, J = 8.1 Hz), 7.60 (1H, td, J = 7.7, 1.8 Hz), 7.82 (1H, dd, J = 8.1, 1.5 Hz), 8.57 (1H, ddd, J = 4.9, 1.6, 0.8 Hz), 10.68 (1H, s).

[0260]

Reference Example 18

Production of ethyl 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0261]



[0262]

To a suspension of the compound of Reference Example 17 (2.26 g, 5.94 mmol) in DMF (20 mL) was added DBU (1.06 mL, 7.09 mmol), and iodomethane (0.74 mL, 12 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 14 hr, water was added, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water, 0.5N sodium hydroxide solution and water, dried by passing through basic silica gel (eluted with ethyl acetate), and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (1.16 g, 50%).

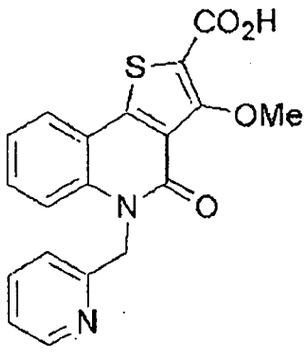
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43 (3H, t, J = 7.1 Hz), 4.17 (3H, s), 4.41 (2H, q, J = 7.1 Hz), 5.70 (2H, br s), 7.14-7.26 (3H, m), 7.45 (1H, ddd, J = 8.6, 7.0, 1.6 Hz), 7.51 (1H, dd, J = 8.6, 0.8 Hz), 7.57 (1H, td, J = 7.7, 1.8 Hz), 7.83 (1H, ddd, J = 7.7, 1.5, 0.3 Hz), 8.57 (1H, ddd, J = 5.0, 2.0, 0.9 Hz).

[0263]

Reference Example 19

Production of 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0264]



[0265]

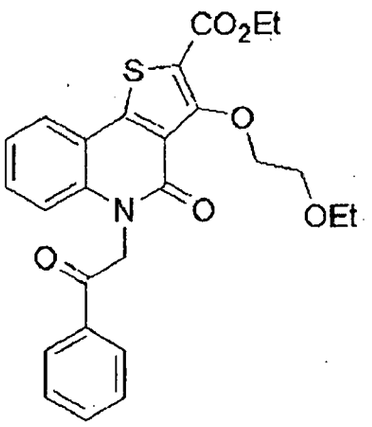
To a suspension of the compound of Reference Example 18 (1.21 g, 3.07 mmol) in THF (10 mL) and ethanol (10 mL) was added 5N aqueous sodium hydroxide solution (1.2 mL, 6.0 mmol). The obtained mixture was stirred at room temperature for 45 min, ethanol (5 mL) was added and the mixture was further stirred for 135 min. The reaction mixture was ice-cooled, neutralized with 1N hydrochloric acid (6.0 mL), and chloroform and water were added. The organic layer was separated, and the aqueous layer was extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from chloroform-diisopropyl ether to give the title compound (1.11 g, 99%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.96 (3H, s), 5.65 (2H, s), 7.23-7.33 (3H, m), 7.43 (1H, d, J = 8.7 Hz), 7.54 (1H, ddd, J = 8.6, 7.3, 1.4 Hz), 7.73 (1H, td, J = 7.7, 1.9 Hz), 7.97-8.02 (1H, m), 8.45-8.48 (1H, m), 13.38 (1H, br s).

[0266]

Reference Example 20

Production of ethyl 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0267]



[0268]

To a suspension of the compound of Reference Example 5 (1.35 g, 3.31 mmol) in DMF (20 mL) were added DBU (1.48 mL, 9.90 mmol) and 2-bromoethylethylether (1.12 mL, 9.93 mmol), and the mixture was stirred at 60°C for 30 hr. Chloroform and water were added to the reaction mixture, the organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layer was washed with 0.5N sodium hydroxide solution and water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/3 - 2/3) and recrystallized from dichloromethane-diisopropyl ether to give the title compound (1.36 g, 86%).

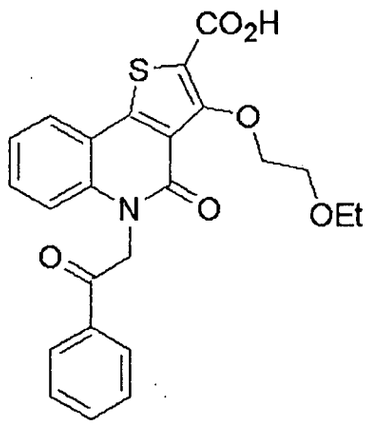
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.17 (3H, t, J = 7.1 Hz), 1.43 (3H, t, J = 7.1 Hz), 3.56 (2H, q, J = 7.1 Hz), 3.89 (2H, dd, J = 5.5, 4.6 Hz), 4.40 (2H, q, J = 7.1 Hz), 4.45 (2H, dd, J = 5.5, 4.6 Hz), 5.85 (2H, s), 6.97 (1H, d, J = 8.1 Hz), 7.21-7.28 (1H, m), 7.45 (1H, ddd, J = 8.7, 7.2, 1.4 Hz), 7.51-7.58 (2H, m), 7.63-7.69 (1H, m), 7.86 (1H, dd, J = 7.8, 1.5 Hz), 8.07-8.12 (2H, m).

[0269]

Reference Example 21

Production of 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0270]



[0271]

To a suspension of the compound of Reference Example 20 (1.20 g, 2.50 mmol) in THF (16 mL) and ethanol (16 mL) was added 5N aqueous sodium hydroxide solution (1.0 mL, 5.0 mmol). The obtained mixture was stirred at room temperature for 3 hr. The reaction mixture was acidified with 1N hydrochloric acid, and water was added. The precipitated crystals were collected by filtration and washed with water to give the title compound (1.09 g, 97%).

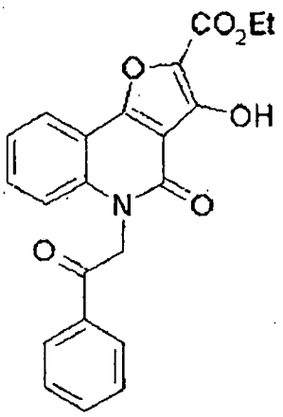
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.01 (3H, t, J = 6.9 Hz), 3.40 (2H, q, J = 6.9 Hz), 3.71 (2H, t, J = 5.0 Hz), 4.30 (2H, t, J = 5.0 Hz), 5.97 (2H, s), 7.33 (1H, t, J = 7.7 Hz), 7.46 (1H, d, J = 8.7 Hz), 7.54-7.66 (3H, m), 7.76 (1H, t, J = 7.2 Hz), 8.02 (1H, d, J = 7.8 Hz), 8.16 (2H, d, J = 7.5 Hz), 13.27 (1H, br s).

[0272]

Reference Example 22

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxylate

[0273]



[0274]

In the same manner as in Reference Example 5, the title compound (1.10 g, 69%) was obtained as a white powder from the compound of Reference Example 4 (1.50 g, 4.06 mmol), a 20% solution (2.76 g, 8.11 mmol) of sodium ethoxide in ethanol and ethyl glycolate (1.01 g, 9.73 mmol).

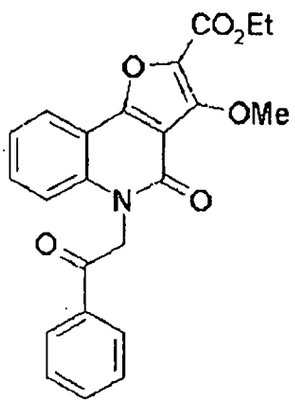
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (3H, t, J = 7.1 Hz), 4.35 (2H, q, J = 7.1 Hz), 5.96 (2H, s), 7.39 (1H, t, J = 7.7 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.60-7.67 (3H, m), 7.74-7.79 (1H, m), 8.05 (1H, dd, J = 7.7, 1.4 Hz), 8.15-8.18 (2H, m), 9.80-11.10 (1H, br).

[0275]

Reference Example 23

Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxylate

[0276]



[0277]

In the same manner as in Reference Example 6, the title compound (250 mg, 23%) was obtained as a white powder from the

compound of Reference Example 22 (1.05 g, 2.68 mmol), DBU (612 mg, 4.02 mmol) and iodomethane (250 μL, 4.02 mmol).

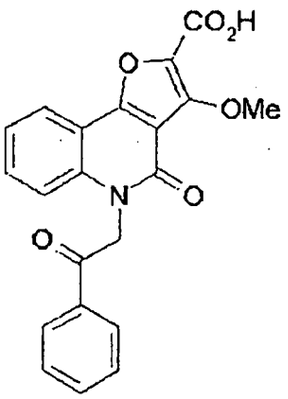
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 7.1 Hz), 4.14 (3H, s), 4.37 (2H, q, J = 7.1 Hz), 5.99 (2H, s), 7.39-7.45 (1H, m), 7.55 (1H, d, J = 8.7 Hz), 7.62-7.68 (3H, m), 7.74-7.80 (1H, m), 8.09 (1H, dd, J = 7.8, 1.5 Hz), 8.16-8.18 (2H, m).

[0278]

Reference Example 24

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxylic acid

[0279]



[0280]

In the same manner as in Reference Example 7, the title compound (160 mg, 72%) was obtained as a white powder from the compound of Reference Example 23 (240 mg, 0.592 mmol), 8N aqueous sodium hydroxide solution (1.0 mL) and ethanol (14 mL).

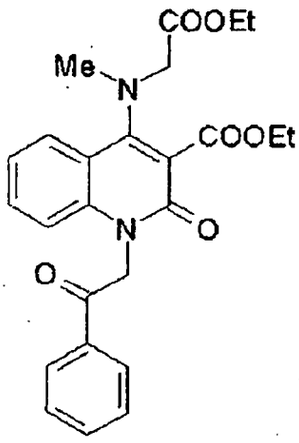
^{1}H-NMR (300 MHz, DMSO-d_6) δ:4.12 (3H, s), 5.99 (2H, s), 7.42 (1H, t, J = 7.6 Hz), 7.54 (1H, d, J = 7.8 Hz), 7.62-7.67 (3H, m), 7.77 (1H, t, J = 7.8 Hz), 8.07 (1H, dd, J = 7.6, 1.5 Hz), 8.16-8.18 (2H, m), 12.60-14.10 (1H, br).

[0281]

Reference Example 25

Production of ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydroquinoline-3-carboxylate

[0282]



[0283]

A mixture of the compound of Reference Example 4 (24.1 g, 65.2 mmol), sarcosine ethyl ester hydrochloride (12.0 g, 78.2 mmol), triethylamine (18.1 mL, 130 mmol) and ethanol (200 mL) was stirred at 85°C for 15 hr, sarcosine ethyl ester hydrochloride (3.00 g, 19.6 mmol) and triethylamine (18.1 mL, 130 mmol) were further added, and the mixture was stirred at 85°C for 7 hr. After cooling, water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (24.6 g, 84%) as a white powder.

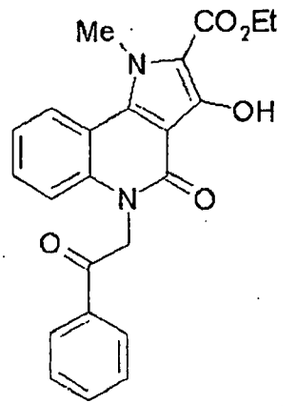
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.21-1.31 (6H, m), 2.93 (3H, s), 3.95 (2H, s), 4.15-4.31 (4H, m), 5.87 (2H, s), 7.31 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.55-7.65 (3H, m), 7.72-7.78 (1H, m), 8.05 (1H, dd, J = 7.8, 1.5 Hz), 8.12-8.15 (2H, m).

[0284]

Reference Example 26

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0285]



[0286]

A mixture of the compound of Reference Example 25 (1.25 g, 2.77 mmol), a 20% solution (1.23 g, 3.33 mmol) of sodium ethoxide in ethanol and ethanol (25 mL) was stirred at 55°C for 15 hr. The reaction mixture was diluted with water, 1N hydrochloric acid (5 mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water, ethanol and ethyl acetate, and recrystallized from dimethylformamide-ethanol to give the title compound (760 mg, 68%) as a white powder.

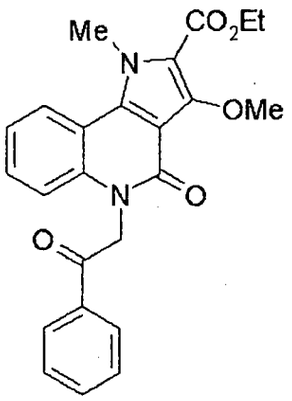
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.33 (3H, t, J = 7.2 Hz), 4.30-4.38 (5H, m), 5.93 (2H, s), 7.30-7.40 (2H, m), 7.48-7.53 (1H, m), 7.61-7.66 (2H, m), 7.73-7.79 (1H, m), 8.15-8.18 (2H, m), 8.34-8.37 (1H, m), 9.00 (1H, s).

[0287]

Reference Example 27

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0288]



[0289]

In the same manner as in Reference Example 6, the title compound (420 mg, 55%) was obtained as a white powder from the compound of Reference Example 26 (740 mg, 1.83 mmol), DBU (410 μL, 2.74 mmol) and iodomethane (171 μL, 2.74 mmol).

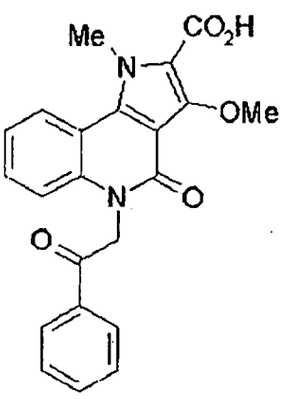
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 7.1 Hz), 3.89 (3H, s), 4.29-4.37 (5H, m), 5.96 (2H, s), 7.30-7.40 (2H, m), 7.48-7.53 (1H, m), 7.61-7.66 (2H, m), 7.73-7.78 (1H, m), 8.15-8.18 (2H, m), 8.38 (1H, dd, J = 8.3, 1.4 Hz).

[0290]

Reference Example 28

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0291]



[0292]

In the same manner as in Reference Example 7, the title compound (345 mg, 91%) was obtained as a white powder from the compound of Reference Example 27 (405 mg, 0.968 mmol), 8N

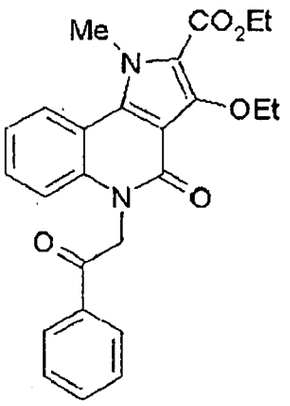
aqueous sodium hydroxide solution (1.5 mL) and ethanol (15 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.88 (3H, s), 4.31 (3H, s), 5.95 (2H, s), 7.29-7.39 (2H, m), 7.46-7.52 (1H, m), 7.61-7.66 (2H, m), 7.73-7.78 (1H, m), 8.16-8.18 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 12.92 (1H, s).

[0293]

Reference Example 29

Production of ethyl 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0294]



[0295]

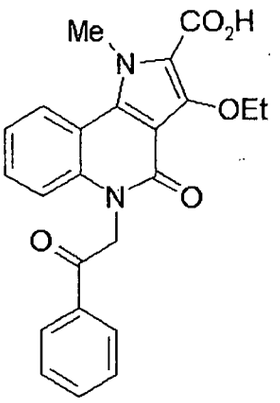
In the same manner as in Reference Example 6, the title compound (2.10 g, quant.) was obtained as a white powder from the compound (1.90 g, 4.70 mmol) of Reference Example 26, DBU (1.05 mL, 7.05 mmol) and iodoethane (564 μL, 7.05 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.27-1.37 (6H, m), 4.16 (2H, q, J = 6.9 Hz), 4.29-4.36 (5H, m), 5.95 (2H, s), 7.27-7.39 (2H, m), 7.50 (1H, t, J = 8.0 Hz), 7.63 (2H, t, J = 7.3 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.17 (2H, d, J = 7.3 Hz), 8.38 (1H, d, J = 8.1 Hz).

[0296]

Reference Example 30

Production of 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0297]



[0298]

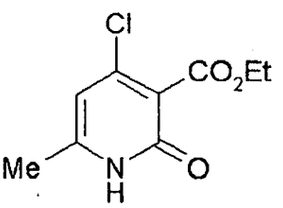
In the same manner as in Reference Example 7, the title compound (1.62 g, 89%) was obtained as a white powder from the compound of Reference Example 29 (1.95 g, 4.51 mmol), 8N aqueous sodium hydroxide solution (2.0 mL) and ethanol (14 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.27 (3H, t, J = 7.0 Hz), 4.16 (2H, q, J = 7.0 Hz), 4.31 (3H, s), 5.95 (2H, s), 7.27-7.39 (2H, m), 7.49 (1H, t, J = 7.4 Hz), 7.63 (2H, t, J = 7.4 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.15-8.18 (2H, m), 8.38 (1H, d, J = 7.2 Hz), 12.83 (1H, s).

[0299]

Reference Example 31

Production of ethyl 4-chloro-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

[0300]



[0301]

A mixture of ethyl 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (3.00 g, 15.2 mmol), phosphorus oxychloride (7.75 mL), n-butyltriethylammonium chloride (13.8 g, 60.8 mmol) and acetonitrile (60 mL) was stirred at 40°C for 30 min and under refluxing conditions for 30 min. After cooling, the reaction mixture was concentrated under reduced pressure, water was added to the residue and the mixture was

extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was washed with ethyl acetate-hexane mixed solution, and dried under reduced pressure to give the title compound (1.45 g, 44%) as a white powder.

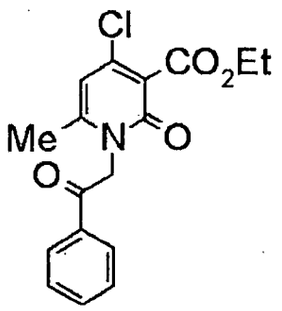
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.26 (3H, t, J = 7.0 Hz), 2.20 (3H, s), 4.25 (2H, q, J = 7.0 Hz), 6.26 (1H, s), 12.29 (1H, s).

[0302]

Reference Example 32

Production of ethyl 4-chloro-6-methyl-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0303]



[0304]

A mixture of the compound of Reference Example 31 (9.00 g, 41.7 mmol), potassium carbonate (17.3 g, 125 mmol), phenacyl bromide (16.6 g, 83.5 mmol) and DMF (100 mL) was stirred at room temperature for 15 hr. The reaction mixture was poured into water (100 mL), and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/9 - 7/3) to give the title compound (3.18 g, 23%) as a white powder.

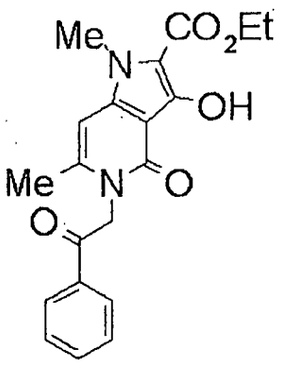
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (3H, t, J = 7.0 Hz), 2.30 (3H, s), 4.25 (2H, q, J = 7.0 Hz), 5.63 (2H, s), 6.54 (1H, d, J = 0.6 Hz), 7.61 (2H, t, J = 7.5 Hz), 7.72-7.78 (1H, m), 8.07-8.10 (2H, m).

[0305]

Reference Example 33

Production of ethyl 3-hydroxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0306]



[0307]

A mixture of the compound of Reference Example 32 (2.00 g, 5.99 mmol), sarcosine ethyl ester hydrochloride (1.84 g, 12.0 mmol), triethylamine (4.98 mL, 36.0 mmol) and ethanol (20 mL) was stirred at 80°C for 15 hr, a 20% solution (3.5 mL) of sodium ethoxide in ethanol was added, and the mixture was stirred at 100°C for 24 hr. After cooling, the reaction mixture was diluted with water (50 mL), 6N hydrochloric acid was added to adjust to pH 3 - 4, and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, and washed with water and ethyl acetate/THF to give the title compound (1.50 g, 68%) as a white powder.

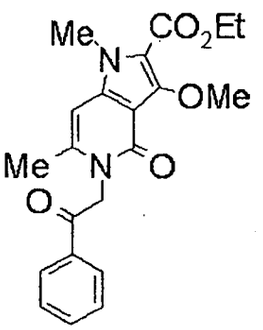
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.31 (3 H, t, J=7.1 Hz), 2.26 (3 H, s), 3.77 (3 H, s), 4.30 (2 H, q, J=7.0 Hz), 5.57 (2 H, s), 6.52 (1 H, s), 7.54-7.67 (2 H, m), 7.69-7.79 (1 H, m), 8.03-8.18 (2 H, m), 8.90 (1 H, s).

[0308]

Reference Example 34

Production of ethyl 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0309]



[0310]

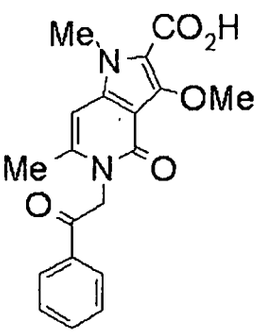
In the same manner as in Reference Example 6, the title compound (390 mg, 26%) was obtained as a white powder from the compound of Reference Example 33 (1.45 g, 3.94 mmol), DBU (882 μL, 5.90 mmol) and iodomethane (367 μL, 5.90 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30 (3 H, t, J=7.1 Hz), 2.28 (3 H, s), 3.81 (3 H, s), 3.86 (3 H, s), 4.27 (2 H, q, J=7.0 Hz), 5.60 (2 H, s), 6.59 (1 H, s), 7.54-7.66 (2 H, m), 7.69-7.79 (1 H, m), 8.05-8.16 (2 H, m).

[0311]

Reference Example 35

Production of 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0312]



[0313]

In the same manner as in Reference Example 7, the title compound (305 mg, 89%) was obtained as a white powder from the compound of Reference Example 34 (370 mg, 0.968 mmol), 8N aqueous sodium hydroxide solution (1 mL) and ethanol (7 mL).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.28 (3 H, s), 3.81 (3 H, s), 3.86

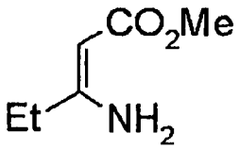
(3 H, s), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, J=7.4 Hz), 7.74 (1 H, t, J=7.3 Hz), 8.11 (2 H, d, J=7.7 Hz), 12.50 (1 H, br s).

[0314]

Reference Example 36

Production of methyl (2Z)-3-aminopenta-2-enoate

[0315]



[0316]

A mixture of methyl 3-oxovalerate (75.0 g, 576 mmol), ammonium acetate (222 g, 2.88 mmol) and methanol (750 mL) was stirred at room temperature for 3 days. The mixture was concentrated under reduced pressure, water (500 mL) was added to the residue and the mixture was extracted with ethyl acetate (200 mL). The extract was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure, and dried to give the title compound (68.5 g, 92%) as a pale-yellow oil.

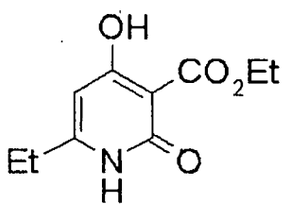
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.06 (3 H, t, J=7.6 Hz), 2.09 (2 H, q, J=7.6 Hz), 3.49 (3 H, s), 4.34 (1 H, s), 6.94 (1 H, s), 7.72 (1 H, br s).

[0317]

Reference Example 37

Production of ethyl 6-ethyl-4-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

[0318]



[0319]

To a solution of the compound of Reference Example 36 (50.0 g, 387 mmol) and diethyl malonate (58.8 mL, 387 mmol) in

ethanol (400 mL) was added a 20% solution (133 g) of sodium ethoxide in ethanol, and the mixture was stirred at 150°C for 15 hr while evaporating ethanol. After cooling, the obtained solid was collected by filtration, washed with ethyl acetate, and dissolved in water. Insoluble material was filtered off, the filtrate was acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water and ethyl acetate-hexane to give the title compound (36.4 g, 45%) as a white powder.

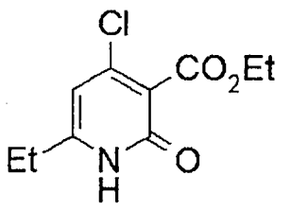
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.12 (3 H, t, J=7.6 Hz), 1.26 (3 H, t, J=7.1 Hz), 2.42 (2 H, q, J=7.6 Hz), 4.25 (2 H, q, J=7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, brs), 12.57 (1 H, s).

[0320]

Reference Example 38

Production of ethyl 4-chloro-6-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

[0321]



[0322]

A mixture of the compound of Reference Example 37 (15.0 g, 71.0 mmol) and phosphorus oxychloride (19.9 mL, 213 mmol) was stirred at 80°C for 30 min. The mixture was concentrated under reduced pressure, ice water was added to the residue, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate to give the title compound (9.80 g, 60%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.15 (3 H, t, J=7.5 Hz), 1.26 (3 H, t, J=7.0 Hz), 2.44-2.55 (2 H, m), 4.25 (2 H, q, J=7.1 Hz), 6.26 (1 H, s), 12.28 (1 H, s).

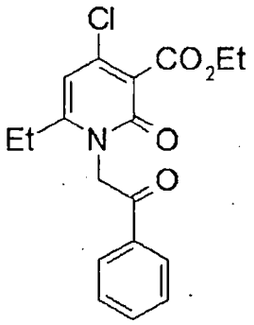
[0323]

Reference Example 39

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-(2-oxo-2-

phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0324]



[0325]

In the same manner as in Reference Example 32, the title compound (1.00 g, 7%) was obtained as a white powder from the compound of Reference Example 38 (9.50 g, 41.4 mmol), potassium carbonate (13.7 g, 99.2 mmol), phenacyl bromide (9.88 g, 49.6 mmol) and DMF (100 mL).

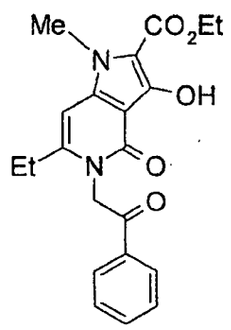
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.14 (3 H, t, J=7.4 Hz), 1.24 (3 H, t, J=7.1 Hz), 2.62 (2 H, q, J=7.4 Hz), 4.25 (2 H, q, J=7.1 Hz), 5.61 (2 H, s), 6.44 (1 H, s), 7.54-7.66 (2 H, m), 7.70-7.79 (1 H, m), 8.05-8.13 (2 H, m).

[0326]

Reference Example 40

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0327]



[0328]

A mixture of the compound of Reference Example 39 (950 mg, 2.73 mmol), sarcosine ethyl ester hydrochloride (839 mg, 5.46

mmol), triethylamine (2.27 mL, 16.4 mmol) and ethanol (10 mL) was stirred at 80°C for 10 hr, triethylamine (2.27 mL, 16.4 mmol) was further added, and the mixture was stirred at 100°C for 15 hr. After cooling, water was added to the reaction mixture, and the mixture was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/methanol=10/1) to give the title compound (698 mg, 67%) as a brown solid.

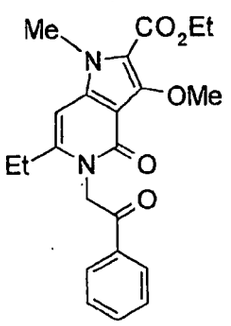
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3 H, t, J=7.4 Hz), 1.31 (3 H, t, J=7.1 Hz), 2.56 (2 H, q, J=7.6 Hz), 3.80 (3 H, s), 4.30 (2 H, q, J=7.2 Hz), 5.55 (2 H, s), 6.43 (1 H, s), 7.60 (2 H, t, J=7.6 Hz), 7.68-7.79 (1 H, m), 8.00-8.21 (2 H, m), 8.90 (1 H, s).

[0329]

Reference Example 41

Production of ethyl 6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0330]



[0331]

In the same manner as in Reference Example 6, the title compound (156 mg, 23%) was obtained as a white powder from the compound of Reference Example 40 (650 mg, 1.70 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.3 Hz), 1.30 (3 H, t, J=7.1 Hz), 2.58 (2 H, q, J=7.4 Hz), 3.84 (3 H, s), 3.85 (3

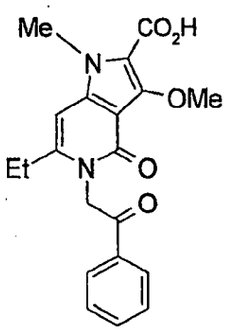
H, s), 4.27 (2 H, q, J=7.0 Hz), 5.58 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.67-7.82 (1 H, m), 8.03-8.19 (2 H, m).

[0332]

Reference Example 42

Production of 6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0333]



[0334]

In the same manner as in Reference Example 7, the title compound (110 mg, 79%) was obtained as a white powder from the compound of Reference Example 41 (150 mg, 0.378 mmol).

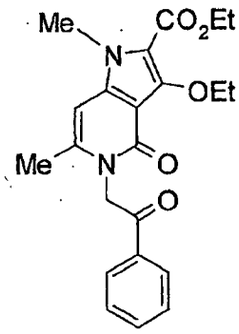
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.3 Hz), 2.57 (2 H, q, J=7.3 Hz), 3.84 (3 H, s), 3.85 (3 H, s), 5.58 (2 H, s), 6.48 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.67-7.86 (1 H, m), 7.97-8.31 (2 H, m), 12.51 (1 H, br s).

[0335]

Reference Example 43

Production of ethyl 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0336]



[0337]

In the same manner as in Reference Example 6, the title compound (560 mg, 52%) was obtained as a white powder from the compound of Reference Example 33 (1.00 g, 2.71 mmol) and iodoethane (326 μL, 4.07 mmol).

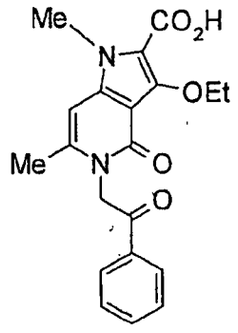
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.24 (3 H, t, J=7.0 Hz), 1.30 (3 H, t, J=7.1 Hz), 2.28 (3 H, s), 3.81 (3 H, s), 4.15 (2 H, q, J=7.0 Hz), 4.26 (2 H, q, J=7.1 Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.78 (1 H, m), 8.06-8.14 (2 H, m).

[0338]

Reference Example 44

Production of 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0339]



[0340]

In the same manner as in Reference Example 7, the title compound (380 mg, 74%) was obtained as a white powder from the compound of Reference Example 43 (550 mg, 1.39 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.22 (3 H, t, J=7.0 Hz), 2.28 (3 H,

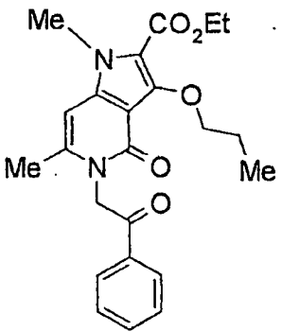
s), 3.81 (3 H, s), 4.16 (2 H, q, J=7.0 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.79 (1 H, m), 8.03-8.16 (2 H, m), 12.38 (1 H, br s).

[0341]

Reference Example 45

Production of ethyl 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0342]



[0343]

In the same manner as in Reference Example 6, the title compound (152 mg, 18%) was obtained as a white powder from the compound (750 mg, 2.04 mmol) of Reference Example 33 and 1-bromopropane (277 μL, 3.05 mmol).

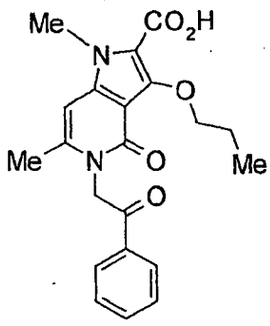
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.94 (3 H, t, J=7.5 Hz), 1.30 (3 H, t, J=7.1 Hz), 1.57-1.73 (2 H, m), 2.28 (3 H, s), 3.80 (3 H, s), 4.08 (2 H, t, J=6.5 Hz), 4.26 (2 H, q, J=7.1 Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.06-8.15 (2 H, m).

[0344]

Reference Example 46

Production of 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0345]



[0346]

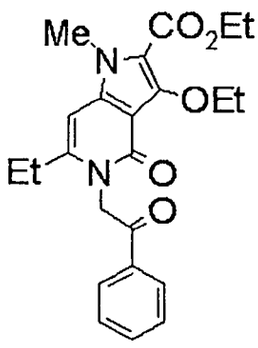
In the same manner as in Reference Example 7, the title compound (105 mg, 81%) was obtained as a white powder from the compound of Reference Example 45 (140 mg, 0.341 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.88-0.94 (3 H, m), 1.58-1.67 (2 H, m), 2.27 (3 H, s), 3.81 (3 H, s), 4.08 (2 H, t, J=6.6 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.55-7.65 (2 H, m), 7.69-7.77 (1 H, m), 8.06-8.14 (2 H, m).

[0347]

Reference Example 47

Production of ethyl 6-ethyl-3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0348]



[0349]

A mixture of the compound of Reference Example 40 (330 mg, 0.863 mmol), potassium carbonate (715 mg, 5.18 mmol), iodoethane (138 μL, 1.73 mmol) and DMF (5 mL) was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over

magnesium sulfate, and concentrated under reduced pressure. The residue was collected by filtration, and dried to give the title compound (189 mg, 46%) as a white powder.

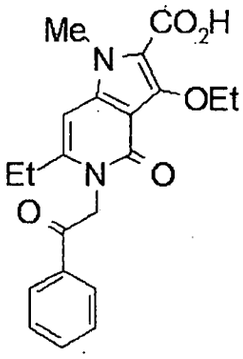
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.35 (9 H, m), 2.57 (2 H, q, J=7.2 Hz), 3.84 (3 H, s), 4.10-4.19 (2 H, m), 4.26 (2 H, q, J=7.2 Hz), 5.58 (2 H, s), 6.49 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.07-8.14 (2 H, m).

[0350]

Reference Example 48

Production of 3-ethoxy-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0351]



[0352]

A solution of the compound of Reference Example 47 (160 mg, 0.390 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (74.0 mg, 50%) as a white powder.

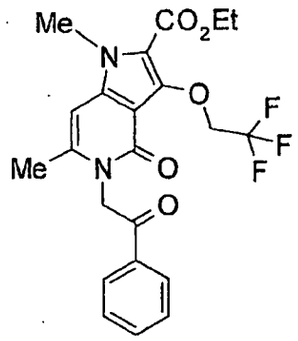
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.25 (6 H, m), 2.57 (2 H, q, J=7.3 Hz), 3.84 (3 H, s), 4.15 (2 H, q, J=7.0 Hz), 5.57 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, J=7.5 Hz), 7.69-7.78 (1 H, m), 8.08-8.15 (2 H, m), 12.35 (1 H, br s).

[0353]

Reference Example 49

Production of ethyl 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0354]



[0355]

A mixture of the compound of Reference Example 33 (750 mg, 2.04 mmol), 1,1,1-trifluoro-2-iodoethane (603 μL, 6.12 mmol), potassium fluoride (119 mg, 2.04 mmol) and dimethyl sulfoxide (10 mL) was stirred at 100°C for 15 hr. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate) to give the title compound (125 mg, 14%) as a white solid.

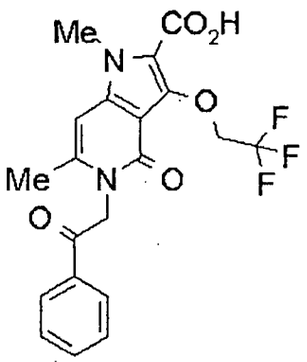
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3 H, t, J=7.2 Hz), 2.30 (3 H, s), 3.83 (3 H, s), 4.19-4.31 (2 H, m), 4.84 (2 H, q, J=9.3 Hz), 5.64 (2 H, s), 6.66 (1 H, s), 7.57-7.66 (2 H, m), 7.69-7.79 (1 H, m), 8.07-8.15 (2 H, m).

[0356]

Reference Example 50

Production of 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0357]



[0358]

A solution of the compound of Reference Example 49 (110 mg, 0.244 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water and acidified with 6N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (78.0 mg, 76%) as a white powder.

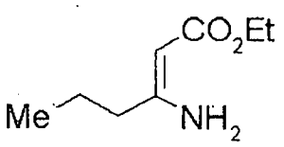
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.29 (3 H, s), 3.83 (3 H, s), 4.82 (2 H, q, J=9.3 Hz), 5.63 (2 H, s), 6.64 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.78 (1 H, m), 8.07-8.15 (2 H, m), 12.57 (1 H, br s).

[0359]

Reference Example 51

Production of ethyl (2Z)-3-aminohex-2-enoate

[0360]



[0361]

In the same manner as in Reference Example 36, the title compound (109 g, quant.) was obtained as a pale-yellow oil from ethyl 3-oxohexanoate (100 g, 632 mmol), ammonium acetate (244 g, 3.16 mmol) and methanol (750 mL).

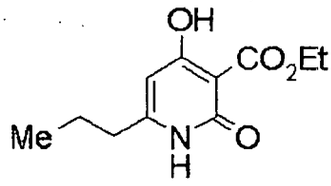
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J=7.4 Hz), 1.11-1.17 (3 H, m), 1.42-1.58 (2 H, m), 2.00-2.07 (2 H, m), 3.96 (2 H, q, J=7.2 Hz), 4.30 (1 H, s), 6.90 (1 H, br s), 7.73 (1 H, br s).

[0362]

Reference Example 52

Production of ethyl 4-hydroxy-2-oxo-6-n-propyl-1,2-dihydropyridine-3-carboxylate

[0363]



[0364]

In the same manner as in Reference Example 37, the title compound (27.5 g, 34%) was obtained as a white powder from the compound of Reference Example 51 (50.0 g, 0.387 mmol), diethyl malonate (58.8 mL, 387 mmol) and ethanol (400 mL).

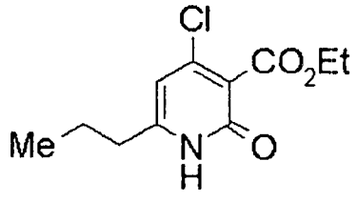
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J=7.4 Hz), 1.26 (3 H, t, J=7.2 Hz), 1.49-1.65 (2 H, m), 2.38 (2 H, t), 4.25 (2 H, q, J=7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, s), 12.56 (1 H, s).

[0365]

Reference Example 53

Production of ethyl 4-chloro-2-oxo-6-propyl-1,2-dihydropyridine-3-carboxylate

[0366]



[0367]

A mixture of the compound of Reference Example 52 (37.0 g, 164 mmol) and phosphorus oxychloride (45.9 mL, 493 mmol) was stirred at 80°C for 30 min. The mixture was concentrated under reduced pressure, and ice water was added to the residue. The precipitated solid was collected by filtration, and washed with water and ethyl acetate to give the title compound (17.6 g, 44%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.87 (3 H, t, J=7.4 Hz), 1.26 (3 H,

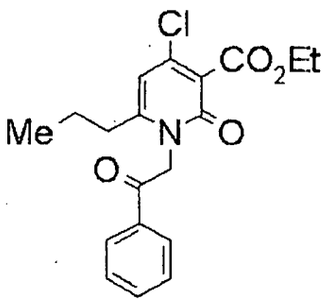
t, J=7.1 Hz), 1.52-1.65 (2 H, m), 2.40-2.48 (2 H, m), 4.25 (2 H, q, J=7.1 Hz), 6.27 (1 H, s), 12.17 (1 H, br s).

[0368]

Reference Example 54

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-6-propyl-1,2-dihydropyridine-3-carboxylate

[0369]



[0370]

In the same manner as in Reference Example 4, the title compound (7.15 g, 28%) was obtained as a white powder from the compound of Reference Example 53 (17.0 g, 69.8 mmol), sodium hydride (60% in oil, 3.07 g, 76.7 mmol), phenacyl bromide (16.7 g, 83.8 mmol) and DMF (150 mL).

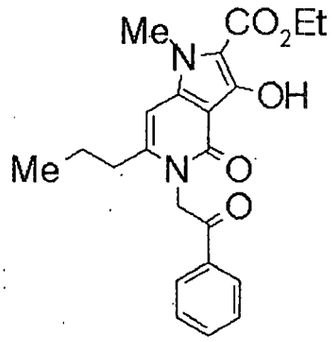
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.91 (3 H, t, J=7.3 Hz), 1.24 (3 H, t, J=7.1 Hz), 1.47-1.64 (2 H, m), 2.55-2.66 (2 H, m), 4.24 (2 H, q, J=7.1 Hz), 5.59 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.80 (1 H, m), 8.06-8.17 (2 H, m).

[0371]

Reference Example 55

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0372]



[0373]

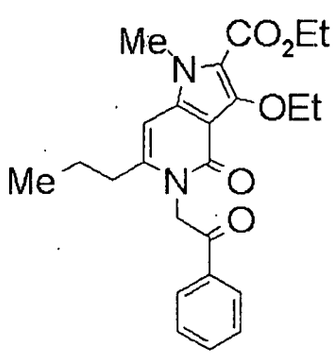
A mixture of the compound of Reference Example 54 (7.00 g, 19.3 mmol), sarcosine ethyl ester hydrochloride (5.94 g, 38.7 mmol), triethylamine (29.7 mL, 193 mmol) and ethanol (100 mL) was stirred for 2 days under refluxing conditions. The mixture was concentrated under reduced pressure, water (200 mL) was added to the residue, and the mixture was acidified with 5N hydrochloric acid (3 mL). The precipitated solid was collected by filtration, and washed with water and hexane-ethyl acetate to give the title compound (5.70 g, 74%) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.92 (3 H, t, J=7.3 Hz), 1.31 (3 H, t, J=7.1 Hz), 1.50-1.65 (2 H, m), 2.49-2.57 (2 H, m), 3.78 (3 H, s), 4.30 (2 H, q, J=7.1 Hz), 5.52 (2 H, s), 6.45 (1 H, s), 7.60 (2 H, t, J=7.5 Hz), 7.68-7.78 (1 H, m), 8.07-8.15 (2 H, m), 8.90 (1 H, br s).

[0374]

Reference Example 56

Production of ethyl 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0375]



[0376]

A mixture of the compound of Reference Example 55 (1.00 g, 8.08 mmol), diethyl sulfate (397 μL, 3.03 mmol), potassium carbonate (1.05 g, 7.57 mmol) and acetone (20 mL) was stirred for 15 hr under refluxing conditions. Water (30 mL) was added to the mixture, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate-hexane to give the title compound (876 mg, 82%) as a white solid.

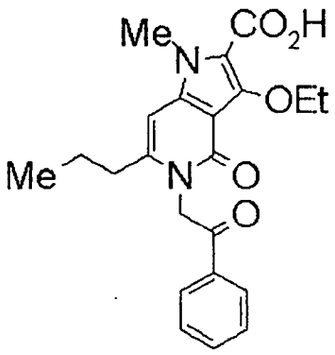
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.93 (3 H, t, J=7.4 Hz), 1.23 (3 H, t, J=7.0 Hz), 1.30 (3 H, t, J=7.1 Hz), 1.52-1.66 (2 H, m), 2.51-2.58 (2 H, m), 3.83 (3 H, s), 4.14 (2 H, q, J=7.1 Hz), 4.26 (2 H, q, J=7.1 Hz), 5.54 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.77 (1 H, m), 8.08-8.15 (2 H, m).

[0377]

Reference Example 57

Production of 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0378]



[0379]

A solution of the compound of Reference Example 56 (850 mg, 2.00 mmol) and 8N aqueous sodium hydroxide solution (2 mL) in ethanol (14 mL) was stirred at 60°C for 30 min. The reaction mixture was diluted with water, acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (705 mg, 89%) as a white powder.

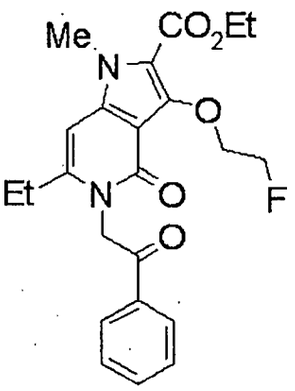
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.93 (3 H, t, J=7.4 Hz), 1.21 (3 H, t, J=7.0 Hz), 1.50-1.66 (2 H, m), 2.50-2.58 (2 H, m), 3.83 (3 H, s), 4.15 (2 H, q, J=7.1 Hz), 5.54 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.69-7.78 (1 H, m), 8.08-8.16 (2 H, m), 12.42 (1 H, br s).

[0380]

Reference Example 58

Production of ethyl 6-ethyl-3-(2-fluoroethoxy)-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0381]



[0382]

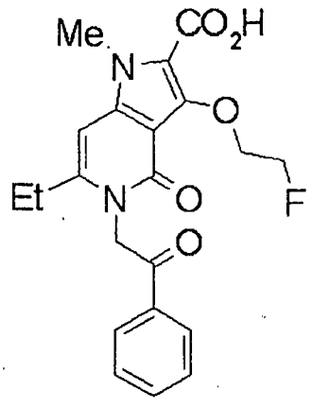
In the same manner as in Reference Example 6, the title compound (649 mg, 77%) was obtained as a white powder from the compound of Reference Example 40 (750 mg, 1.96 mmol), DBU (440 μL, 2.94 mmol) and 1-fluoro-2-iodoethane (512 mg, 2.94 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.3 Hz), 1.30 (3 H, t, J=7.1 Hz), 2.58 (2 H, q, J=7.3 Hz), 3.85 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.32-4.36 (1 H, m), 4.42-4.47 (1 H, m), 4.53-4.59 (1 H, m), 4.69-4.75 (1 H, m), 5.58 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.08-8.14 (2 H, m).

[0383]

Reference Example 59

Production of 6-ethyl-3-(2-fluoroethoxy)-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0384]



[0385]

A solution of the compound of Reference Example 58 (620 mg, 1.45 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 30 min. The reaction mixture was diluted with water, acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (470 mg, 56%) as a white powder.

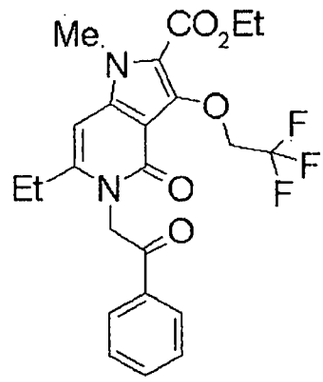
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.4 Hz), 2.58 (2 H, q, J=7.4 Hz), 3.85 (3 H, s), 4.32-4.36 (1 H, m), 4.42-4.47 (1 H, m), 4.54-4.59 (1 H, m), 4.70-4.74 (1 H, m), 5.58 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.09-8.15 (2 H, m), 12.48 (1 H, br s).

[0386]

Reference Example 60

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0387]



[0388]

A mixture of the compound of Reference Example 40 (1.00 g, 2.61 mmol), 1,1,1-trifluoro-2-iodoethane (1.29 mL, 13.1 mmol), cesium carbonate (4.27 g, 13.1 mmol) and dimethyl sulfoxide (10 mL) was stirred at 100°C for 5 hr. The reaction mixture was filtered, the filtrate was diluted with 1N hydrochloric acid (30 mL), and the mixture was extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; hexane/ethyl acetate=9/1 - 0/10) to give the title compound (278 mg, 23%) as a white solid.

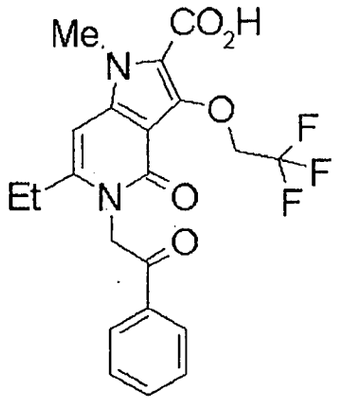
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.4 Hz), 1.28 (3 H, t, J=7.1 Hz), 2.59 (2 H, q, J=7.4 Hz), 3.86 (3 H, s), 4.26 (2 H, q, J=7.1 Hz), 4.83 (2 H, q, J=9.3 Hz), 5.62 (2 H, s), 6.56 (1 H, s), 7.61 (2 H, t, J=7.5 Hz), 7.70-7.78 (1 H, m), 8.08-8.14 (2 H, m).

[0389]

Reference Example 61

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0390]



[0391]

A solution of the compound of Reference Example 60 (270 mg, 0.581 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was diluted with water, acidified with 5N hydrochloric acid, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (235 mg, 93%) as a white powder.

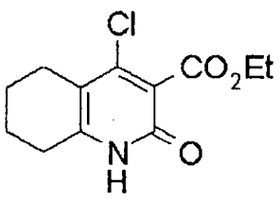
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J=7.4 Hz), 2.58 (2 H, q, J=7.4 Hz), 3.86 (3 H, s), 4.82 (2 H, q, J=9.2 Hz), 5.61 (2 H, s), 6.54 (1 H, s), 7.61 (2 H, t, J=7.6 Hz), 7.70-7.77 (1 H, m), 8.07-8.16 (2 H, m), 12.74 (1 H, br s).

[0392]

Reference Example 62

Production of ethyl 4-chloro-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate

[0393]



[0394]

A mixture of ethyl 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (26.0 g, 110 mmol) and phosphorus oxychloride (51.3 mL) was stirred at 130°C for 1.5 hr. After cooling, the reaction mixture was concentrated under

reduced pressure, and ice was added to the residue. The mixture was neutralized with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed successively with saturated sodium hydrogen carbonate solution, water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was collected by filtration, and washed with ethyl acetate-hexane to give the title compound (4.65 g, 17%) as a white solid.

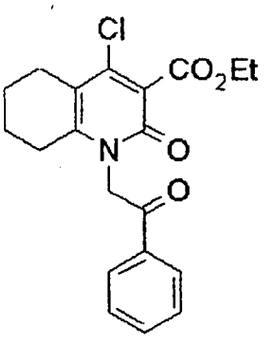
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (3 H, t, J=7.1 Hz), 1.61-1.74 (4 H, m), 2.37-2.45 (2 H, m), 2.51-2.57 (2 H, m), 4.24 (2 H, q, J=7.2 Hz), 12.09 (1 H, s).

[0395]

Reference Example 63

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate

[0396]



[0397]

In the same manner as in Reference Example 4, the title compound (710 mg, 16%) was obtained as a white powder from the compound of Reference Example 62 (3.00 g, 11.7 mmol), sodium hydride (60% in oil, 516 mg, 12.9 mmol) and phenacyl bromide (2.57 g, 12.9 mmol).

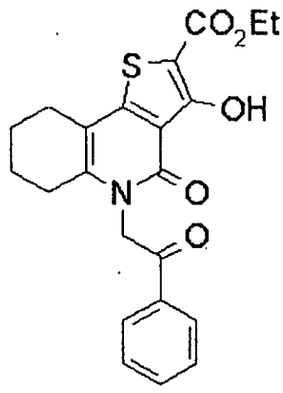
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (3H, t, J = 7.1 Hz), 1.60-1.80 (4H, m), 2.50-2.65 (4H, m), 4.26 (2H, q, J = 7.1 Hz), 5.66 (2H, s), 7.61 (2H, t, J = 7.4 Hz), 7.74 (1H, t, J = 7.4 Hz), 8.09 (2H, d, J = 7.4 Hz).

[0398]

Reference Example 64

Production of ethyl 3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylate

[0399]



[0400]

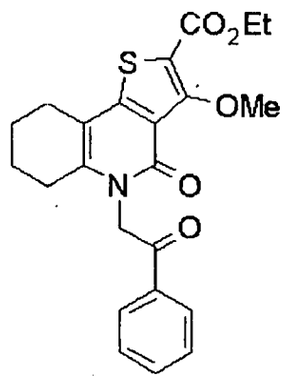
In the same manner as in Reference Example 5, the title compound (751 mg, 100%) was obtained as a white powder from the compound of Reference Example 63 (690 mg, 1.85 mmol), 20% solution (1.26 g, 3.69 mmol) of sodium ethoxide in ethanol, ethyl thioglycolate (486 μL, 4.43 mmol) and ethanol (15 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.29 (3H, t, J = 7.0 Hz), 1.65-1.85 (4H, m), 2.50-2.65 (4H, m), 4.28 (2H, q, J = 7.0 Hz), 5.72 (2H, s), 7.62 (2H, t, J = 7.7 Hz), 7.73-7.78 (1H, m), 8.10-8.13 (2H, m), 10.39 (1H, s).

[0401]

Reference Example 65

Production of ethyl 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylate

[0402]



[0403]

In the same manner as in Reference Example 6, the title compound (238 mg, 31%) was obtained as a white powder from the compound of Reference Example 64 (740 mg, 1.80 mmol), iodomethane (168 μL, 2.70 mmol), DBU (404 μL, 2.70 mmol) and DMF (15 mL).

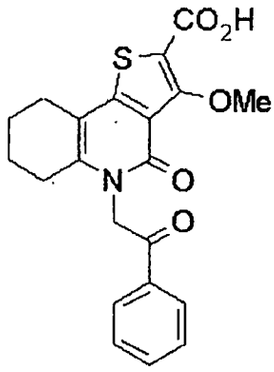
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.31 (3H, t, J = 7.0 Hz), 1.65-1.85 (4H, m), 2.45-2.65 (4H, m), 3.89 (3H, s), 4.29 (2H, q, J = 7.0 Hz), 5.67 (2H, s), 7.62 (2H, t, J = 7.4 Hz), 7.75 (1H, t, J = 7.4 Hz), 8.11 (2H, d, J = 7.4 Hz).

[0404]

Reference Example 66

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxylic acid

[0405]



[0406]

A solution of the compound of Reference Example 65 (220 mg, 0.517 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in ethanol (7 mL) was stirred at 60°C for 1 hr. The reaction mixture was acidified with 6N hydrochloric acid (1.5 mL), and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (162 mg, 79%) as a white powder.

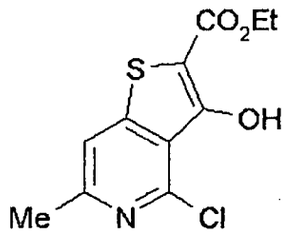
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.66-1.88 (4H, m), 2.52-2.61 (4H, m), 3.86 (3H, s), 5.66 (2H, s), 7.62 (2H, t, J = 7.6 Hz), 7.70-7.79 (1H, m), 8.03-8.11 (2H, m), 13.12 (1H, s).

[0407]

Reference Example 67

Production of ethyl 4-chloro-3-hydroxy-6-methylthieno[3,2-c]pyridine-2-carboxylate

[0408]



[0409]

To a suspension of ethyl 2,4-dichloro-6-methylpyridine-3-carboxylate (10.0 g, 42.7 mmol) in acetonitrile (45 mL) were added potassium carbonate (8.85 g, 64.1 mmol) and ethyl thioglycolate (4.68 mL, 42.7 mmol), and the mixture was stirred for 15 hr under refluxing conditions. The reaction mixture was diluted with water (150 mL), 6N hydrochloric acid (15mL) was added and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water and ethanol-diisopropyl ether (1/1), and dried under reduced pressure to give the title compound (10.9 g, 94%) as a white powder.

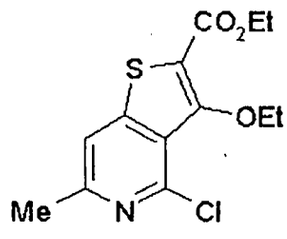
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (3H, t, J = 7.1 Hz), 2.54 (3H, s), 4.36 (2H, q, J = 7.1 Hz), 7.87 (1H, s), 10.75 (1H, s).

[0410]

Reference Example 68

Production of ethyl 4-chloro-3-ethoxy-6-methylthieno[3,2-c]pyridine-2-carboxylate

[0411]



[0412]

In the same manner as in Reference Example 6, the title compound (4.30 g, 78%) was obtained as a white powder from the compound of Reference Example 67 (4.97 g, 18.3 mmol), DBU (4.10 mL, 27.4 mmol) and iodoethane (2.19 mL, 27.4 mmol).

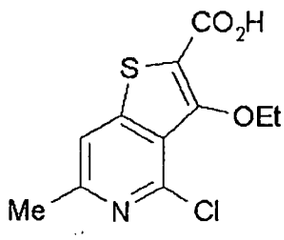
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.33 (3H, t, J = 7.2 Hz), 1.43 (3H, t, J = 7.1 Hz), 2.54 (3H, s), 4.25 (2H, q, J = 7.0 Hz), 4.34 (2H, q, J = 7.1 Hz), 7.92 (1H, s).

[0413]

Reference Example 69

Production of 4-chloro-3-ethoxy-6-methylthieno[3,2-c]pyridine-2-carboxylic acid

[0414]



[0415]

A mixed solution of the compound of Reference Example 68 (4.30 g, 14.3 mmol) and 8N aqueous sodium hydroxide solution (15 mL) in THF (22 mL)-ethanol (22 mL) was stirred for 5 hr under refluxing conditions. The reaction mixture was acidified with 6N hydrochloric acid (22 mL) and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (3.80 g, 97%) as a white powder.

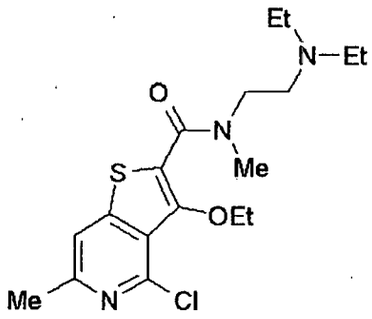
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40 (3H, t, J = 6.9 Hz), 2.54 (3H, s), 4.26 (2H, q, J = 6.9 Hz), 7.90 (1H, s), 13.65 (1H, s).

[0416]

Reference Example 70

Production of 4-chloro-N-[2-(diethylamino)ethyl]-3-ethoxy-N,6-dimethylthieno[3,2-c]pyridine-2-carboxamide

[0417]



[0418]

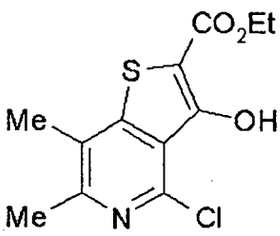
In the same manner as in Example 25, the title compound (800 mg, 59%) was obtained as a colorless oil from the compound of Reference Example 69 (1.00 g, 3.68 mmol) and N,N-diethyl-N'-methylethane-1,2-diamine (773 μL, 4.78 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.65-1.10 (6H, m), 1.33 (3H, t, J = 6.9 Hz), 2.20-2.70 (6H, m), 2.53 (3H, s), 3.04 (3H, s), 3.35-3.65 (2H, m), 4.05-4.20 (2H, m), 7.89 (1H, s).

[0419]

Reference Example 71

Production of ethyl 4-chloro-3-hydroxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylate

[0420]



[0421]

A 20% solution (1.73 g, 5.08 mmol) of sodium ethoxide in ethanol was diluted with ethanol (5 mL), and ethyl thioglycolate (610 mg, 5.08 mmol) was added. Ethyl 2,4-dichloro-5,6-dimethylpyridine-3-carboxylate (630 mg, 2.54 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 hr. 2N Hydrochloric acid (3 mL) was added to the reaction mixture and the mixture was partitioned between brine and ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated. The obtained solid was washed with diisopropyl ether-hexane, and dried under

reduced pressure to give the title compound (374 mg, 52%) as a white powder.

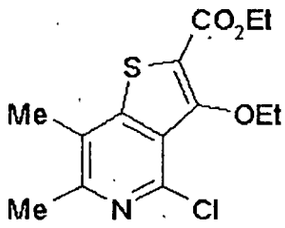
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43 (3H, t, J = 7.2 Hz), 2.40 (3H, s), 2.61 (3H, s), 4.44 (2H, q, J = 7.2 Hz), 10.63 (1H, s).

[0422]

Reference Example 72

Production of ethyl 4-chloro-3-ethoxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylate

[0423]



[0424]

In the same manner as in Reference Example 6, the title compound (350 mg, 91%) was obtained as a white solid from the compound of Reference Example 71 (350 mg, 1.22 mmol), DBU (380 mg, 2.02 mmol) and iodoethane (315 mg, 2.02 mmol).

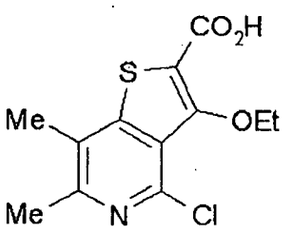
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43 (3H, t, J = 7.2 Hz), 1.54 (3H, t, J = 7.2 Hz), 2.42 (3H, s), 2.60 (3H, s), 4.31 (2H, q, J = 7.2 Hz), 4.41 (2H, q, J = 7.2 Hz).

[0425]

Reference Example 73

Production of 4-chloro-3-ethoxy-6,7-dimethylthieno[3,2-c]pyridine-2-carboxylic acid

[0426]



[0427]

A mixed solution of the compound of Reference Example 72 (250 mg, 0.80 mmol) and 4N aqueous sodium hydroxide solution

(2 mL) in THF (2 mL)-ethanol (1 mL) was stirred at room temperature for 18 hr. The reaction mixture was partitioned between 1N hydrochloric acid and ethyl acetate, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (210 mg, 92%) as a white solid.

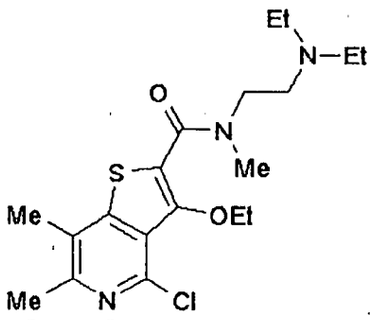
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40 (3H, t, J= 7.1 Hz), 2.40 (3H, s), 2.53 (3H, s), 4.25 (2H, q, J = 7.0 Hz).

[0428]

Reference Example 74

Production of 4-chloro-N-[2-(diethylamino)ethyl]-3-ethoxy-N,6,7-trimethylthieno[3,2-c]pyridine-2-carboxamide

[0429]



[0430]

In the same manner as in Example 25, the title compound (230 mg, 79%) was obtained as a colorless oil from the compound of Reference Example 73 (210 mg, 0.73 mmol) and N,N-diethyl-N'-methylethane-1,2-diamine (144 mg, 1.10 mmol).

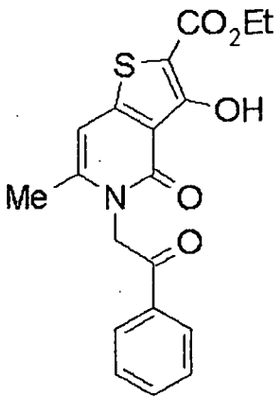
^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.80-1.10 (6H, m), 1.42 (3H, t, J = 6.9 Hz), 2.30-2.50 (5H, m), 2.60-2.80 (7H, m), 3.19 (3H, s), 3.45-3.70 (2H, m), 4.18 (2H, q, J = 7.0 Hz).

[0431]

Reference Example 75

Production of ethyl 3-hydroxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0432]



[0433]

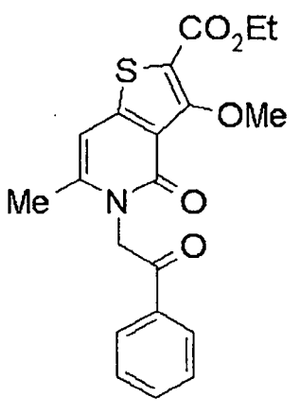
In the same manner as in Reference Example 5, the title compound (8.31 g, 88%) was obtained as a white powder from the compound of Reference Example 32 (8.50 g, 25.5 mmol), ethyl thioglycolate (6.70 mL, 61.1 mmol), a 20% solution (17.4 g, 51.0 mmol) of sodium ethoxide in ethanol and ethanol (100 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3H, t, J=7.2 Hz), 2.33 (3H, s), 4.27 (2H, q, J=7.1 Hz), 5.71 (2H, s), 6.93 (1H, d, J=0.9 Hz), 7.62 (2H, t, J=7.5 Hz), 7.69-7.83 (1H, m), 8.01-8.21 (2H, m), 10.34 (1H, s).

[0434]

Reference Example 76

Production of ethyl 3-methoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0435]



[0436]

A mixture of the compound of Reference Example 75 (3.00 g, 8.08 mmol), dimethyl sulfate (4.58 mL, 48.4 mmol), potassium carbonate (3.35 g, 24.2 mmol) and acetone (60 mL) was stirred

for 3 days under refluxing conditions. Water (120 mL) was added to the mixture, and the precipitated solid was collected by filtration, and washed with water, ethanol and ethyl acetate to give the title compound (2.45 g, 79%) as a white solid.

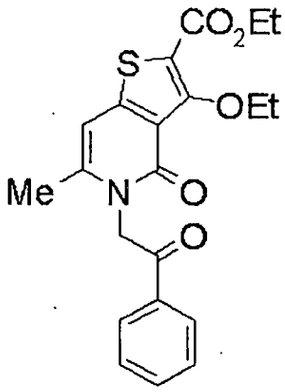
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30 (3H, t, J=7.1 Hz), 2.31 (3H, s), 3.88 (3H, s), 4.28 (2H, q, J=7.2 Hz), 5.66 (2H, s), 6.85 (1H, d, J=0.8 Hz), 7.58-7.67 (2H, m), 7.70-7.80 (1H, m), 8.06-8.15 (2H, m).

[0437]

Reference Example 77

Production of ethyl 3-ethoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0438]



[0439]

In the same manner as in Reference Example 6, the title compound (585 mg, 54%) was obtained as a white powder from the compound of Reference Example 75 (1.00 g, 2.69 mmol), DBU (604 μL, 4.04 mmol) and iodoethane (323 μL, 4.04 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.23-1.35 (6H, m), 2.31 (3H, s), 4.14 (2H, q, J=7.0 Hz), 4.27 (2H, q, J=7.1 Hz), 5.67 (2H, s), 6.84 (1H, d, J=0.8 Hz), 7.57-7.67 (2H, m), 7.71-7.79 (1H, m), 8.07-8.15 (2H, m).

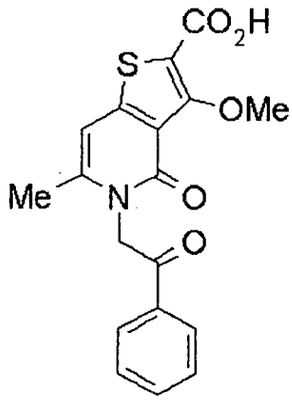
[0440]

Reference Example 78

Production of 3-methoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic

acid

[0441]



[0442]

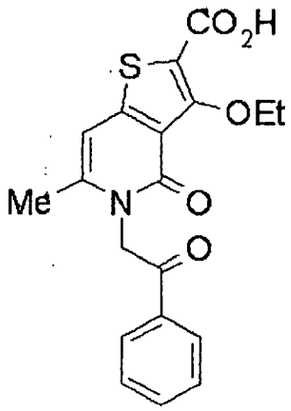
In the same manner as in Reference Example 7, the title compound (1.25 g, 67%) was obtained as a white powder from the compound of Reference Example 76 (2.00 g, 5.19 mmol), 8N aqueous sodium hydroxide solution (3 mL) and ethanol (21 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.31 (3H, m), 3.86 (3H, s), 5.66 (2H, s), 6.83 (1H, d, J=0.8 Hz), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 8.08-8.17 (2H, m), 13.07 (1H, br s).

[0443]

Reference Example 79

Production of 3-ethoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid

[0444]



[0445]

In the same manner as in Reference Example 7, the title compound (311 mg, 67%) was obtained as a white powder from the compound of Reference Example 77 (500 mg, 1.25 mmol), 8N

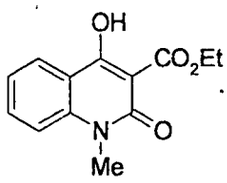
aqueous sodium hydroxide solution (1 mL) and ethanol (7 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.27 (3H, t, J=7.0 Hz), 2.30 (3H, s), 4.14 (2H, q, J=7.0 Hz), 5.66 (2H, s), 6.82 (1H, s), 7.58-7.66 (2H, m), 7.71-7.79 (1H, m), 8.08-8.17 (2H, m), 13.05 (1H, br s).

[0446]

Reference Example 80

Production of ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0447]



[0448]

To a solution of diethyl malonate (68.0 g, 0.425 mol) in DMF (400 mL) was added sodium hydride (66% in oil, 10.8 g, 0.30 mol) under ice-cooling, and the mixture was stirred at the same temperature for 5 min and at room temperature for 15 min. N-Methylisatoic anhydride (50.8 g, 0.287 mol) was added to the obtained mixture by small portions, and the mixture was stirred at 120°C for 3 hr. Diisopropyl ether (500 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration and washed with diisopropyl ether. The obtained solid was suspended in a mixture of methanol (250 mL) and water (500 mL), 5N hydrochloric acid (60 mL) was added dropwise, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was washed with diisopropyl ether to give the title compound (41.4 g, 58%).

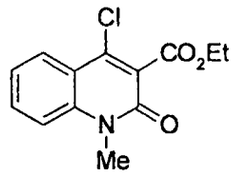
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.49 (3H, t, J = 7.1 Hz), 3.66 (3H, s), 4.51 (2H, q, J = 7.1 Hz), 7.23-7.30 (1H, m), 7.32 (1H, d, J = 8.7 Hz), 7.69 (1H, ddd, J = 8.7, 7.1, 1.6 Hz), 8.19 (1H, dd, J = 8.0, 1.6 Hz), 14.21 (1H, s).

[0449]

Reference Example 81

Production of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0450]



[0451]

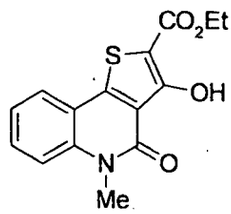
A mixture of the compound of Reference Example 80 (58.0 g, 0.235 mol) and phosphorus oxychloride (33 mL, 0.35 mol) was stirred at 110°C for 30 min. The reaction mixture was concentrated under reduced pressure, and ice water and ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, 1N sodium hydroxide solution (3 times) and water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (47.7 g, 76%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.1 Hz), 3.73 (3H, s), 4.48 (2H, q, J = 7.1 Hz), 7.35 (1H, ddd, J = 8.7, 7.1, 1.0 Hz), 7.40 (1H, d, J = 8.7 Hz), 7.68 (1H, ddd, J = 8.7, 7.1, 1.4 Hz), 8.07 (1H, dd, J = 8.0, 1.4 Hz).

[0452]

Reference Example 82

Production of ethyl 3-hydroxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0453]



[0454]

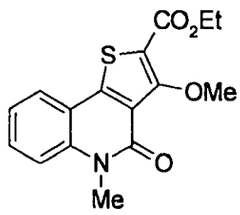
A 20% solution (23.2 g, 68 mmol) of sodium ethoxide in ethanol was diluted with ethanol (70 mL), ethyl thioglycolate (9.0 mL, 82 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 10 min. The compound of Reference Example 81 (9.04 g, 34.0 mmol) was added to this mixture, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was neutralized with ice water and 2N hydrochloric acid (40 mL) under ice-cooling, and the mixture was extracted twice with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was recrystallized from THF-diisopropyl ether to give the title compound (9.12 g, 88%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 4.41 (2H, q, J = 7.2 Hz), 7.34 (1H, ddd, J = 7.9, 7.2, 0.8 Hz), 7.44-7.49 (1H, m), 7.63 (1H, ddd, J = 8.6, 7.2, 1.4 Hz), 7.83 (1H, dd, J = 7.9, 1.4 Hz), 10.76 (1H, s).

[0455]

Reference Example 83

Production of ethyl 3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0456]



[0457]

To a suspension of the compound of Reference Example 82 (3.04 g, 10.0 mmol) in DMF (30 mL) was added DBU (1.65 mL, 11 mmol), and iodomethane (0.81 mL, 13 mmol) was added to the obtained solution under ice-cooling. The obtained mixture was stirred at room temperature for 21 hr, water was added and the precipitated solid was collected by filtration. This was dissolved in ethanol by heating, treated with activated carbon,

filtered, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the mixture was washed with water and 0.5N sodium hydroxide solution, filtered through Celite (trade name), further washed twice with water, and concentrated under reduced pressure. The residue was recrystallized from ethanol-diisopropyl ether to give the title compound (1.51 g, 48%).

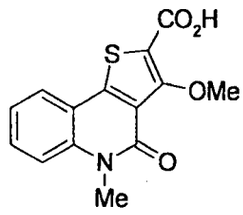
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.2 Hz), 3.76 (3H, s), 4.14 (3H, s), 4.40 (2H, q, J = 7.2 Hz), 7.24-7.31 (1H, m), 7.41 (1H, d, J = 8.7 Hz), 7.59 (1H, ddd, J = 8.7, 7.3, 1.5 Hz), 7.84 (1H, dd, J = 8.1, 1.5 Hz).

[0458]

Reference Example 84

Production of 3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0459]



[0460]

To a suspension of the compound of Reference Example 83 (1.90 g, 5.99 mmol) in THF (20 mL) and ethanol (20 mL) was added 5N sodium hydroxide solution (2.4 mL, 12 mmol). The obtained mixture was stirred at room temperature for 1.5 hr. 1N Hydrochloric acid (13 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, and recrystallized from methanol to give the title compound (1.14 g, 66%).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.66 (3H, d, J = 1.1 Hz), 3.95 (3H, s), 7.30-7.37 (1H, m), 7.58-7.71 (2H, m), 7.94-8.00 (1H, m).

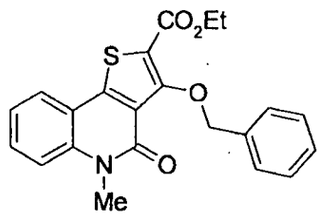
[0461]

Reference Example 85

Production of ethyl 3-(benzyloxy)-5-methyl-4-oxo-4,5-

dihydrothieno[3,2-c]quinoline-2-carboxylate

[0462]



[0463]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (10 mL) was added DBU (0.592 mL, 3.96 mmol), and benzylbromide (0.510 mL, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 15 hr. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2 - 2/1) to give the title compound (980 mg, 75%).

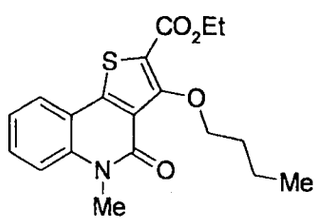
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.36 (3H, t, J = 7.2 Hz), 3.78 (3H, s), 4.36 (2H, q, J = 7.2 Hz), 5.34 (2H, s), 7.24-7.44 (5H, m), 7.59 (1H, ddd, J = 8.6, 7.1, 1.4 Hz), 7.63-7.69 (2H, m), 7.85 (1H, dd, J = 7.8, 1.4 Hz).

[0464]

Reference Example 86

Production of ethyl 3-butoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0465]



[0466]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (10 mL) was added DBU (0.592 mL, 3.96 mmol), and 1-iodobutane (0.488 mL, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 15 hr. Ethyl acetate and water were added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2 - 2/1) to give the title compound (1.05 g, 89%).

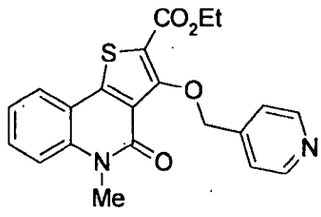
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.01 (3H, t, J = 7.5 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.50-1.66 (2H, m), 1.87-1.99 (2H, m), 3.74 (3H, s), 4.28 (2H, t, J = 6.6 Hz), 4.39 (2H, q, J = 7.2 Hz), 7.27 (1H, ddd, J = 8.0, 7.1, 0.9 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.58 (1H, ddd, J = 8.6, 7.1, 1.4 Hz), 7.81-7.86 (1H, m).

[0467]

Reference Example 87

Production of ethyl 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0468]



[0469]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.18 mL, 7.89 mmol), and 4-(chloromethyl)pyridine hydrochloride (704 mg, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 18 hr, at 45°C for

2 hr, and at 60°C for 18 hr. DBU (1.18 mL, 7.89 mmol) and 4-(chloromethyl)pyridine hydrochloride (704 mg, 4.29 mmol) were added, and the mixture was stirred at 60°C for 10 hr. Chloroform and water were added to the reaction mixture, the organic layer was separated, and the aqueous layer was extracted with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (678 mg, 53%).

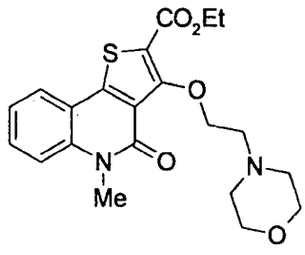
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.35 (3H, t, J = 7.2 Hz), 3.77 (3H, s), 4.37 (2H, q, J = 7.2 Hz), 5.36 (2H, s), 7.27-7.34 (1H, m), 7.43 (1H, d, J = 8.4 Hz), 7.58-7.65 (3H, m), 7.86 (1H, dd, J = 7.8, 1.2 Hz), 8.61-8.65 (2H, m).

[0470]

Reference Example 88

Production of ethyl 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0471]



[0472]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.18 mL, 7.89 mmol), and 4-(2-chloroethyl)morpholine hydrochloride (798 mg, 4.29 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 17 hr. Chloroform and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-diisopropyl

ether to give the title compound (2.16 g, 85%).

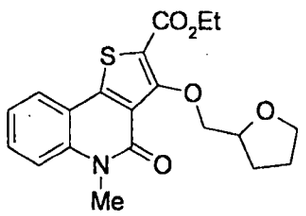
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.41 (3H, t, J = 7.1 Hz), 2.63 (4H, br t, J = 4.7 Hz), 2.96 (2H, t, J = 5.7 Hz), 3.72 (4H, br t, J = 4.7 Hz), 3.74 (3H, s), 4.38 (2H, q, J = 7.1 Hz), 4.43 (2H, t, J = 5.7 Hz), 7.24-7.31 (1H, m), 7.40 (1H, d, J = 8.5 Hz), 7.58 (1H, ddd, J = 8.5, 7.2, 1.5 Hz), 7.81-7.86 (1H, m).

[0473]

Reference Example 89

Production of ethyl 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0474]



[0475]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (0.740 mL, 4.95 mmol), and 2-(bromomethyl)tetrahydrofuran (90% containing) (0.617 mL, 4.9 mmol) was added to the obtained solution. The obtained mixture was stirred at 40°C for 19 hr and at 80°C for 23 hr, DBU (0.740 mL, 4.95 mmol) and 2-(bromomethyl)tetrahydrofuran (90% containing) (0.617 mL, 4.9 mmol) were added, and the mixture was stirred at 80°C for 66 hr. Ethyl acetate and water were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=3/17 - 2/1) and crystallized from ethyl acetate-diisopropyl ether to give the title compound (821 mg, 64%).

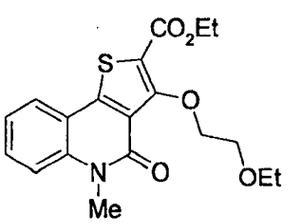
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.2 Hz), 1.84-2.19 (4H, m), 3.74 (3H, s), 3.76-3.85 (1H, m), 3.89-3.98 (1H, m), 4.22-4.49 (5H, m), 7.27 (1H, ddd, J = 8.0, 7.1, 1.0 Hz), 7.39 (1H, d, J = 8.1 Hz), 7.58 (1H, ddd, J = 8.6, 7.1, 1.4 Hz), 7.81-7.86 (1H, m).

[0476]

Reference Example 90

Production of ethyl 3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0477]



[0478]

To a suspension of the compound of Reference Example 82 (1.00 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.48 mL, 9.90 mmol), and 1-bromo-2-ethoxyethane (1.12 mL, 9.93 mmol) was added to the obtained solution. The obtained mixture was stirred at 60°C for 24 hr. Ethyl acetate and water were added to the reaction mixture, the organic layer was separated, and aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/1) and crystallized from ethyl acetate-hexane to give the title compound (986 mg, 80%).

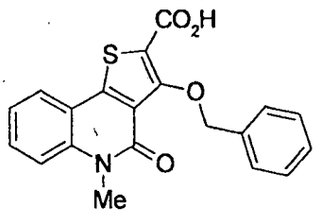
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.19 (3H, t, J = 7.0 Hz), 1.43 (3H, t, J = 7.1 Hz), 3.59 (2H, q, J = 7.0 Hz), 3.74 (3H, s), 3.93 (2H, t, J = 5.0 Hz), 4.40 (2H, q, J = 7.1 Hz), 4.46 (2H, t, J = 5.0 Hz), 7.26-7.31 (1H, m), 7.40 (1H, d, J = 8.5 Hz), 7.58 (1H, ddd, J = 8.5, 7.2, 1.4 Hz), 7.84 (1H, dd, J = 8.0, 1.4 Hz).

[0479]

Reference Example 91

Production of 3-(benzyloxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0480]



[0481]

To a solution of the compound of Reference Example 85 (867 mg, 2.20 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (0.88 mL, 4.4 mmol). The obtained mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid (5.0 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (665 mg, 83%).

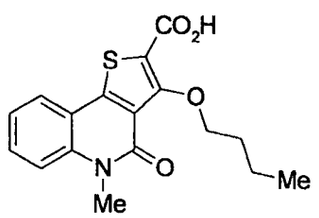
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.69 (3H, s), 5.22 (2H, s), 7.30-7.41 (4H, m), 7.57-7.72 (4H, m), 7.98 (1H, d, J = 8.1 Hz), 13.31 (1H, br s).

[0482]

Reference Example 92

Production of 3-butoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0483]



[0484]

To a solution of the compound of Reference Example 86 (923 mg, 2.57 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (1.0 mL, 5.0 mmol). The

obtained mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid (6.0 mL) was added to the reaction mixture, and the precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (872 mg, quantitative).

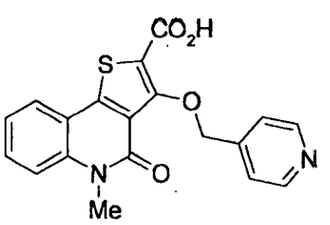
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.94 (3H, t, J = 7.5 Hz), 1.41-1.55 (2H, m), 1.71-1.82 (2H, m), 3.65 (3H, s), 4.16 (2H, t, J = 6.6 Hz), 7.32 (1H, t, J = 7.2 Hz), 7.54-7.70 (2H, m), 7.91-7.98 (1H, m), 13.21 (1H, br s).

[0485]

Reference Example 93

Production of 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0486]



[0487]

To a suspension of the compound of Reference Example 87 (723 mg, 1.83 mmol) in THF (6 mL) and ethanol (6 mL) was added 5N aqueous sodium hydroxide solution (0.74 mL, 3.7 mmol). The obtained mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (3.7 mL) was added to the reaction mixture and the mixture was diluted with water. The precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (424 mg, 63%).

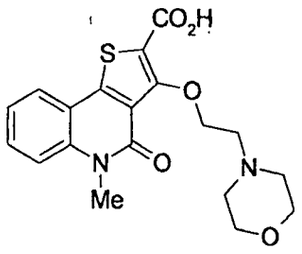
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.67 (3H, s), 5.28 (2H, s), 7.32-7.38 (1H, m), 7.59-7.72 (4H, m), 7.98 (1H, dd, J = 7.8, 1.2 Hz), 8.59 (2H, dd, J = 4.5, 1.5 Hz).

[0488]

Reference Example 94

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0489]



[0490]

To a suspension of the compound of Reference Example 88 (832 mg, 2.00 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (0.80 mL, 4.0 mmol). The obtained mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (4.0 mL) was added to the reaction mixture and the mixture was diluted with water, and concentrated under reduced pressure. Methanol was added to the residue and the mixture was concentrated under reduced pressure, and crystallized from water-methanol to give the title compound (477 mg, 61%).

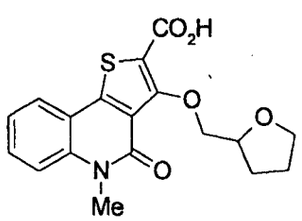
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.00-3.20 (6H, m), 3.67 (3H, s), 3.84 (4H, br t, J = 4.4 Hz), 4.53 (2H, br t, J = 5.0 Hz), 7.31 (1H, ddd, J = 8.0, 6.3, 1.8 Hz), 7.55-7.67 (2H, m), 7.88-7.91 (1H, m).

[0491]

Reference Example 95

Production of 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0492]



[0493]

To a suspension of the compound of Reference Example 89 (728 mg, 1.88 mmol) in THF (6 mL) and ethanol (6 mL) was added

5N aqueous sodium hydroxide solution (0.76 mL, 3.8 mmol). The obtained mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid (3.8 mL) was added to the reaction mixture and the mixture was diluted with water and the mixture was extracted 3 times with chloroform. The combined organic layer was washed with aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The obtained solid was washed with diisopropyl ether to give the title compound (659 mg, 97%).

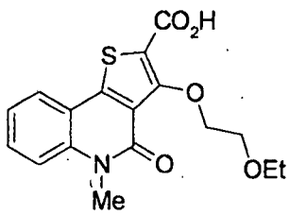
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.73-2.04 (4H, m), 3.56-3.78 (2H, m), 3.65 (3H, s), 4.02-4.10 (1H, m), 4.19-4.30 (2H, m), 7.29-7.37 (1H, m), 7.57-7.71 (2H, m), 7.92-7.99 (1H, m), 13.20 (1H, br s).

[0494]

Reference Example 96

Production of 3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0495]



[0496]

To a suspension of the compound of Reference Example 90 (826 mg, 2.20 mmol) in THF (7 mL) and ethanol (7 mL) was added 5N aqueous sodium hydroxide solution (0.88 mL, 4.4 mmol). The obtained mixture was stirred at room temperature for 2.5 hr, 5N aqueous sodium hydroxide solution (4.4 mL, 22 mmol) was added, and the mixture was stirred at 50°C for 3.5 hr. The reaction mixture was acidified with 1N hydrochloric acid and diluted with water, and the precipitated solid was collected by filtration, washed with water, and air dried to give the title compound (719 mg, 94%).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.03 (3H, t, J = 6.9 Hz), 3.44 (2H,

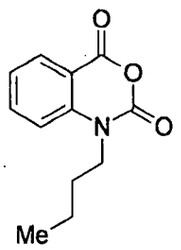
q, J = 6.9 Hz), 3.66 (3H, s), 3.75 (2H, t, J = 5.0 Hz), 4.33 (2H, t, J = 5.0 Hz), 7.33 (1H, t, J = 7.4 Hz), 7.58-7.71 (2H, m), 7.96 (1H, d, J = 8.1 Hz), 13.21 (1H, br s).

[0497]

Reference Example 97

Production of 1-butyl-2H-3,1-benzoxazine-2,4(1H)-dione

[0498]



[0499]

To a solution of isatoic anhydride (8.16 g, 50.0 mmol) in DMF (100 mL) was added sodium hydride (66% in oil, 2.00 g, 55 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. 1-Iodobutane (8.5 mL, 75 mmol) was added to the obtained mixture and the mixture was stirred at room temperature for 64 hr. Ice water was added to the reaction mixture and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed twice with water and concentrated under reduced pressure to give the title compound (10.5 g), which was used for the next reaction without purification.

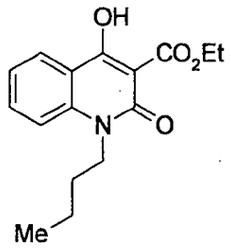
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.01 (3H, t, J = 7.4 Hz), 1.48 (2H, sext, J = 7.4 Hz), 1.69-1.81 (2H, m), 4.02-4.10 (2H, m), 7.17 (1H, d, J = 8.6 Hz), 7.25-7.32 (1H, m), 7.75 (1H, ddd, J = 8.6, 7.4, 1.7 Hz), 8.16 (1H, dd, J = 7.8, 1.7 Hz).

[0500]

Reference Example 98

Production of ethyl 1-butyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0501]



[0502]

To a solution of diethyl malonate (12.0 g, 74.9 mmol) in DMF (70 mL) was added sodium hydride (66% in oil, 2.00 g, 55 mmol) under ice-cooling, and the mixture was stirred at the same temperature for 10 min. A solution of the compound of Reference Example 97 (10.5 g) in DMF (20 mL) was added dropwise to the obtained mixture, and the mixture was stirred at 120°C for 6 hr. The reaction mixture was concentrated under reduced pressure, ice water was added to the residue and the obtained aqueous layer was washed with diethyl ether. The aqueous layer was weakly acidified with 5N hydrochloric acid (12 mL) under ice-cooling, and extracted twice with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/9 - 1/2) to give the title compound (9.96 g, 69%, 2 steps) as a solid.

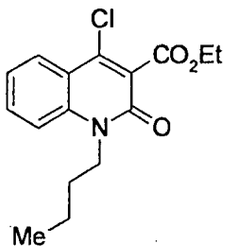
^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.99 (3H, t, J = 7.4 Hz), 1.482 (2H, sext, J = 7.4 Hz), 1.485 (3H, t, J = 7.1 Hz), 1.64-1.76 (2H, m), 4.17-4.26 (2H, m), 4.50 (2H, q, J = 7.1 Hz), 7.20-7.26 (1H, m), 7.29 (1H, d, J = 8.4 Hz), 7.66 (1H, ddd, J = 8.6, 7.4, 1.6 Hz), 8.18 (1H, dd, J = 8.3, 1.6 Hz), 14.20 (1H, s).

[0503]

Reference Example 99

Production of ethyl 1-butyl-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0504]



[0505]

A mixture of the compound of Reference Example 98 (9.73 g, 33.6 mmol) and phosphorus oxychloride (4.7 mL, 50 mmol) was stirred at 110°C for 30 min. The reaction mixture was concentrated under reduced pressure, and ice water and ethyl acetate were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, saturated sodium hydrogen carbonate solution and water (twice), and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (eluate; ethyl acetate/hexane=1/9 - 1/3), and the fractions containing the desired product were combined, and washed with 1N sodium hydroxide solution and water (twice). The insoluble material was filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (6.07 g, 59%).

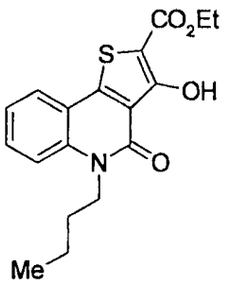
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.00 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.42-1.56 (2H, m), 1.67-1.79 (2H, m), 4.23-4.31 (2H, m), 4.47 (2H, q, J = 7.2 Hz), 7.33 (1H, ddd, J = 8.1, 7.2, 0.9 Hz), 7.37-7.41 (1H, m), 7.66 (1H, ddd, J = 8.7, 7.2, 1.4 Hz), 8.07 (1H, dd, J = 8.1, 1.4 Hz).

[0506]

Reference Example 100

Production of ethyl 5-butyl-3-hydroxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0507]



[0508]

A 20% solution (16.0 g, 47 mmol) of sodium ethoxide in ethanol was diluted with ethanol (45 mL), ethyl thioglycolate (6.2 mL, 55 mmol) was added to the obtained solution, and the mixture was stirred at room temperature for 10 min. The compound of Reference Example 99 (7.21 g, 23.4 mmol) was added to this mixture, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was neutralized with ice water and 2N hydrochloric acid (25 mL) under ice-cooling, and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed twice with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (6.44 g, 80%).

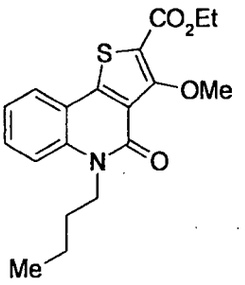
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.02 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.44-1.58 (2H, m), 1.71-1.83 (2H, m), 4.29-4.36 (2H, m), 4.41 (2H, q, J = 7.2 Hz), 7.32 (1H, ddd, J = 8.0, 7.2, 0.9 Hz), 7.43-7.48 (1H, m), 7.61 (1H, ddd, J = 8.6, 7.3, 1.6 Hz), 7.81-7.86 (1H, m), 10.81 (1H, s).

[0509]

Reference Example 101

Production of ethyl 5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0510]



[0511]

To a suspension of the compound of Reference Example 100 (3.11 g, 9.00 mmol) in DMF (30 mL) was added DBU (1.62 mL, 10.8 mmol), and iodomethane (1.12 mL, 18.0 mmol) was added to the obtained solution. The obtained mixture was stirred at room temperature for 14 hr, water was added and the mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water and 0.5N aqueous sodium hydroxide solution, filtered through Celite (trade name), further washed twice with water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/1) and recrystallized from ethyl acetate-hexane to give the title compound (1.03 g, 32%).

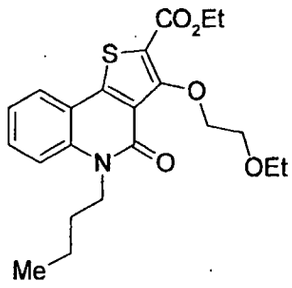
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.01 (3H, t, J = 7.4 Hz), 1.40-1.60 (2H, m), 1.42 (3H, t, J = 7.2 Hz), 1.69-1.81 (2H, m), 4.14 (3H, s), 4.28-4.36 (2H, m), 4.40 (2H, q, J = 7.2 Hz), 7.22-7.29 (1H, m), 7.39 (1H, d, J = 8.5 Hz), 7.57 (1H, ddd, J = 8.5, 7.1, 1.4 Hz), 7.84 (1H, dd, J = 8.0, 1.4 Hz).

[0512]

Reference Example 102

Production of ethyl 5-butyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0513]



[0514]

To a suspension of the compound of Reference Example 100 (1.14 g, 3.30 mmol) in DMF (20 mL) was added DBU (1.48 mL, 9.90 mmol), and 1-bromo-2-ethoxyethane (1.12 mL, 9.93 mmol) was added to the obtained solution. The obtained mixture was stirred at 60°C for 30 hr and ethyl acetate and water were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 0.5N aqueous sodium hydroxide solution and water, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluate; ethyl acetate/hexane=1/4 - 1/2) to give the title compound (1.28 g, 93%) as a solid.

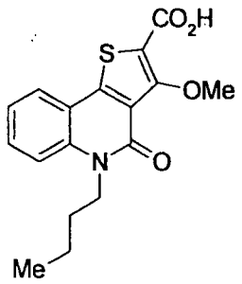
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.01 (3H, t, J = 7.4 Hz), 1.18 (3H, t, J = 7.0 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.43-1.57 (2H, m), 1.65-1.79 (2H, m), 3.58 (2H, q, J = 7.0 Hz), 3.92 (2H, dd, J = 5.6, 4.7 Hz), 4.30 (2H, br t, J = 7.8 Hz), 4.39 (2H, q, J = 7.2 Hz), 4.47 (2H, t, J = 5.1 Hz), 7.21-7.28 (1H, m), 7.37 (1H, d, J = 8.5 Hz), 7.56 (1H, ddd, J = 8.5, 7.1, 1.4 Hz), 7.83 (1H, dd, J = 8.1, 1.4 Hz).

[0515]

Reference Example 103

Production of 5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0516]



[0517]

To a suspension of the compound of Reference Example 101 (1.81 g, 5.04 mmol) in THF (15 mL) and ethanol (15 mL) was added 5N aqueous sodium hydroxide solution (2.0 mL, 10 mmol). The obtained mixture was stirred at room temperature for 1.5 hr. The reaction mixture was ice-cooled, 1N hydrochloric acid (15 mL) and ethyl acetate were added, and the precipitated solid was collected by filtration, and washed with water and ethyl acetate to give a solid. The filtrate was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue and the solid obtained earlier were combined, and the mixture was recrystallized from methanol-diisopropyl ether to give the title compound (1.43 g, 86%).

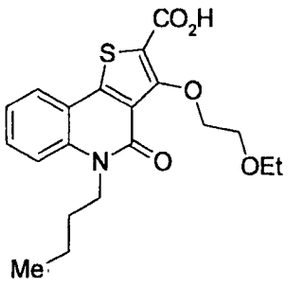
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.95 (3H, t, J = 7.3 Hz), 1.43 (2H, sext, J = 7.3 Hz), 1.56-1.68 (2H, m), 3.95 (3H, s), 4.29 (2H, t, J = 7.5 Hz), 7.29-7.36 (1H, m), 7.60-7.71 (2H, m), 7.95-8.00 (1H, m).

[0518]

Reference Example 104

Production of 5-butyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic acid

[0519]



[0520]

To a solution of the compound of Reference Example 102 (1.16 g, 2.78 mmol) in THF (9 mL) and ethanol (9 mL) was added 5N aqueous sodium hydroxide solution (1.12 mL, 5.6 mmol). The obtained mixture was stirred at room temperature for 2.5 hr, 5N aqueous sodium hydroxide solution (4.48 mL, 22 mmol) was added, and the mixture was stirred at 50°C for 3 hr. The reaction mixture was acidified with 1N hydrochloric acid, and extracted twice with chloroform. The combined organic layer was washed with water, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-diisopropyl ether to give the title compound (965 mg, 89%).

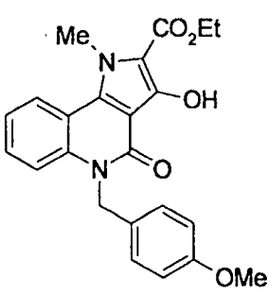
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.95 (3H, t, J = 7.3 Hz), 1.02 (3H, t, J = 7.0 Hz), 1.43 (2H, sext, J = 7.3 Hz), 1.56-1.68 (2H, m), 3.43 (2H, q, J = 7.0 Hz), 3.74 (2H, t, J = 5.0 Hz), 4.24-4.40 (2H, m), 4.30 (2H, t, J = 5.0 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.59-7.71 (2H, m), 7.97 (1H, d, J = 7.5 Hz), 13.20 (1H, br s).

[0521]

Reference Example 105

Production of ethyl 3-hydroxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0522]



[0523]

In the same manner as in Reference Example 25, ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (14.7 g, 63%) was obtained as a white powder from the compound of Reference Example 10 (19.2 g, 51.6 mmol).

In the same manner as in Reference Example 26, the title compound (10.35 g, 49%) was obtained as a white solid from the ethyl 4-[(2-ethoxy-2-oxoethyl)(methyl)amino]-1-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxylate (14.73 g).

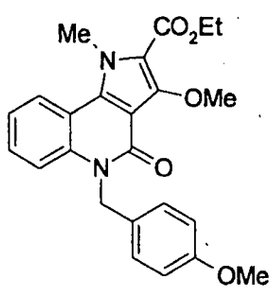
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.33 (3H, t, J = 7.1 Hz), 3.69 (3H, s), 4.27 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.47 (2H, s), 6.86 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.27-7.30 (1H, m), 7.48 (2H, d, J = 3.3 Hz), 8.32 (1H, d, J = 8.1 Hz), 9.10 (1H, s).

[0524]

Reference Example 106

Production of ethyl 3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0525]



[0526]

In the same manner as in Reference Example 6, the title compound (6.51 g, 61%) was obtained as a pale-yellow solid from the compound of Reference Example 105 (10.4 g, 25.5 mmol).

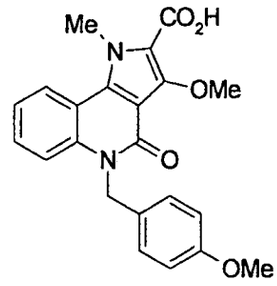
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 7.1 Hz), 3.69 (3H, s), 3.94 (3H, s), 4.26 (3H, s), 4.34 (2H, q, J = 7.1 Hz), 5.51 (2H, br s), 6.86 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.25-7.31 (1H, m), 7.47 (2H, d, J = 3.6 Hz), 8.34 (1H, d, J = 8.1 Hz).

[0527]

Reference Example 107

Production of 3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0528]



[0529]

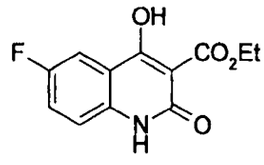
In the same manner as in Reference Example 28, the title compound (5.67 g, 96%) was obtained as a pale-yellow solid from the compound of Reference Example 106 (6.50 g, 15.5 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.70 (3H, s), 3.94 (3H, s), 4.28 (3H, s), 5.51 (2H, br s), 6.86 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 8.4 Hz), 7.25-7.30 (1H, m), 7.46 (2H, d, J = 3.9 Hz), 8.34 (1H, d, J = 8.4 Hz), 12.90 (1H, br s).

[0530]

Reference Example 110

Production of ethyl 6-fluoro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0531]



[0532]

In the same manner as in Reference Example 1, the title compound (8.60 g, 56%) was obtained as a pale-yellow solid from ethyl 2-amino-5-fluorobenzoate (10.3 g, 61.0 mmol), diethyl malonate (9.2 mL, 61.0 mmol), a 20% solution (21.0 g, 61.0 mmol) of sodium ethoxide in ethanol and ethanol (70 mL). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.52 (3H, t, J = 7.2 Hz), 4.54 (2H, q,

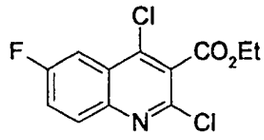
J = 7.1 Hz), 7.20-7.29 (1H, m), 7.31-7.42 (1H, m), 7.75 (1H, dd, J = 8.6, 2.7 Hz), 11.02 (1H, br s), 14.31 (1H, s).

[0533]

Reference Example 111

Production of ethyl 2,4-dichloro-6-fluoroquinoline-3-carboxylate

[0534]



[0535]

In the same manner as in Reference Example 2, the title compound (2.2 g, 96%) was obtained as a white solid from the compound of Reference Example 110 (2.0 g, 7.8 mmol) and phosphorus oxychloride (9.0 mL).

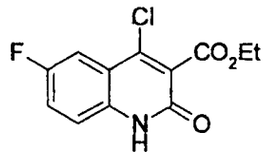
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.46 (3H, t, J = 7.1 Hz), 4.54 (2H, q, J = 7.2 Hz), 7.54-7.68 (1H, m), 7.86 (1H, dd, J = 9.1, 2.8 Hz), 8.07 (1H, dd, J = 9.2, 5.2 Hz).

[0536]

Reference Example 112

Production of ethyl 4-chloro-6-fluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate

[0537]



[0538]

In the same manner as in Reference Example 3, the title compound (1.6 g, 79%) was obtained as a white solid from the compound of Reference Example 111 (2.2 g, 7.5 mmol), sodium acetate (615 mg, 7.5 mmol) and acetic acid (20 mL).

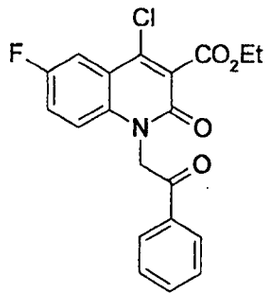
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.40-1.51 (3H, m), 4.46-4.57 (2H, m), 7.36-7.46 (2H, m), 7.69 (1H, dd, J = 9.1, 1.9 Hz), 12.36 (1H, br s).

[0539]

Reference Example 113

Production of ethyl 4-chloro-6-fluoro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydroquinoline-3-carboxylate

[0540]



[0541]

In the same manner as in Reference Example 4, the title compound (1.3 g, 57%) was obtained as a pale-yellow solid from the compound of Reference Example 112 (1.6 g, 5.9 mmol), sodium hydride (60% in oil, 248 mg, 6.2 mmol), phenacyl bromide (1.3 g, 6.5 mmol) and DMF (20 mL).

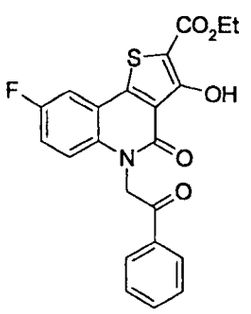
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.1 Hz), 4.47 (2H, q, J = 7.1 Hz), 5.79 (2H, s), 7.00 (1H, dd, J = 9.3, 4.2 Hz), 7.27-7.38 (1H, m), 7.49-7.61 (2H, m), 7.63-7.73 (1H, m), 7.80 (1H, dd, J = 9.1, 2.8 Hz), 8.02-8.12 (2H, m).

[0542]

Reference Example 114

Production of ethyl 8-fluoro-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0543]



[0544]

In the same manner as in Reference Example 5, the title compound (1.3 g, 94%) was obtained as a yellow solid from the compound of Reference Example 113 (1.3 g, 3.3 mmol), a 20% solution (2.3 g, 6.7 mmol) of sodium ethoxide in ethanol, ethyl thioglycolate (0.97 g, 8.0 mmol) and ethanol (14 mL).

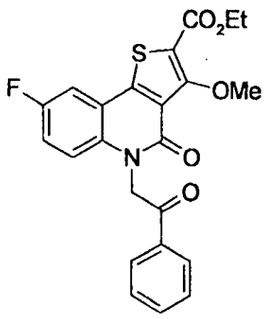
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.2 Hz), 6.02 (2H, s), 7.47-7.58 (1H, m), 7.59-7.70 (3H, m), 7.72-7.82 (1H, m), 8.00 (1H, dd, J = 8.7, 2.8 Hz), 8.11-8.21 (2H, m), 10.52 (1H, br s).

[0545]

Reference Example 115

Production of ethyl 8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylate

[0546]



[0547]

In the same manner as in Reference Example 6, the title compound (880 mg, 65%) was obtained as a yellow solid from the compound of Reference Example 114 (1.3 g, 3.1 mmol), iodomethane (0.31 mL, 5.0 mmol), DBU (0.75 mL, 5.0 mmol) and DMF (40 mL).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43 (3H, t, J = 7.5 Hz), 4.12 (3H, s), 4.42 (2H, q, J = 7.2 Hz), 5.84 (2H, s), 6.98 (1H, dd, J = 9.3, 4.2 Hz), 7.16-7.25 (1H, m), 7.49-7.60 (3H, m), 7.64-7.72 (1H, m), 8.03-8.15 (2H, m).

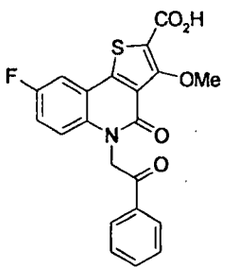
[0548]

Reference Example 116

Production of 8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxylic

acid

[0549]



[0550]

In the same manner as in Reference Example 7, the title compound (602 mg, 73%) was obtained as a pale-brown solid from the compound of Reference Example 115 (880 mg, 2.0 mmol), 8N aqueous sodium hydroxide solution (5.7 mL), ethanol (32 mL) and THF (9.1 mL).

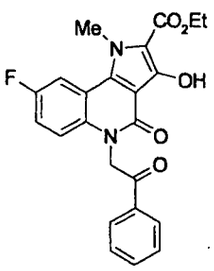
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.92 (3H, s), 5.98 (2H, s), 7.39-7.60 (2H, m), 7.60-7.69 (2H, m), 7.72-7.81 (1H, m), 7.91-8.01 (1H, m), 8.12-8.23 (2H, m).

[0551]

Reference Example 117

Production of ethyl 8-fluoro-3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0552]



[0553]

In the same manner as in Reference Example 25, the title compound (4.1 g, 83%) was obtained as a pale-brown solid from the compound of Reference Example 113 (4.6 g, 12 mmol), sarcosine ethyl ester hydrochloride (4.5 g, 30 mmol), triethylamine (6.0 mL, 43 mmol), ethanol (35 mL), a 20%

solution (3.4 g, 9.9 mmol) of sodium ethoxide in ethanol and ethanol (35 mL).

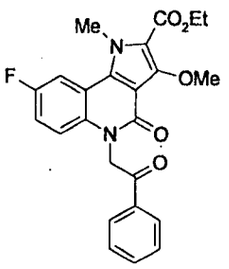
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.33 (3H, t, J = 8.9 Hz), 4.26-4.42 (5H, m), 5.94 (2H, s), 7.33-7.50 (2H, m), 7.58-7.69 (2H, m), 7.71-7.80 (1H, m), 8.03-8.23 (3H, m), 9.01 (1H, br s).

[0554]

Reference Example 118

Production of ethyl 8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate

[0555]



[0556]

A solution of the compound of Reference Example 117 (3.4 g, 8.0 mmol), dimethylsulfuric acid (1.1 mL, 12 mmol) and DBU (2.4 mL, 16 mmol) in DMF (100 mL) was stirred at room temperature for 2.5 hr. Dimethylsulfuric acid (1.1 mL, 12 mmol) and DBU (2.4 mL, 16 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 1 day. Dimethylsulfuric acid (0.75 mL, 8.0 mmol) and DBU (1.8 mL, 11 mmol) were further added, and the mixture was stirred at room temperature for 21 hr and diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (2.8 g, 80%) as a white solid.

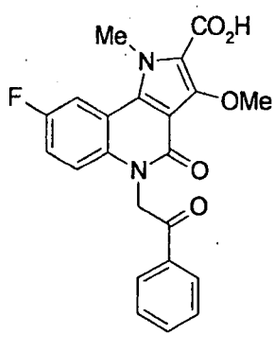
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 7.1 Hz), 3.88 (3H, s), 4.21-4.42 (5H, m), 5.96 (2H, s), 7.28-7.51 (2H, m), 7.55-7.69 (2H, m), 7.71-7.81 (1H, m), 7.98-8.39 (3H, m).

[0557]

Reference Example 119

Production of 8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0558]



[0559]

In the same manner as in Reference Example 7, the title compound (2.4 g, 90%) was obtained as a pale-yellow solid from the compound of Reference Example 118 (2.8 g, 6.4 mmol).

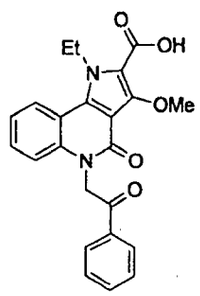
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.85 (3H, s), 4.30 (3H, s), 5.95 (2H, s), 7.19-7.49 (2H, m), 7.53-7.69 (2H, m), 7.70-7.82 (1H, m), 7.97-8.26 (3H, m).

[0560]

Reference Example 120

Production of 1-ethyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid

[0561]



[0562]

A solution of the compound of Reference Example 4 (1.0 g, 2.7 mmol), N-ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (3.8 mL, 27 mmol) in 1-butanol (10 mL) was heated under reflux for 6 hr. N-Ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) was added and the

mixture was heated under reflux for 17 hr. N-Ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (0.41 mL, 3.0 mmol) were added, and the mixture was heated under reflux for 6 hr, and N-ethylglycine ethyl ester hydrochloride (499 mg, 3.0 mmol) and triethylamine (0.41 mL, 3.0 mmol) were added, and the mixture was heated under reflux for 6 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure. A mixture of the obtained solid, a 20% solution (777 mg, 2.3 mmol) of sodium ethoxide in ethanol and ethanol (150 mL) was stirred at room temperature for 5 hr. A 20% solution (777 mg, 2.3 mmol) of sodium ethoxide in ethanol was added, and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with water, neutralized with 5N hydrochloric acid, and the mixture was stirred for 30 min. The precipitated solid was collected by filtration, washed with water, dried under reduced pressure, and recrystallized from DMF-diethyl ether. To a solution of the obtained solid and DBU (0.19 mL, 1.3 mmol) in DMF (8.0 mL) was added dimethylsulfuric acid (0.092 mL, 0.97 mmol) under ice-cooling, and the mixture was stirred at room temperature for 14 hr. DBU (0.19 mL, 1.3 mmol) and dimethylsulfuric acid (0.092 mL, 0.97 mmol) were further added under ice-cooling, and the mixture was stirred at room temperature for 4 hr, and diluted with water. The precipitated solid was collected by filtration, the obtained solid was washed with water, and dried under reduced pressure. A mixed solution of the obtained solid and 8N sodium hydroxide solution (1.4 mL) in THF (2.3 mL)-ethanol (8.0 mL) was stirred at room temperature for 15 hr. 8N Sodium hydroxide solution (0.70 mL) was added, and the mixture was stirred at room temperature for 3.5 hr. 8N Sodium hydroxide solution (0.14 mL) was further added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was neutralized with 1N hydrochloric acid and concentrated under reduced

pressure, and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (180 mg, 16%) as a white solid.

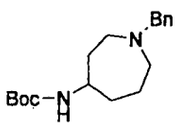
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.51 (3H, t, J = 6.5 Hz), 3.86 (3H, s), 4.85 (2H, q, J = 7.0 Hz), 5.97 (2H, s), 7.27-7.43 (2H, m), 7.44-7.54 (1H, m), 7.58-7.69 (2H, m), 7.71-7.83 (1H, m), 8.01-8.45 (3H, m), 12.89 (1H, br s).

[0563]

Reference Example 121

Production of tert-butyl (1-benzylazepan-4-yl)carbamate

[0564]



[0565]

To a solution of 1-benzylazepan-4-amine (400 mg, 2.0 mmol) and triethylamine (0.82 mL, 5.9 mmol) in THF (5.0 mL) was added di-tert-butyl dicarbonate (591 mg, 2.7 mmol) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=10/90 - 100/0) to give the title compound (447 mg, quant.) as a colorless oil.

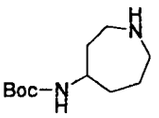
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.45 (9H, s), 1.53-1.77 (5H, m), 1.78-1.93 (1H, m), 2.37-2.58 (2H, m), 2.61-2.83 (2H, m), 3.61 (2H, s), 3.73-4.00 (1H, m), 4.92-5.27 (1H, m), 7.07-7.44 (5H, m).

[0566]

Reference Example 122

Production of tert-butyl azepan-4-ylcarbamate

[0567]



[0568]

A solution of the compound of Reference Example 121 (447 mg, 1.5 mmol) and palladium-carbon (65 mg) in ethanol (10 mL) was stirred at room temperature for 4.5 hr under a hydrogen atmosphere. Palladium-carbon was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (10 mL), palladium-carbon (120 mg) was added, and the mixture was stirred at room temperature for 4.5 hr under a hydrogen atmosphere. Palladium-carbon was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (315 mg, quant.) as a colorless oil.

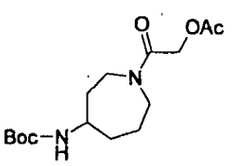
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.34-1.76 (13H, m), 1.78-2.07 (2H, m), 2.39-2.70 (1H, m), 2.71-3.04 (4H, m), 3.66-3.94 (1H, m), 4.60-5.01 (1H, m).

[0569]

Reference Example 123

Production of 2-{4-[(tert-butoxycarbonyl)amino]azepan-1-yl}-2-oxoethyl acetate

[0570]



[0571]

In the same manner as in Example 544, the title compound (220 mg, 96%) was obtained as a white solid from the compound of Reference Example 122 (157 mg, 0.73 mmol).

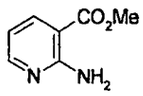
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.37-1.55 (11H, m), 1.61-2.00 (4H, m), 2.07-2.23 (4H, m), 3.21-3.77 (4H, m), 4.35-4.59 (1H, m), 4.59-4.81 (2H, m).

[0572]

Reference Example 124

Production of methyl 2-aminopyridine-3-carboxylate

[0573]



[0574]

To a solution of 2-aminopyridine-3-carboxylic acid (4.3 g, 31 mmol) in methanol (62 mL) was added dropwise sulfuric acid (31 mL) under ice-cooling, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was stirred at 70°C for 15 hr, and neutralized with sodium bicarbonate under ice-cooling. The reaction mixture was extracted twice with ethyl acetate, and the extracts were combined, and washed with brine. The extract was dried over magnesium sulfate, and concentrated under reduced pressure to give the title compound (4.3 g, 90%) as a white solid.

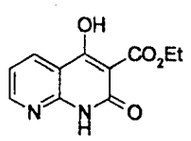
^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.89 (3H, s), 6.38 (2H, br s), 6.63 (1H, dd, J = 7.8, 4.8 Hz), 8.13 (1H, dd, J = 7.7, 1.9 Hz), 8.22 (1H, dd, J = 4.7, 1.9 Hz).

[0575]

Reference Example 125

Production of ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0576]



[0577]

In the same manner as in Reference Example 1, the title compound (2.6 g, 53%) was obtained as a pale-red solid from the compound of Reference Example 124 (3.1 g, 21 mmol).

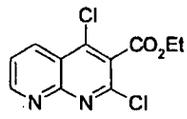
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.1 Hz), 7.27 (1H, dd, J = 7.9, 4.7 Hz), 8.22-8.38 (1H, m), 8.60 (1H, dd, J = 4.6, 1.8 Hz), 11.86 (1H, s), 13.29 (1H, br s).

[0578]

Reference Example 126

Production of ethyl 2,4-dichloro-1,8-naphthyridine-3-carboxylate

[0579]



[0580]

In the same manner as in Reference Example 2, the title compound (2.3 g, 77%) was obtained as a pale-yellow solid from the compound of Reference Example 125 (2.6 g, 11 mmol).

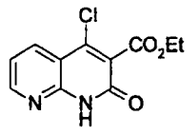
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.47 (3H, t, J = 7.2 Hz), 4.56 (2H, q, J = 7.2 Hz), 7.67 (1H, dd, J = 8.4, 4.2 Hz), 8.62 (1H, dd, J = 8.3, 1.9 Hz), 9.21 (1H, dd, J = 4.2, 1.9 Hz).

[0581]

Reference Example 127

Production of ethyl 4-chloro-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0582]



[0583]

In the same manner as in Reference Example 3, the title compound (1.5 g, 71%) was obtained as a white solid from the compound of Reference Example 126 (2.2 g, 8.3 mmol).

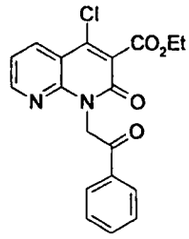
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.31 (3H, t, J = 7.1 Hz), 4.37 (2H, q, J = 7.1 Hz), 7.43 (1H, dd, J = 8.1, 4.7 Hz), 8.33 (1H, dd, J = 8.1, 1.7 Hz), 8.69 (1H, dd, J = 4.7, 1.7 Hz), 12.88 (1H, br s).

[0584]

Reference Example 128

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate

[0585]



[0586]

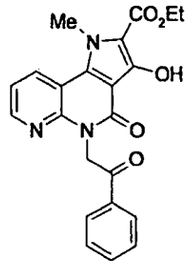
In the same manner as in Reference Example 4, the title compound (1.1 g, 51%) was obtained as a pale-yellow oil from the compound of Reference Example 127 (1.5 g, 5.7 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.1 Hz), 4.48 (2H, q, J = 7.1 Hz), 5.98 (2H, s), 7.27-7.33 (1H, m), 7.48-7.58 (2H, m), 7.59-7.69 (1H, m), 8.02-8.12 (2H, m), 8.36 (1H, dd, J = 8.0, 1.8 Hz), 8.54 (1H, dd, J = 4.7, 1.7 Hz).

[0587]

Reference Example 129

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxylate

[0588]



[0589]

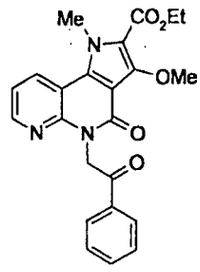
In the same manner as in Reference Example 33, the title compound (653 mg, 55%) was obtained as a pale-yellow solid from the compound of Reference Example 128 (1.1 g, 2.9 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.45 (3H, t, J = 7.1 Hz), 4.36 (3H, s), 4.46 (2H, q, J = 7.2 Hz), 6.00 (2H, s), 7.20 (1H, dd, J = 7.9, 4.7 Hz), 7.45-7.58 (2H, m), 7.58-7.69 (1H, m), 8.02-8.15 (2H, m), 8.33-8.51 (2H, m), 8.70 (1H, s).

[0590]

Reference Example 130

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxylate

[0591]



[0592]

In the same manner as in Reference Example 115, the title compound (420 mg, 79%) was obtained as a white solid from the compound of Reference Example 129 (512 mg, 1.3 mmol).

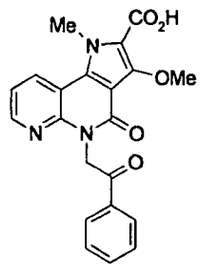
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 7.1 Hz), 3.91 (3H, s), 4.24-4.44 (5H, m), 5.97 (2H, s), 7.36 (1H, dd, J = 8.1, 4.5 Hz), 7.55-7.69 (2H, m), 7.68-7.82 (1H, m), 8.06-8.24 (2H, m), 8.46 (1H, dd, J = 4.6, 1.4 Hz), 8.75 (1H, dd, J = 8.1, 1.5 Hz).

[0593]

Reference Example 131

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxylic acid

[0594]



[0595]

In the same manner as in Reference Example 7, the title compound (264 mg, 75%) was obtained as a white solid from the

compound of Reference Example 130 (380 mg, 0.91 mmol).

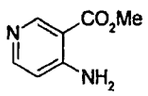
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.90 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.35 (1H, dd, J = 8.1, 4.7 Hz), 7.54-7.68 (2H, m), 7.69-7.81 (1H, m), 8.03-8.27 (2H, m), 8.33-8.56 (1H, m), 8.75 (1H, d, J = 7.2 Hz), 13.04 (1H, br s).

[0596]

Reference Example 132

Production of methyl 4-aminopyridine-3-carboxylate

[0597]



[0598]

In the same manner as in Reference Example 124, the title compound (4.9 g, 89%) was obtained as a pale-yellow solid from 4-aminopyridine-3-carboxylic acid (5.0 g, 36 mmol), sulfuric acid (36 mL) and methanol (72 mL).

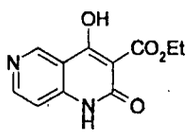
^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.91 (3H, s), 6.20 (2H, br s), 6.51 (1H, d, J = 5.9 Hz), 8.20 (1H, d, J = 6.0 Hz), 8.90 (1H, s).

[0599]

Reference Example 133

Production of ethyl 4-hydroxy-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0600]



[0601]

In the same manner as in Reference Example 1, the title compound (3.5 g, 49%) was obtained as a pale-yellow powder from the compound of Reference Example 132 (4.7 g, 31 mmol).

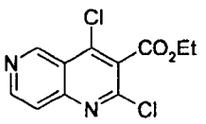
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3H, t, J = 7.1 Hz), 4.26 (2H, q, J = 7.0 Hz), 7.20 (1H, d, J = 6.0 Hz), 8.50 (1H, d, J = 6.0 Hz), 8.92-9.09 (1H, m), 11.66 (1H, br s).

[0602]

Reference Example 134

Production of ethyl 2,4-dichloro-1,6-naphthyridine-3-carboxylate

[0603]



[0604]

In the same manner as in Reference Example 2, the title compound (2.7 g, 66%) was obtained as a pale-yellow solid from the compound of Reference Example 133 (3.5 g, 15 mmol).

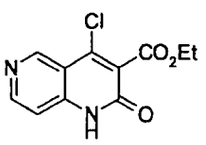
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.47 (3H, t, J = 7.2 Hz), 4.56 (2H, q, J = 7.1 Hz), 7.87 (1H, dd, J = 5.9, 0.8 Hz), 8.92 (1H, d, J = 5.9 Hz), 9.66 (1H, d, J = 0.9 Hz).

[0605]

Reference Example 135

Production of ethyl 4-chloro-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0606]



[0607]

In the same manner as in Reference Example 3, the title compound (733 mg, 30%) was obtained as a pale-brown solid from the compound of Reference Example 134 (2.6 g, 9.7 mmol).

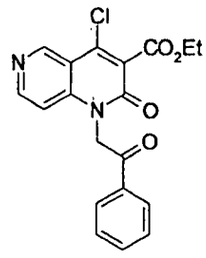
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.31 (3H, t, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 7.29 (1H, d, J = 5.7 Hz), 8.63 (1H, d, J = 5.7 Hz), 9.06 (1H, s), 12.72 (1H, br s).

[0608]

Reference Example 136

Production of ethyl 4-chloro-2-oxo-1-(2-oxo-2-phenylethyl)-1,2-dihydro-1,6-naphthyridine-3-carboxylate

[0609]



[0610]

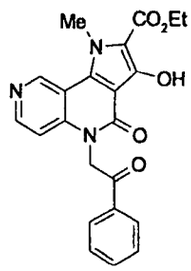
In the same manner as in Reference Example 4, the title compound (344 mg, 33%) was obtained as a pale-yellow solid from the compound of Reference Example 135 (710 mg, 2.8 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42 (3H, t, J = 7.2 Hz), 4.48 (2H, q, J = 7.2 Hz), 5.73 (2H, s), 6.86 (1H, d, J = 5.9 Hz), 7.49-7.63 (2H, m), 7.64-7.79 (1H, m), 7.95-8.19 (2H, m), 8.64 (1H, br s), 9.30 (1H, br s).

[0611]

Reference Example 137

Production of ethyl 3-hydroxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxylate

[0612]



[0613]

A mixture of the compound of Reference Example 136 (574 mg, 1.6 mmol), sarcosine ethyl ester hydrochloride (286 mg, 1.9 mmol), triethylamine (0.65 mL, 4.7 mmol), and ethanol (29 mL) was heated under reflux for 2.5 hr. Sarcosine ethyl ester hydrochloride (286 mg, 1.9 mmol) and triethylamine (0.43 mL, 3.1 mmol) were further added and the mixture was heated under reflux for 5.5 hr. Sarcosine ethyl ester hydrochloride (286 mg, 1.9 mmol) and triethylamine (0.65 mL, 4.7 mmol) were added and

the mixture was heated under reflux for 46 hr. Triethylamine (0.65 mL, 4.7 mmol) was added, and the mixture was heated under reflux for 3 hr. Triethylamine (0.65 mL, 4.7 mmol) was added and the mixture was heated under reflux for 64 hr. Triethylamine (0.65 mL, 4.7 mmol) was further added and the mixture was heated under reflux for 3 hr. Triethylamine (0.65 mL, 4.7 mmol) was further added and the mixture was heated under reflux for 3 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was acidified with 20% aqueous citric acid solution and stirred for 30 min under ice-cooling. The precipitated solid was collected by filtration, the obtained solid was washed with water, and dried under reduced pressure. The solid was washed with ethyl acetate-hexane mixed solvent and hexane to give the title compound (485 mg, 77%) as a pale-brown powder.

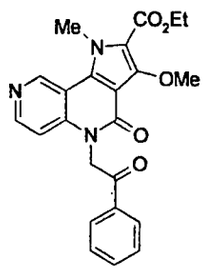
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34 (3H, t, J = 7.1 Hz), 4.27-4.43 (5H, m), 5.91 (2H, s), 7.42 (1H, d, J = 6.0 Hz), 7.58-7.69 (2H, m), 7.71-7.82 (1H, m), 8.08-8.23 (2H, m), 8.50 (1H, d, J = 5.9 Hz), 9.07 (1H, br s), 9.49 (1H, s).

[0614]

Reference Example 138

Production of ethyl 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxylate

[0615]



[0616]

In the same manner as in Reference Example 115, the title compound (313 mg, 64%) was obtained as a white solid from the

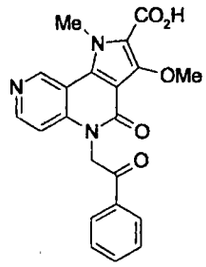
compound of Reference Example 137 (471 mg, 1.2 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35 (3H, t, J = 6.0 Hz), 3.88 (3H, s), 4.28-4.40 (5H, m), 5.94 (2H, s), 7.43 (1H, d, J = 6.0 Hz), 7.59-7.69 (2H, m), 7.72-7.82 (1H, m), 8.11-8.22 (2H, m), 8.51 (1H, d, J = 6.0 Hz), 9.52 (1H, s).

[0617]

Reference Example 139

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxylic acid

[0618]



[0619]

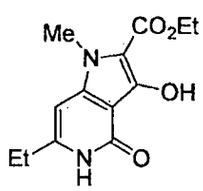
In the same manner as in Reference Example 7, the title compound (259 mg, 92%) was obtained as a white solid from the compound of Reference Example 138 (301 mg, 0.72 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.87 (3H, s), 4.36 (3H, s), 5.94 (2H, s), 7.42 (1H, d, J = 6.0 Hz), 7.57-7.70 (2H, m), 7.71-7.83 (1H, m), 8.07-8.26 (2H, m), 8.49 (1H, d, J = 5.9 Hz), 9.51 (1H, s), 13.01 (1H, br s).

[0620]

Reference Example 140

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0621]



[0622]

In the same manner as in Reference Example 40, the title compound (4.87 g, 85%) was obtained as a brown powder from the compound of Reference Example 38 (5.00 g, 21.8 mmol).

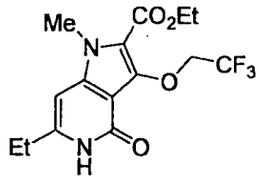
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.6 Hz), 1.30 (3H, t, J = 7.1 Hz), 2.39-2.49 (2H, m), 3.73 (3H, s), 4.29 (2H, q, J = 7.1 Hz), 6.25 (1H, s), 8.87 (1H, br s), 10.81 (1H, br s).

[0623]

Reference Example 141

Production of ethyl 6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0624]



[0625]

A mixture of the compound of Reference Example 140 (200 mg, 0.757 mmol), cesium carbonate (271 mg, 0.832 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.109 mL, 0.757 mmol), dimethyl sulfoxide (2.0 mL) and DMF (2.0 mL) was stirred at 60°C for 2 hr. The reaction mixture was diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water and diisopropyl ether, and dried under reduced pressure to give the title compound (161 mg, 61%) as a white solid.

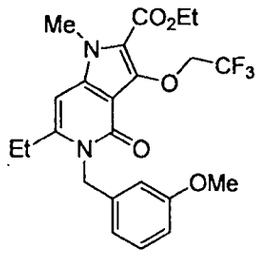
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.5 Hz), 1.27 (3H, t, J = 7.0 Hz), 2.51-2.56 (2H, m), 3.79 (3H, s), 4.24 (2H, q, J = 7.0 Hz), 4.97 (2H, q, J = 9.3 Hz), 6.38 (1H, s), 11.06 (1H, br s).

[0626]

Reference Example 142

Production of ethyl 6-ethyl-5-(3-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0627]



[0628]

A mixture of the compound of Reference Example 141 (500 mg, 1.44 mmol), sodium tert-butoxide (180 mg, 1.87 mmol), lithium bromide (250 mg, 2.88 mmol), 1-(chloromethyl)-3-methoxybenzene (0.313 mL, 2.16 mmol), DME (8.0 mL) and DMF (2.0 mL) was stirred at 60°C for 13 hr. Water (50 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=3/97 - 70/30) to give the title compound (508 mg, 76%) as a yellow oil.

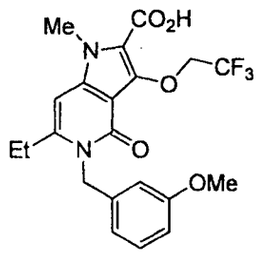
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.14-1.36 (6H, m), 2.60 (2H, q, J = 7.2 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.26 (2H, q, J = 7.2 Hz), 4.89 (2H, q, J = 9.3 Hz), 5.28 (2H, br s), 6.44-6.67 (3H, m), 6.74-6.95 (1H, m), 7.22 (1H, t, J = 7.9 Hz).

[0629]

Reference Example 143

Production of 6-ethyl-5-(3-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0630]



[0631]

In the same manner as in Reference Example 49, the title

compound (333 mg, 66%) was obtained as a white powder from the compound of Reference Example 142 (508 mg, 1.09 mmol).

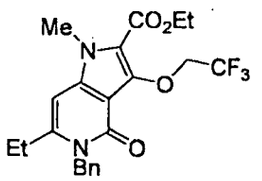
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.87 (2H, q, J = 9.4 Hz), 5.30 (2H, br s), 6.43-6.67 (3H, m), 6.81 (1H, dd, J = 7.9, 2.3 Hz), 7.22 (1H, t, J = 7.9 Hz), 12.70 (1H, br s).

[0632]

Reference Example 144

Production of ethyl 5-benzyl-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0633]



[0634]

In the same manner as in Reference Example 142, the title compound (312 mg, 62%) was obtained as a yellow oil from the compound of Reference Example 141 (400 mg, 1.16 mmol) and benzyl bromide (0.207 mL, 1.74 mmol).

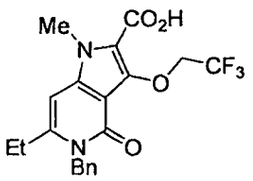
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.61 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 4.89 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.54 (1H, s), 7.03-7.09 (2H, m), 7.20-7.27 (1H, m), 7.28-7.36 (2H, m).

[0635]

Reference Example 145

Production of 5-benzyl-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0636]



[0637]

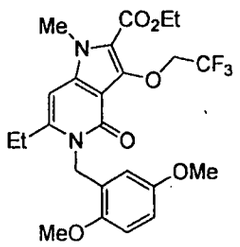
In the same manner as in Reference Example 49, the title compound (213 mg, 73%) was obtained as a white powder from the compound of Reference Example 144 (312 mg, 0.715 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.87 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.52 (1H, s), 7.01-7.10 (2H, m), 7.17-7.39 (3H, m), 12.73 (1H, br s).

[0638]

Reference Example 146

Production of ethyl 5-(2,5-dimethoxybenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0639]



[0640]

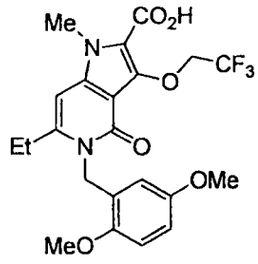
In the same manner as in Reference Example 142, the title compound (121 mg, 21%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 2-(chloromethyl)-1,4-dimethoxybenzene (325 mg, 1.74 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.53-2.61 (2H, m), 3.56 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 4.26 (2H, q, J = 7.2 Hz), 4.87 (2H, q, J = 9.3 Hz), 5.19 (2H, br s), 5.93 (1H, d, J = 3.0 Hz), 6.58 (1H, s), 6.79 (1H, dd, J = 8.9, 3.0 Hz), 6.97 (1H, d, J = 8.9 Hz).

[0641]

Reference Example 147

Production of 5-(2,5-dimethoxybenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0642]



[0643]

In the same manner as in Reference Example 49, the title compound (82.7 mg, 72%) was obtained as a white powder from the compound of Reference Example 146 (121 mg, 0.244 mmol).

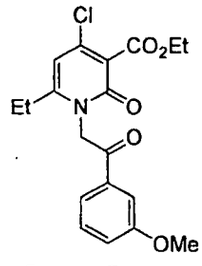
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.3 Hz), 2.52-2.60 (2H, m), 3.56 (3H, s), 3.83 (3H, s), 3.86 (3H, s), 4.85 (2H, q, J = 9.3 Hz), 5.19 (2H, br s), 5.92 (1H, d, J = 3.0 Hz), 6.56 (1H, s), 6.79 (1H, dd, J = 9.0, 3.0 Hz), 6.97 (1H, d, J = 9.0 Hz), 12.74 (1H, br s).

[0644]

Reference Example 148

Production of ethyl 4-chloro-6-ethyl-1-[2-(3-methoxyphenyl)-2-oxoethyl]-2-oxo-1,2-dihydropyridine-3-carboxylate

[0645]



[0646]

In the same manner as in Reference Example 142, the title compound (879 mg, 53%) was obtained as a yellow oil from the compound of Reference Example 38 (1.00 g, 4.35 mmol) and 2-bromo-1-(3-methoxyphenyl)ethanone (1.99 g, 8.71 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13 (3H, t, J = 7.4 Hz), 1.24 (3H,

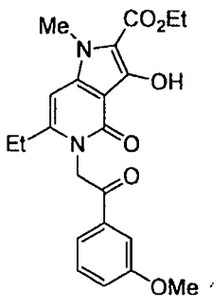
t, J = 7.1 Hz), 2.61 (2H, q, J = 7.4 Hz), 3.85 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 5.60 (2H, s), 6.44 (1H, s), 7.28-7.35 (1H, m), 7.48-7.59 (2H, m), 7.66-7.74 (1H, m).

[0647]

Reference Example 149

Production of ethyl 6-ethyl-3-hydroxy-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0648]



[0649]

In the same manner as in Reference Example 40, the title compound (526 mg, 55%) was obtained as a green powder from the compound of Reference Example 148 (879 mg, 2.33 mmol).

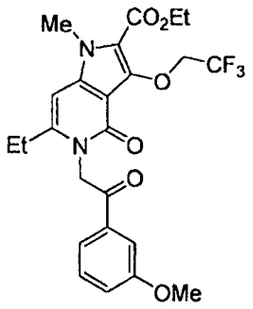
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.4 Hz), 1.31 (3H, t, J = 7.1 Hz), 2.52-2.61 (2H, m), 3.80 (3H, s), 3.85 (3H, s), 4.30 (2H, q, J = 7.1 Hz), 5.54 (2H, s), 6.43 (1H, s), 7.26-7.36 (1H, m), 7.48-7.60 (2H, m), 7.68-7.76 (1H, m), 8.89 (1H, br s).

[0650]

Reference Example 150

Production of ethyl 6-ethyl-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0651]



[0652]

A mixture of the compound of Reference Example 149 (470 mg, 1.14 mmol), cesium carbonate (446 mg, 1.37 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.197 mL, 1.37 mmol) and DMF (4.7 mL) was stirred at room temperature for 1 hr. The reaction mixture was diluted with water, and the precipitated solid was collected by filtration. The obtained solid was washed with water, diisopropyl ether and ethanol, and dried under reduced pressure to give the title compound (423 mg, 75%) as a green powder.

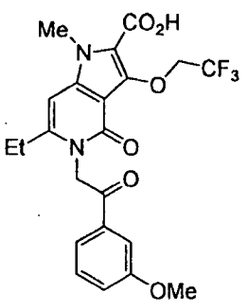
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.2 Hz), 2.59 (2H, q, J = 7.3 Hz), 3.83-3.90 (6H, m), 4.26 (2H, q, J = 7.2 Hz), 4.83 (2H, q, J = 9.3 Hz), 5.61 (2H, s), 6.55 (1H, s), 7.27-7.34 (1H, m), 7.48-7.61 (2H, m), 7.68-7.76 (1H, m).

[0653]

Reference Example 151

Production of 6-ethyl-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0654]



[0655]

In the same manner as in Reference Example 49, the title

compound (300 mg, 86%) was obtained as a brown powder from the compound of Reference Example 150 (370 mg, 0.748 mmol).

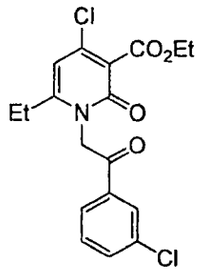
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 2.58 (2H, q, J = 7.3 Hz), 3.83-3.91 (6H, m), 4.82 (2H, q, J = 9.3 Hz), 5.60 (2H, s), 6.54 (1H, s), 7.26-7.37 (1H, m), 7.47-7.62 (2H, m), 7.67-7.83 (1H, m), 12.70 (1H, br s).

[0656]

Reference Example 152

Production of ethyl 4-chloro-1-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylate

[0657]



[0658]

In the same manner as in Reference Example 142, the title compound (486 mg, 29%) was obtained as a white powder from the compound of Reference Example 38 (1.50 g, 6.53 mmol) and 2-bromo-1-(3-chlorophenyl)ethanone (2.02 g, 8.65 mmol).

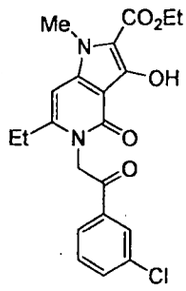
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.14 (3H, t, J = 7.4 Hz), 1.24 (3H, t, J = 7.1 Hz), 2.63 (2H, q, J = 7.4 Hz), 4.25 (2H, q, J = 7.1 Hz), 5.61 (2H, s), 6.45 (1H, s), 7.59-7.70 (1H, m), 7.77-7.86 (1H, m), 8.00-8.07 (1H, m), 8.08-8.17 (1 H, m).

[0659]

Reference Example 153

Production of ethyl 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-3-hydroxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0660]



[0661]

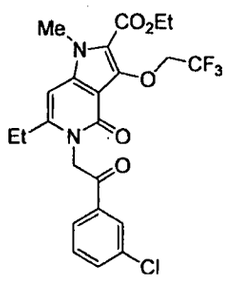
In the same manner as in Reference Example 40, the title compound (460 mg, 87%) was obtained as a green powder from the compound of Reference Example 152 (486 mg, 1.27 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.4 Hz), 1.31 (3H, t, J = 7.0 Hz), 2.57 (2H, q, J = 7.4 Hz), 3.80 (3H, s), 4.30 (2H, q, J = 7.0 Hz), 5.53 (2H, s), 6.44 (1H, s), 7.61-7.68 (1H, m), 7.80 (1H, ddd, J = 7.8, 2.0, 0.9 Hz), 8.05 (1H, dt, J = 7.8, 0.9 Hz), 8.13 (1H, t, J = 2.0 Hz), 8.90 (1H, s).

[0662]

Reference Example 154

Production of ethyl 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0663]



[0664]

In the same manner as in Reference Example 150, the title compound (348 mg, 63%) was obtained as a green powder from the compound of Reference Example 153 (460 mg, 1.10 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.1 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.86 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 4.83 (2H, q, J = 9.3 Hz), 5.61 (2H, s), 6.56 (1H, s), 7.61-7.69 (1H, m), 7.78-7.84 (1H, m), 8.03-8.09

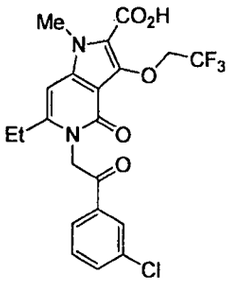
(1H, m), 8.14 (1H, t, J = 1.7 Hz).

[0665]

Reference Example 155

Production of 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0666]



[0667]

In the same manner as in Reference Example 49, the title compound (192 mg, 59%) was obtained as a brown powder from the compound of Reference Example 154 (348 mg, 0.698 mmol).

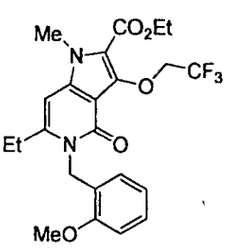
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 2.60 (2H, q, J = 7.3 Hz), 3.86 (3H, s), 4.81 (2H, q, J = 9.2 Hz), 5.60 (2H, s), 6.55 (1H, s), 7.58-7.71 (1H, m), 7.76-7.86 (1H, m), 8.00-8.10 (1H, m), 8.14 (1H, t, J = 1.7 Hz), 12.72 (1H, br s).

[0668]

Reference Example 156

Production of ethyl 6-ethyl-5-(2-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0669]



[0670]

In the same manner as in Reference Example 142, the title compound (138 mg, 26%) was obtained as a white powder from the

compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-(chloromethyl)-2-methoxybenzene (272 mg, 1.74 mmol).

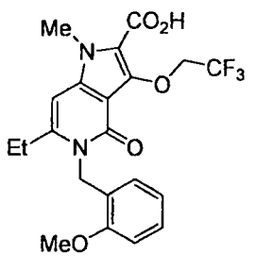
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.53-2.61 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 4.86 (2H, q, J = 9.3 Hz), 5.22 (2H, br s), 6.41 (1H, dd, J = 7.5, 1.2 Hz), 6.57 (1H, s), 6.82 (1H, td, J = 7.5, 0.9 Hz), 7.01-7.09 (1H, m), 7.18-7.28 (1H, m).

[0671]

Reference Example 157

Production of 6-ethyl-5-(2-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0672]



[0673]

In the same manner as in Reference Example 49, the title compound (104 mg, 80%) was obtained as a white powder from the compound of Reference Example 156 (138 mg, 0.296 mmol).

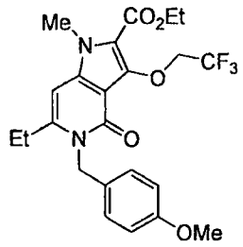
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.3 Hz), 2.53-2.60 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 4.84 (2H, q, J = 9.3 Hz), 5.22 (2H, br s), 6.40 (1H, dd, J = 7.5, 1.3 Hz), 6.55 (1H, s), 6.82 (1H, td, J = 7.5, 0.9 Hz), 7.00-7.11 (1H, m), 7.16-7.31 (1H, m), 12.72 (1H, br s).

[0674]

Reference Example 158

Production of ethyl 6-ethyl-5-(4-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0675]



[0676]

In the same manner as in Reference Example 142, the title compound (175 mg, 43%) was obtained as a white powder from the compound of Reference Example 141 (300 mg, 0.866 mmol) and 1-(chloromethyl)-4-methoxybenzene (0.175 mL, 1.30 mmol).

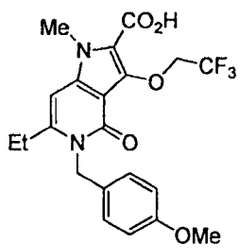
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.62 (2H, q, J = 7.2 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.26 (2H, q, J = 7.2 Hz), 4.90 (2H, q, J = 9.3 Hz), 5.26 (2H, br s), 6.51 (1H, s), 6.82-6.92 (2H, m), 6.97-7.08 (2H, m).

[0677]

Reference Example 159

Production of 6-ethyl-5-(4-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0678]



[0679]

In the same manner as in Reference Example 49, the title compound (157 mg, 96%) was obtained as a white powder from the compound of Reference Example 158 (175 mg, 0.375 mmol).

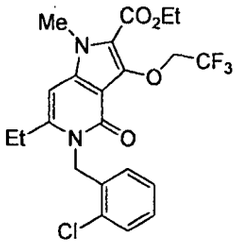
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 2.62 (2H, q, J = 7.3 Hz), 3.71 (3H, s), 3.84 (3H, s), 4.88 (2H, q, J = 9.3 Hz), 5.26 (2H, br s), 6.49 (1H, s), 6.81-6.92 (2H, m), 6.96-7.09 (2H, m), 12.70 (1H, br s).

[0680]

Reference Example 160

Production of ethyl 5-(2-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0681]



[0682]

In the same manner as in Reference Example 142, the title compound (163 mg, 30%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-2-(chloromethyl)benzene (0.226 mL, 1.74 mmol).

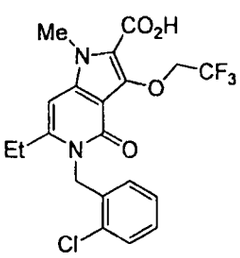
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.53-2.62 (2H, m), 3.87 (3H, s), 4.27 (2H, q, J = 7.1 Hz), 4.86 (2H, q, J = 9.3 Hz), 5.32 (2H, s), 6.55 (1H, dd, J = 7.6, 1.5 Hz), 6.62 (1H, s), 7.21-7.33 (2H, m), 7.52 (1H, dd, J = 7.7, 1.3 Hz).

[0683]

Reference Example 161

Production of 5-(2-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0684]



[0685]

In the same manner as in Reference Example 49, the title compound (138 mg, 90%) was obtained as a white powder from the compound of Reference Example 160 (163 mg, 0.346 mmol).

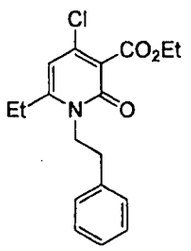
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.4 Hz), 2.52-2.62 (2H, m), 3.87 (3H, s), 4.83 (2H, q, J = 9.3 Hz), 5.32 (2H, s), 6.50 (1H, dd, J = 7.7, 1.6 Hz), 6.60 (1H, s), 7.22-7.33 (2H, m), 7.52 (1H, dd, J = 7.7, 1.3 Hz), 12.76 (1H, br s).

[0686]

Reference Example 162

Production of ethyl 4-chloro-6-ethyl-2-oxo-1-(2-phenylethyl)-1,2-dihydropyridine-3-carboxylate

[0687]



[0688]

In the same manner as in Reference Example 142, the title compound (480 mg, 16%) was obtained as a white powder from the compound of Reference Example 38 (2.00 g, 8.71 mmol) and (2-bromoethyl)benzene (1.77 mL, 11.3 mmol).

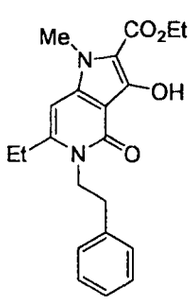
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.14 (3H, t, J = 7.4 Hz), 1.28 (3H, t, J = 7.1 Hz), 2.63 (2H, q, J = 7.4 Hz), 2.85-2.93 (2H, m), 4.07-4.15 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 6.30 (1H, s), 7.19-7.28 (3H, m), 7.28-7.38 (2H, m).

[0689]

Reference Example 163

Production of ethyl 6-ethyl-3-hydroxy-1-methyl-4-oxo-5-(2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0690]



[0691]

In the same manner as in Reference Example 40, the title compound (481 mg, 80%) was obtained as a white powder from the compound of Reference Example 162 (480 mg, 1.44 mmol).

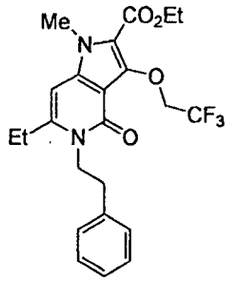
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20 (3H, t, J = 7.3 Hz), 1.31 (3H, t, J = 7.1 Hz), 2.63 (2H, q, J = 7.3 Hz), 2.80-2.94 (2H, m), 3.75 (3H, s), 4.01-4.16 (2H, m), 4.30 (2H, q, J = 7.1 Hz), 6.34 (1H, s), 7.11-7.41 (5H, m), 8.94 (1H, br s).

[0692]

Reference Example 164

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0693]



[0694]

In the same manner as in Reference Example 150, the title compound (185 mg, 31%) was obtained as a white powder from the compound of Reference Example 163 (482 mg, 1.31 mmol).

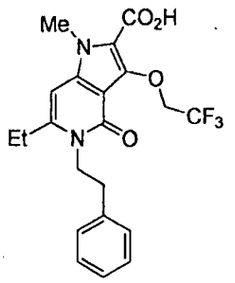
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.22 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.2 Hz), 2.67 (2H, q, J = 7.3 Hz), 2.82-2.94 (2H, m), 3.82 (3H, s), 4.10-4.20 (2H, m), 4.26 (2H, q, J = 7.2 Hz), 4.90 (2H, q, J = 9.3 Hz), 6.46 (1H, s), 7.15-7.38 (5H, m).

[0695]

Reference Example 165

Production of 6-ethyl-1-methyl-4-oxo-5-(2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0696]



[0697]

In the same manner as in Reference Example 49, the title compound (143 mg, 83%) was obtained as a brown powder from the compound of Reference Example 164 (185 mg, 0.411 mmol).

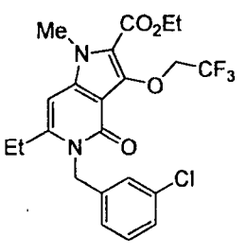
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.21 (3H, t, J = 7.2 Hz), 2.66 (2H, q, J = 7.2 Hz), 2.81-2.94 (2H, m), 3.81 (3H, s), 4.05-4.30 (2H, m), 4.89 (2H, q, J = 9.3 Hz), 6.44 (1H, s), 7.09-7.48 (5H, m), 12.67 (1H, br s).

[0698]

Reference Example 166

Production of ethyl 5-(3-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0699]



[0700]

In the same manner as in Reference Example 142, the title compound (325 mg, 60%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-3-(chloromethyl)benzene (357 mg, 1.74 mmol).

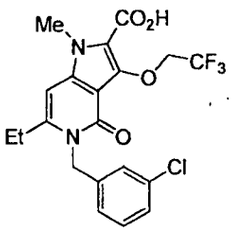
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.4 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.60 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 4.26 (2H, q, J = 7.4 Hz), 4.88 (2H, q, J = 9.3 Hz), 5.33 (2H, br s), 6.56 (1H, s), 6.96-7.05 (1H, m), 7.10-7.18 (1H, m), 7.27-7.43 (2H, m).

[0701]

Reference Example 167

Production of 5-(3-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0702]



[0703]

In the same manner as in Reference Example 49, the title compound (281 mg, 92%) was obtained as a white powder from the compound of Reference Example 166 (325 mg, 0.690 mmol).

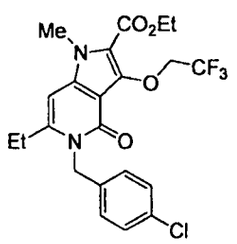
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.2 Hz), 2.60 (2H, q, J = 7.2 Hz), 3.85 (3H, s), 4.86 (2H, q, J = 9.3 Hz), 5.34 (2H, br s), 6.54 (1H, s), 6.95-7.05 (1H, m), 7.10-7.18 (1H, m), 7.26-7.43 (2H, m), 12.74 (1H, s).

[0704]

Reference Example 168

Production of ethyl 5-(4-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0705]



[0706]

In the same manner as in Reference Example 142, the title compound (213 mg, 39%) was obtained as a white powder from the compound of Reference Example 141 (400 mg, 1.16 mmol) and 1-chloro-4-(chloromethyl)benzene (357 mg, 1.74 mmol).

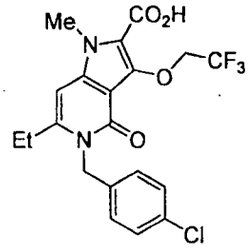
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.1 Hz), 2.60 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 4.26 (2H, q, J = 7.3 Hz), 4.88 (2H, q, J = 9.3 Hz), 5.32 (2H, br s), 6.55 (1H, s), 7.03-7.16 (2H, m), 7.66-7.43 (2H, m).

[0707]

Reference Example 169

Production of 5-(4-chlorobenzyl)-6-ethyl-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0708]



[0709]

In the same manner as in Reference Example 49, the title compound (188 mg, 94%) was obtained as a white powder from the compound of Reference Example 168 (213 mg, 0.452 mmol).

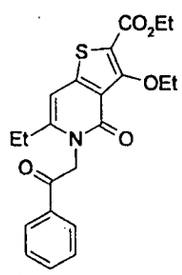
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 2.59 (2H, q, J = 7.3 Hz), 3.84 (3H, s), 4.86 (2H, q, J = 9.3 Hz), 5.32 (2H, br s), 6.53 (1H, s), 7.01-7.20 (2H, m), 7.28-7.49 (2H, m), 12.75 (1H, br s).

[0710]

Reference Example 170

Production of ethyl 3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate

[0711]



[0712]

In the same manner as in Reference Example 5, ethyl 6-ethyl-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate was obtained from the compound of Reference Example 39 (3.6 g, 10.3 mmol), ethyl thioglycolate (14.4 mL, 103 mmol) and triethylamine (2.3 mL, 20.6 mmol). The title compound (900 mg, 47%) was obtained as a white solid from the thus-obtained ethyl 6-ethyl-3-hydroxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylate (1.8 g, 4.7 mmol) by a method similar to that in Reference Example 43.

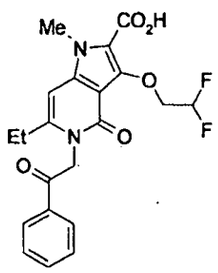
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.4 Hz), 1.23-1.36 (6H, m), 2.61 (2H, q, J = 7.4 Hz), 4.14 (2H, q, J = 7.1 Hz), 4.28 (2H, q, J = 7.0 Hz), 5.65 (2H, s), 6.83 (1H, s), 7.62 (2H, t, J = 7.6 Hz), 7.70-7.79 (1H, m), 8.12 (2H, d, J = 7.2 Hz).

[0713]

Reference Example 171

Production of 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0714]



[0715]

In the same manner as in Reference Example 56, ethyl 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate was obtained from the compound of Reference Example 40 (500 mg, 1.31 mmol), 2,2-difluoroethyl trifluoromethanesulfonate (336 mg, 1.57 mmol) and cesium carbonate (554 mg, 1.70 mmol). The title compound (314 mg, 83%) was obtained as a white powder from the thus-obtained

ethyl 3-(2,2-difluoroethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (400 mg, 0.90 mmol) by a method similar to that in Reference Example 59.

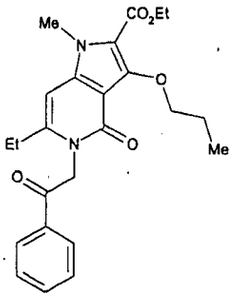
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.2 Hz), 2.58 (2H, q, J = 7.3 Hz), 3.85 (3H, s), 4.40 (2H, td, J = 14.6, 1.2 Hz), 5.60 (2H, s), 6.26 (1H, tt, J = 55.0, 3.9 Hz), 6.77 (1H, s), 7.58-7.76 (3H, m), 8.12 (2H, d, J = 7.5 Hz), 12.50-12.70 (1H, br).

[0716]

Reference Example 172

Production of ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0717]



[0718]

In the same manner as in Reference Example 56, the title compound (177 mg, 83%) was obtained as a brown powder from the compound of Reference Example 40 (191 mg, 0.50 mmol), dipropyl sulfate (364 mg, 2.0 mmol), potassium carbonate (414 mg, 3.0 mmol) and acetone (20 mL).

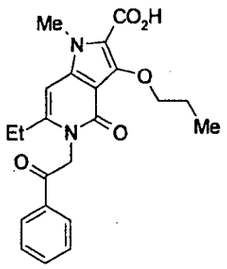
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.01 (3 H, t, J = 7.5 Hz), 1.28 (3H, t, J = 7.3 Hz), 1.40 (3H, t, J = 7.5 Hz), 1.75-1.89 (2H, m), 2.51 (2 H, q, J = 7.2 Hz), 3.88 (3 H, s), 4.21 (2 H, t, J = 6.7 Hz), 4.36 (2H, q, J = 7.2 Hz), 5.59 (2 H, s), 6.19 (1 H, s), 7.47-7.56 (2 H, m), 7.59-7.67 (1 H, m), 8.02-8.09 (2H, m).

Reference Example 173

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic

acid

[0719]



[0720]

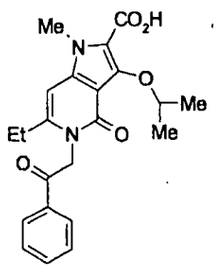
In the same manner as in Reference Example 59, the title compound (237 mg, 93%) was obtained as a pale-yellow powder from the compound of Reference Example 172 (274 mg, 0.65 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.91 (3 H, t, J = 7.5 Hz), 1.18 (3H, t, J = 7.3 Hz), 1.55-1.70 (2H, m), 2.57 (2 H, q, J = 7.4 Hz), 3.84 (3 H, s), 4.07 (2 H, t, J = 6.5 Hz), 5.58 (2 H, s), 6.47 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.07-8.16 (2H, m), 12.42 (1 H, s).

[0721]

Reference Example 174

Production of 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0722]



[0723]

In the same manner as in Reference Example 56, ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (291 mg, 46%) was obtained as a pale-purple powder from the compound of Reference Example 40 (574 mg, 1.50 mmol),

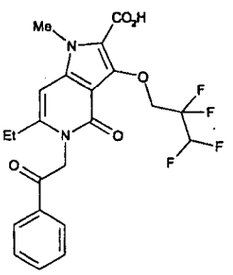
potassium carbonate (1.04 g, 7.5 mmol) and diisopropyl sulfate (1.37 g, 7.5 mmol). The title compound (242 mg, 97%) was obtained as a colorless powder from the thus-obtained ethyl 6-ethyl-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (267 mg, 0.63 mmol) by a method similar to that in Reference Example 59.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.23 (9 H, m), 2.57 (2 H, q, J = 7.5 Hz), 3.84 (3 H, s), 4.65-4.80 (1H, m), 5.58 (2 H, s), 6.47 (1 H, s), 7.56-7.66 (2 H, m), 7.69-7.78 (1 H, m), 8.07-8.16 (2H, m), 12.29 (1 H, s).

Reference Example 175

Production of 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0724]



[0725]

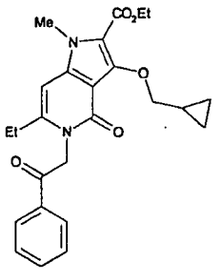
In the same manner as in Reference Example 150, ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (460 mg, 93%) was obtained as a gray powder from the compound of Reference Example 40 (382 mg, 1.00 mmol), 2,2,3,3-tetrafluoropropyl trifluoromethanesulfonate (913 mg, 3.46 mmol), cesium carbonate (391 mg, 1.20 mmol) and DMF (10 mL). The title compound (310 mg, 95%) was obtained as a gray powder from the thus-obtained ethyl 6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate (348 mg, 0.70 mmol) by a method similar to that in Reference Example 59.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3 H, t, J = 7.3 Hz), 2.58 (2 H, q, J = 7.3 Hz), 3.86 (3 H, s), 4.70 (2H, t, J = 13.1 Hz), 5.62 (2 H, s), 6.54 (1 H, s), 6.73 (1H, tt, J = 52.6, 6.1 Hz), 7.56-7.66 (2H, m), 7.69-7.79 (1H, m), 8.07-8.17 (2H, m), 12.93 (1H, br s).

Reference Example 176

Production of ethyl 3-(cyclopropylmethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylate

[0726]



[0727]

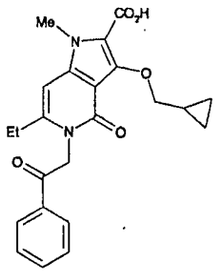
In the same manner as in Reference Example 150, the title compound (65 mg, 15%) was obtained as a yellow powder from the compound of Reference Example 40 (382 mg, 1.00 mmol), cesium carbonate (358 mg, 1.10 mmol), cyclopropylmethyl methanesulfonate (750 mg, 5.00 mmol) and DMF (10 mL).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.29-0.36 (2 H, m), 0.49-0.57 (2H, m), 1.24-1.37 (1H, m), 1.28 (3H, t, J = 7.3 Hz), 1.41 (3H, t, J = 7.1 Hz), 2.51 (2 H, q, J = 7.4 Hz), 3.88 (3 H, s), 4.10 (2 H, d, J = 7.2 Hz), 4.37 (2H, q, J = 7.1 Hz), 5.59 (2H, s), 6.19 (1H, s), 7.47-7.55 (2H, m), 7.59-7.67 (1H, m), 8.02-8.10 (2H, m).

Reference Example 177

Production of 3-(cyclopropylmethoxy)-6-ethyl-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxylic acid

[0728]



[0729]

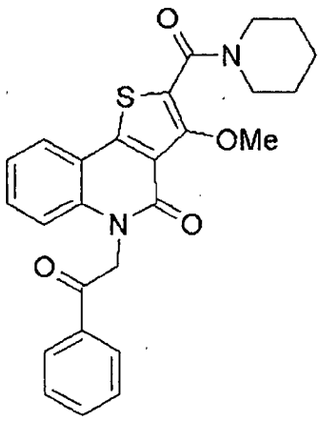
In the same manner as in Reference Example 59, the title compound (112 mg, 83%) was obtained as a colorless powder from the compound of Reference Example 176 (144 mg, 0.33 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.17-0.27 (2H, m), 0.39-0.48 (2H, m), 1.03-1.22 (1H, m), 1.18 (3H, t, J = 7.3 Hz), 2.56 (2 H, q, J = 7.3 Hz), 3.84 (3 H, s), 3.94 (2H, d, J = 7.0 Hz), 5.58 (2 H, s), 6.46 (1H, s), 7.56-7.65 (2H, m), 7.69-7.77 (1H, m), 8.07-8.15 (2H, m), 12.43 (1H, br s).

[0730]

Example 1

Production of 3-methoxy-5-(2-oxo-2-phenylethyl)-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[0731]



[0732]

A solution (0.10 M, 0.600 mL, 60 μmol) of the compound of Reference Example 7 in DMF was diluted with DMF (0.200 mL), and a solution (1.0 M, 0.063 mL, 63 μmol) of piperidine in DMF and a solution (0.50 M, 0.126 mL, 63 μmol) of HOBt and WSCD in 1:1 mixture in DMF were added. The obtained mixture was

agitated at room temperature for 13 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (8.5 mg, 31%).

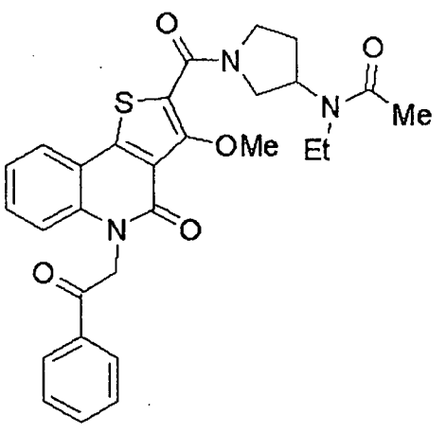
LC/MS 461 (M+H).

[0733]

Example 2

Production of N-ethyl-N-(1-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}pyrrolidin-3-yl)acetamide

[0734]



[0735]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and N-ethyl-N-pyrrolidin-3-ylacetamide.

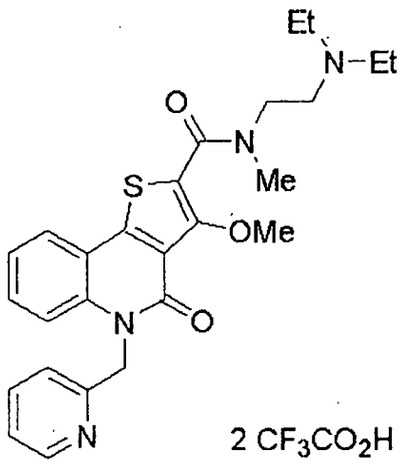
LC/MS 532 (M+H).

[0736]

Example 3

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[0737]



[0738]

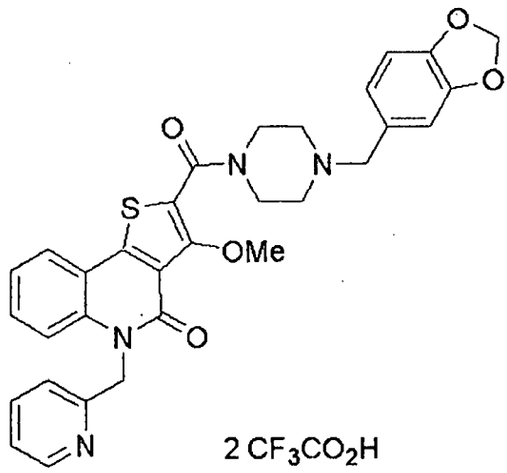
To a solution (0.12 M, 0.40 mL, 48 μmol) of the compound of Reference Example 19 in DMF were added a solution (0.66 M, 0.10 mL, 63 μmol) of N,N-diethyl-N'-methylethane-1,2-diamine in DMF and a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was agitated at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (33.2 mg, 98%). LC/MS 479 (M+H).

[0739]

Example 4

Production of 2-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}-3-methoxy-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[0740]



[0741]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-(1,3-benzodioxol-5-ylmethyl)piperazine.

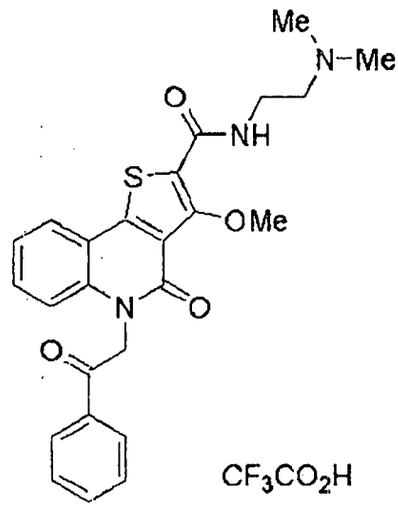
LC/MS 569 (M+H).

[0742]

Example 5

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0743]



[0744]

To a solution (0.15 M, 0.40 mL, 60 μmol) of the compound of Reference Example 7 in DMF were added a solution (0.66 M, 0.10 mL, 63 μmol) of N,N-dimethylethane-1,2-diamine in DMF and

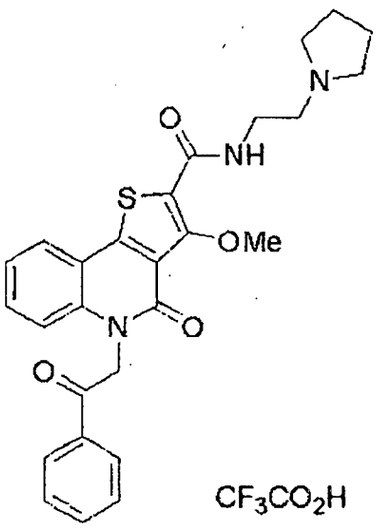
a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was agitated at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, and the organic layer was filtered through a Teflon (registered trade mark) filter to separate from the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (25.2 mg, 73%).
LC/MS 464 (M+H).

[0745]

Example 6

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0746]



[0747]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 2-pyrrolidin-1-ylethanamine.
LC/MS 490 (M+H).

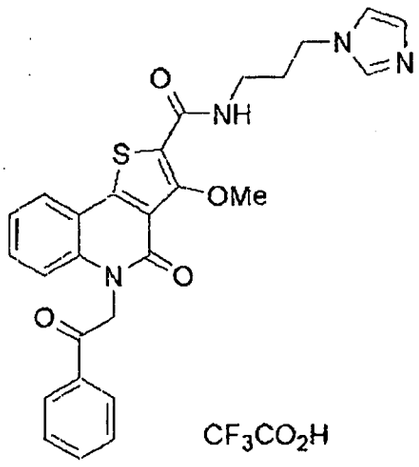
[0748]

Example 7

Production of N-[3-(1H-imidazol-1-yl)propyl]-3-methoxy-4-oxo-

5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0749]



[0750]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-(1H-imidazol-1-yl)propan-1-amine.

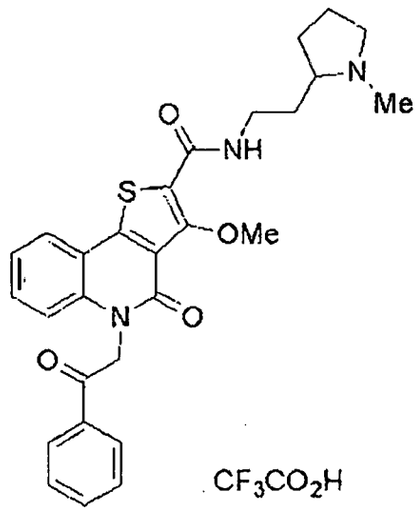
LC/MS 501 (M+H).

[0751]

Example 8

Production of 3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0752]



[0753]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 7 and 2-(1-methylpyrrolidin-2-yl)ethanamine.

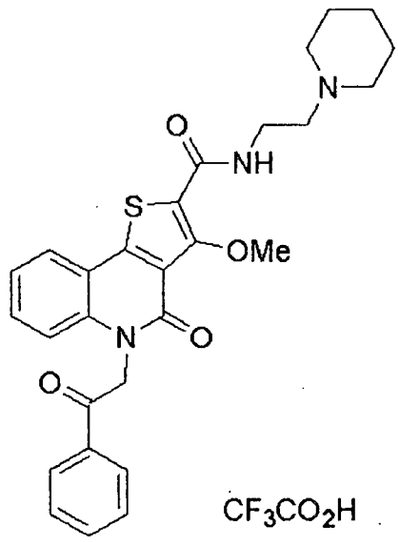
LC/MS 504 (M+H).

[0754]

Example 9

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0755]



[0756]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 2-piperidin-1-ylethanamine.

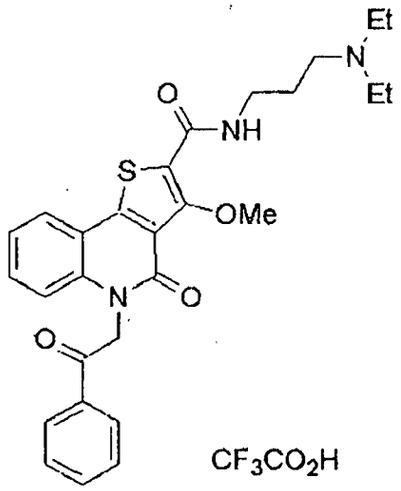
LC/MS 504 (M+H).

[0757]

Example 10

Production of N-[3-(diethylamino)propyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0758]



[0759]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and N,N-diethylpropane-1,3-diamine.

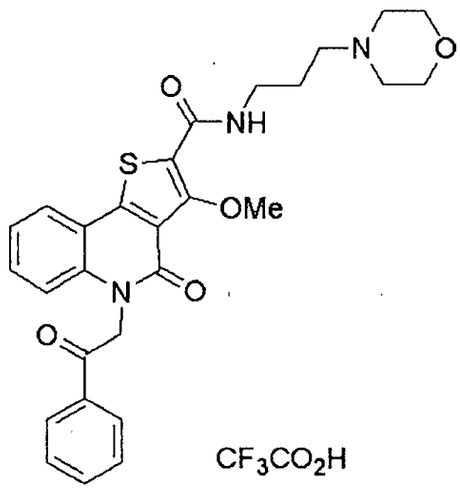
LC/MS 506 (M+H).

[0760]

Example 11

Production of 3-methoxy-N-(3-morpholin-4-ylpropyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0761]



[0762]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-morpholin-4-ylpropan-1-amine.

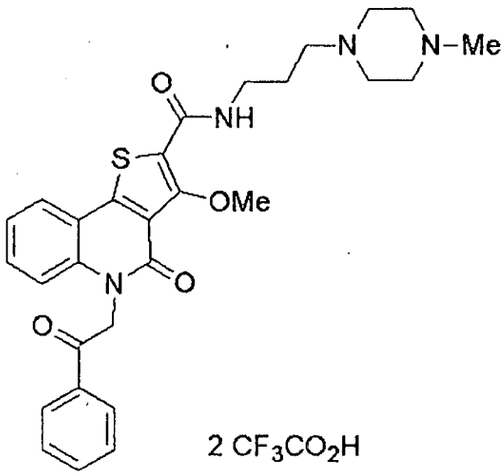
LC/MS 520 (M+H).

[0763]

Example 12

Production of 3-methoxy-N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[0764]



[0765]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-(4-methylpiperazin-1-yl)propan-1-amine.

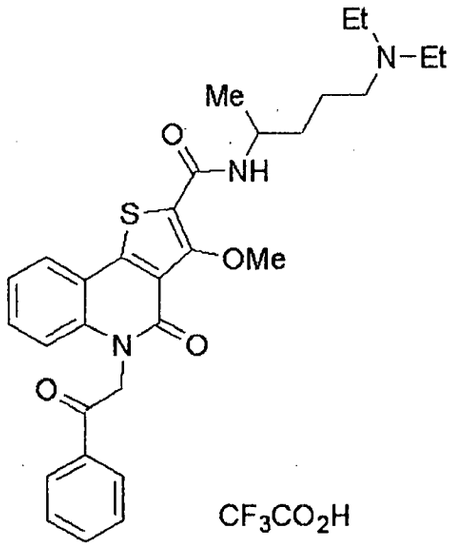
LC/MS 533 (M+H).

[0766]

Example 13

Production of N-[4-(diethylamino)-1-methylbutyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0767]



[0768]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and N^1,N^1-diethylpentane-1,4-diamine.

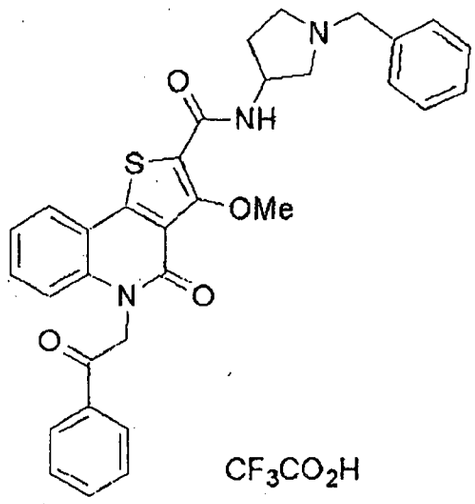
LC/MS 534 (M+H).

[0769]

Example 14

Production of N-(1-benzylpyrrolidin-3-yl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0770]



[0771]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-

benzylpyrrolidin-3-amine.

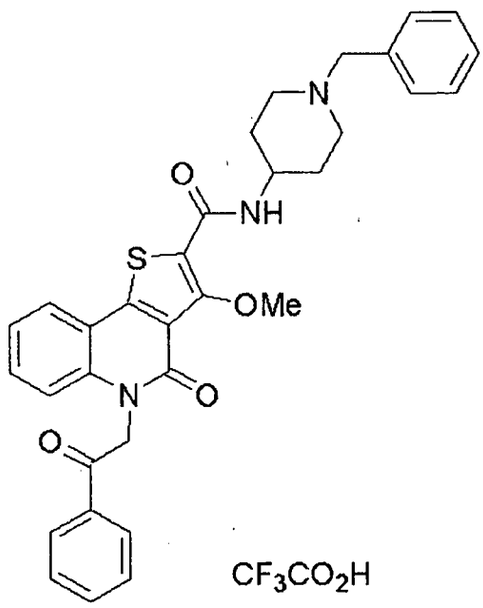
LC/MS 552 (M+H).

[0772]

Example 15

Production of N-(1-benzylpiperidin-4-yl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0773]



[0774]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-benzylpiperidin-4-amine.

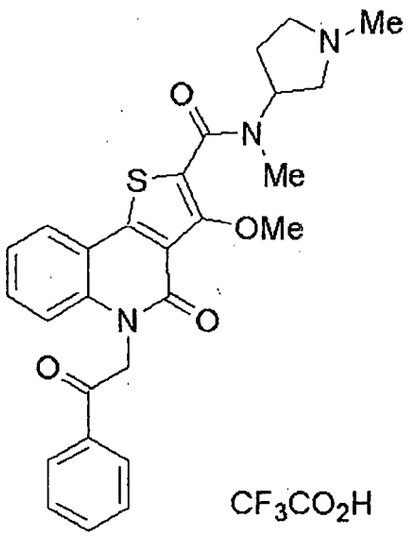
LC/MS 566 (M+H).

[0775]

Example 16

Production of 3-methoxy-N-methyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0776]



[0777]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and N,1-dimethylpyrrolidin-3-amine.

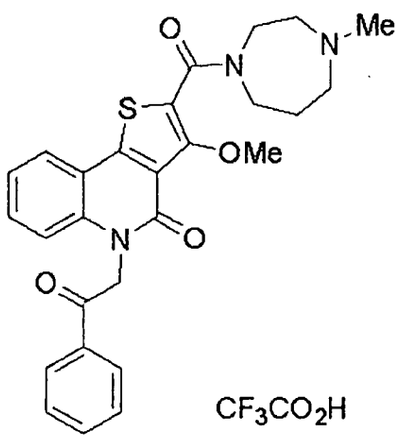
LC/MS 490 (M+H).

[0778]

Example 17

Production of 3-methoxy-2-[(4-methyl-1,4-diazepan-1-yl)carbonyl]-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[0779]



[0780]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-methyl-1,4-diazepane.

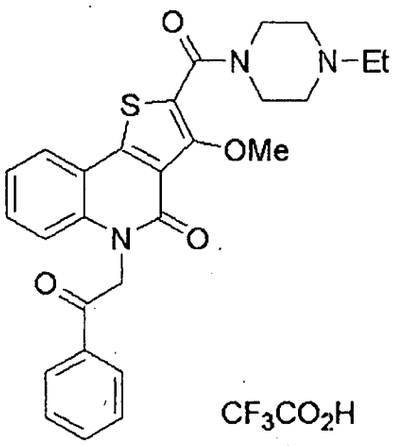
LC/MS 490 (M+H).

[0781]

Example 18

Production of 2-[(4-ethylpiperazin-1-yl)carbonyl]-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[0782]



[0783]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-ethylpiperazine.

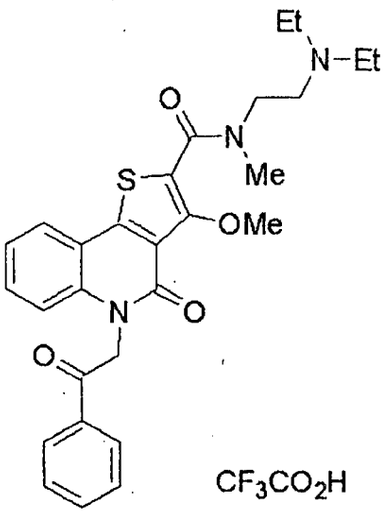
LC/MS 490 (M+H).

[0784]

Example 19

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0785]



[0786]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and N,N-diethyl-N'-methylethane-1,2-diamine.

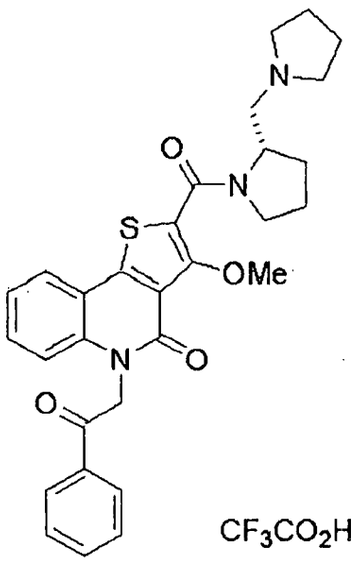
LC/MS 506 (M+H).

[0787]

Example 20

Production of 3-methoxy-5-(2-oxo-2-phenylethyl)-2-{[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[0788]



[0789]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-

[(2S)-pyrrolidin-2-ylmethyl]pyrrolidine.

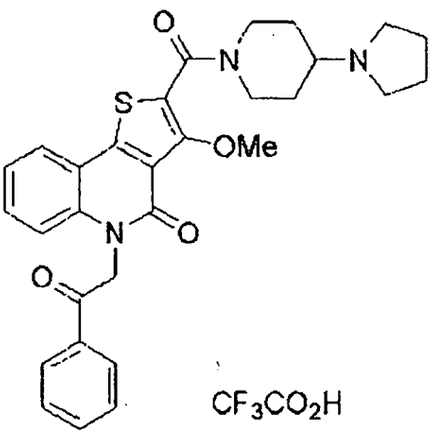
LC/MS 530 (M+H).

[0790]

Example 21

Production of 3-methoxy-5-(2-oxo-2-phenylethyl)-2-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[0791]



[0792]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 4-pyrrolidin-1-ylpiperidine.

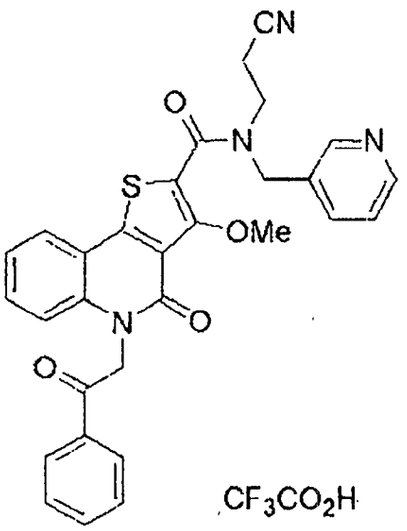
LC/MS 530 (M+H).

[0793]

Example 22

Production of N-(2-cyanoethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-3-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0794]



[0795]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 3-[(pyridin-3-ylmethyl)amino]propanenitrile.

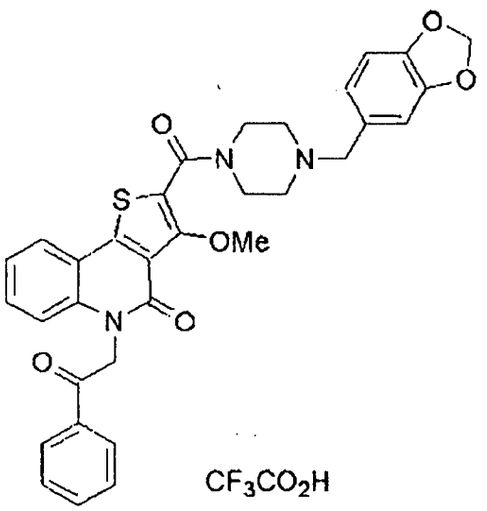
LC/MS 537 (M+H).

[0796]

Example 23

Production of 2-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[0797]



[0798]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-

(1,3-benzodioxol-5-ylmethyl)piperazine.

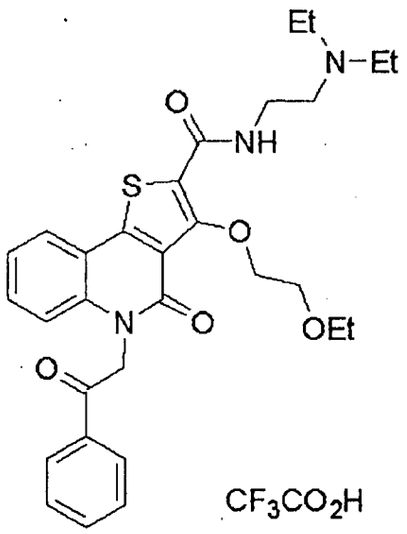
LC/MS 596 (M+H).

[0799]

Example 24

Production of N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[0800]



[0801]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N,N-diethylethane-1,2-diamine.

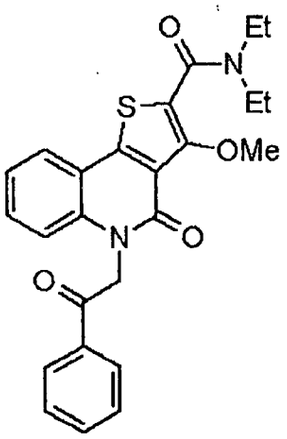
LC/MS 550 (M+H).

[0802]

Example 25

Production of N,N-diethyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0803]



[0804]

To a solution of the compound of Reference Example 7 (130 mg, 0.33 mmol), diethylamine (36 mg, 0.49 mmol) and HOBt (67 mg, 0.49 mmol) in DMF (4 mL) was added WSCD (94 mg, 0.49 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate), and the obtained oil was recrystallized from ethyl acetate-diethyl ether to give the title compound (104 mg, 70%) as white crystals.

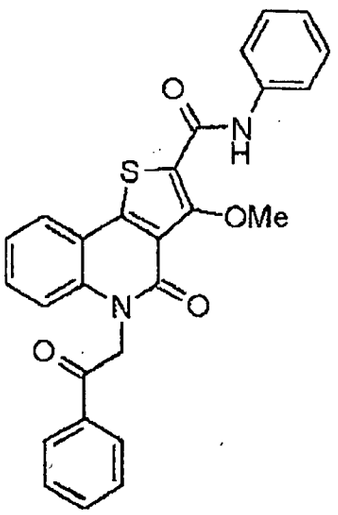
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15 (6H, t, J = 7.1 Hz), 3.39-3.50 (4H, m), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, J = 7.5 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.56 (1H, td, J = 8.7, 1.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.96 (1H, dd, J = 7.8, 1.2 Hz), 8.18 (2H, d, J = 7.5 Hz).

[0805]

Example 26

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-phenyl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0806]



[0807]

In the same manner as in Example 25, the title compound (163 mg, 63%) was obtained as pale-orange crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and aniline (48 μL, 0.51 mmol).

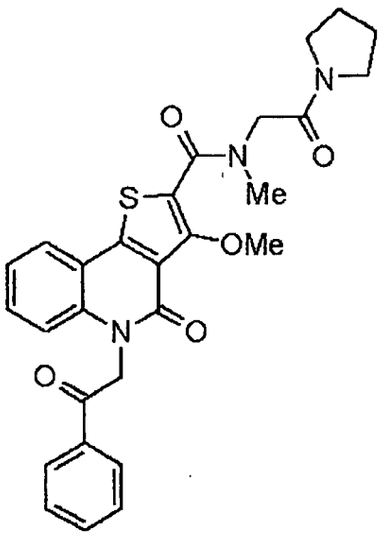
^{1}H-NMR (300 MHz, DMSO-d_6) δ:4.15 (3H, s), 6.02 (2H, s), 7.12-7.21 (1H, m), 7.32-7.44 (3H, m), 7.48-7.55 (1H, m), 7.56-7.70 (3H, m), 7.71-7.82 (3H, m), 8.09 (1H, dd, J = 7.9, 1.3 Hz), 8.14-8.24 (2H, m), 9.74 (1H, s).

[0808]

Example 27

Production of 3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-oxo-2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0809]



[0810]

A mixed solution of the compound of Example 120 (400 mg, 0.81 mmol) and a 2N aqueous sodium hydroxide solution (10 mL) in THF (10 mL)-ethanol (5 mL) was stirred at room temperature for 2 hr. The reaction mixture was neutralized with 2N hydrochloric acid (10 mL), and concentrated under reduced pressure. The residue was partitioned between saturated brine and ethyl acetate, and the aqueous phase was extracted with ethyl acetate. The organic phase was combined, dried over magnesium sulfate, and concentrated under reduced pressure to give N-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}-N-methylglycine (380 mg, 100%) as a white solid.

The title compound (84 mg, 40%) was obtained as white crystals from the thus-obtained N-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}-N-methylglycine (190 mg, 0.41 mmol) and pyrrolidine (44 mg, 0.61 mmol) by a method similar to that in Example 25.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.75-2.05 (4H, m), 3.20 (1H, s), 3.27 (2H, s), 3.45-3.56 (4H, m), 4.01 (1H, s), 4.13 (2H, s), 4.23 (0.6H, br s), 4.29 (1.4H, s), 5.86 (2H, s), 7.03 (1H, d, J = 8.4 Hz), 7.23-7.28 (1H, m), 7.45 (1H, t, J = 8.0 Hz), 7.55 (2H, t, J = 7.5 Hz), 7.67 (1H, t, J = 7.2 Hz), 7.82 (1H, dd, J =

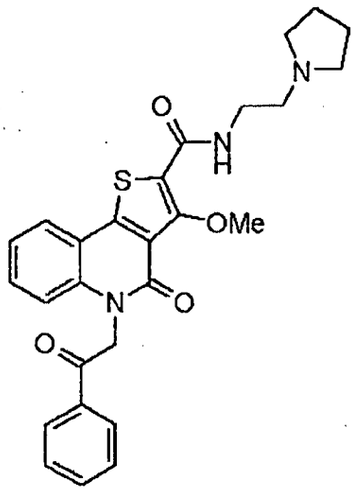
8.1, 1.2 Hz), 8.10-8.12 (2H, m).

[0811]

Example 28

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0812]



[0813]

In the same manner as in Example 25, the title compound (1.54 g, 67%) was obtained as white crystals from the compound of Reference Example 7 (1.85 g, 4.69 mmol) and 1-(2-aminoethyl)pyrrolidine (642 mg, 5.63 mmol).

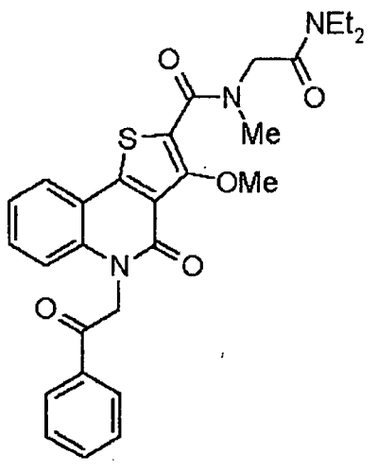
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.72 (4H, br s), 2.45-2.60 (4H, br), 2.64 (2H, t, J = 6.3 Hz), 3.44 (2H, t, J = 5.9 Hz), 4.01 (3H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.8 Hz), 7.49 (1H, d, J = 8.1 Hz), 7.55-7.67 (3H, m), 7.70 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 8.1, 1.5 Hz), 8.16-8.19 (3H, m).

[0814]

Example 29

Production of N-[2-(diethylamino)-2-oxoethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0815]



[0816]

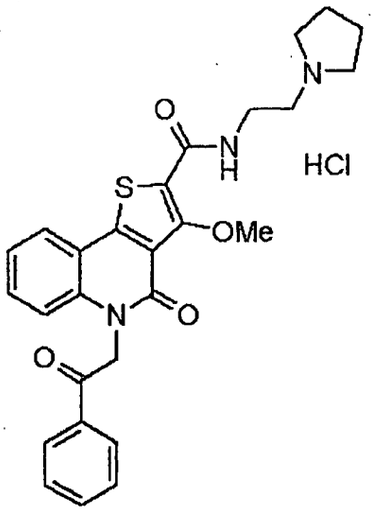
In the same manner as in Example 25, the title compound (124 mg, 58%) was obtained as white crystals from N-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}-N-methylglycine (190 mg, 0.41 mmol) obtained in Example 27 and diethylamine (45 mg, 0.61 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.05-1.31 (6H, m), 3.18 (1.2H, s), 3.26 (1.8H, s), 3.34-3.47 (4H, m), 4.01 (1.2H, s), 4.10 (1.8H, s), 4.30 (0.8H, s), 4.36 (1.2H, s), 5.85 (2H, s), 7.03 (1H, d, J = 8.4 Hz), 7.23-7.28 (1H, m), 7.46 (1H, t, J = 7.4 Hz), 7.55 (2H, t, J = 7.5 Hz), 7.67 (1H, t, J = 7.4 Hz), 7.82 (1H, d, J = 6.9 Hz), 8.11 (2H, d, J = 7.2 Hz).

[0817]

Example 30

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0818]



[0819]

To a solution of the compound of Example 28 (200 mg, 0.41 mmol) in ethyl acetate (25 mL) was added 4N hydrogen chloride ethyl acetate solution (0.11 mL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (162 mg, 75%) as a white powder.

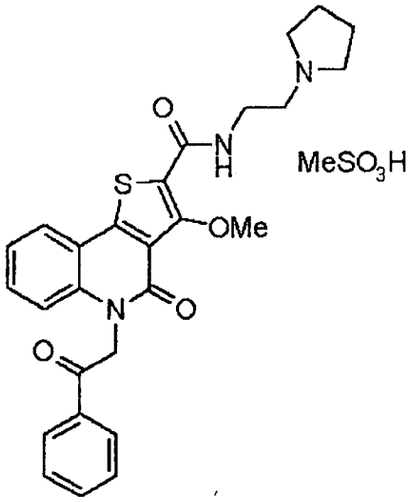
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.77-2.10 (4H, m), 2.95-3.10 (2H, br), 3.29-3.40 (2H, m), 3.55-3.75 (4H, m), 4.07 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.4 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.4 Hz), 8.06 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m), 8.31 (1H, t, J = 6.0 Hz), 10.33 (1H, br s).

[0820]

Example 31

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide methanesulfonate

[0821]



[0822]

To a solution of the compound of Example 28 (200 mg, 0.41 mmol) in ethyl acetate (25 mL) was added a solution of methanesulfonic acid (39 mg, 0.41 mmol) in ethyl acetate (5 mL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (197 mg, 82%) as a white powder.

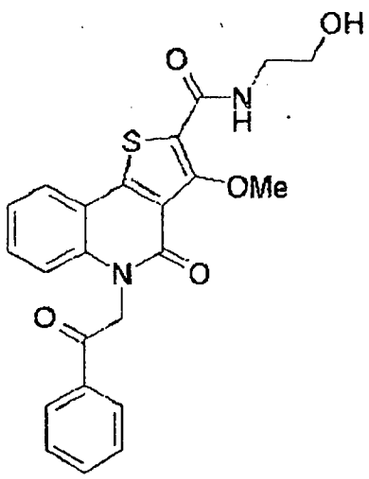
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.65-2.10 (4H, m), 2.30 (3H, s), 3.00-3.20 (2H, br), 3.35-3.45 (2H, br), 3.60-3.75 (4H, m), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.2 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.5 Hz), 8.06 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m), 8.29 (1H, t, J = 5.9 Hz), 9.30-9.45 (1H, br).

[0823]

Example 32

Production of N-(2-hydroxyethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0824]



[0825]

In the same manner as in Example 25, the title compound (65.8 mg, 67%) was obtained as a white powder from the compound of Reference Example 7 (89.0 mg, 0.226 mmol) and 2-aminoethanol (16.3 μL, 0.271 mmol).

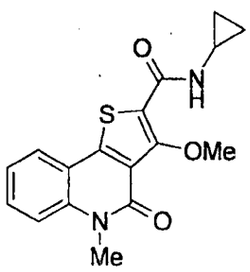
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.40-3.46 (2H, m), 3.54-3.59 (2H, m), 4.03 (3H, s), 4.87 (1H, t, J = 5.3 Hz), 5.99 (2H, s), 7.32-7.38 (1H, m), 7.48-7.67 (4H, m), 7.74-7.79 (1H, m), 8.00-8.06 (2H, m), 8.16-8.19 (2H, m).

[0826]

Example 33

Production of N-cyclopropyl-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0827]



[0828]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and cyclopropanamine.

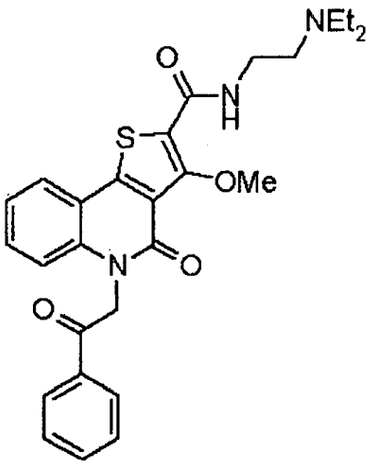
LC/MS 329 (M+H).

[0829]

Example 34

Production of N-[2-(diethylamino)ethyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0830]



[0831]

In the same manner as in Example 25, the title compound (500 mg, 80%) was obtained as white crystals from the compound of Reference Example 7 (500 mg, 1.27 mmol) and N,N-diethylethylenediamine (220 mg, 1.90 mmol).

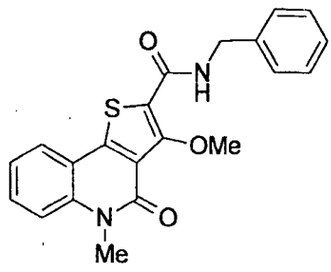
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.00 (6H, t, J = 7.1 Hz), 2.50-2.62 (6H, m), 3.37-3.42 (2H, m), 4.03 (3H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.4 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.55-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 7.8, 1.5 Hz), 8.12 (1H, t, J = 5.1 Hz), 8.16-8.19 (2H, m).

[0832]

Example 35

Production of N-benzyl-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0833]



[0834]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 1-phenylmethanamine.

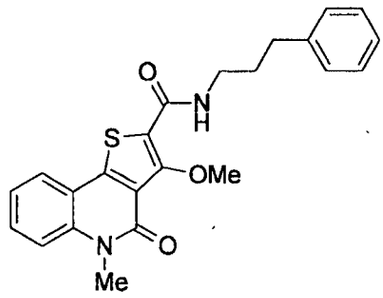
LC/MS 379 (M+H).

[0835]

Example 36

Production of 3-methoxy-5-methyl-4-oxo-N-(3-phenylpropyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0836]



[0837]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 3-phenylpropan-1-amine.

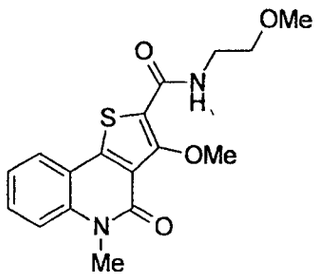
LC/MS 407 (M+H).

[0838]

Example 37

Production of 3-methoxy-N-(2-methoxyethyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0839]



[0840]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 2-methoxyethanamine.

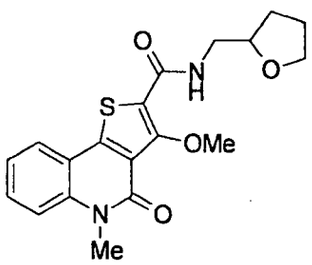
LC/MS 347 (M+H).

[0841]

Example 38

Production of 3-methoxy-5-methyl-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0842]



[0843]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 1-(tetrahydrofuran-2-yl)methanamine.

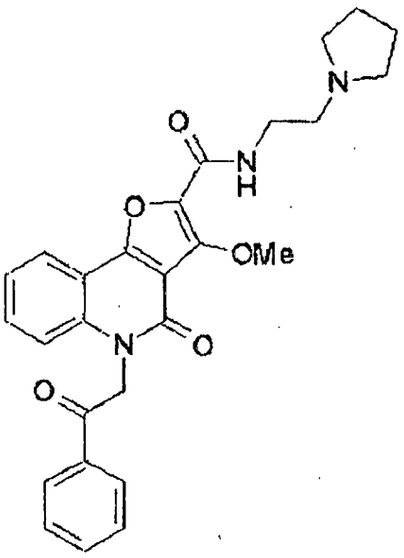
LC/MS 373 (M+H).

[0844]

Example 39

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxamide

[0845]



[0846]

In the same manner as in Example 25, the title compound (125 mg, 66%) was obtained as a white powder from the compound of Reference Example 24 (150 mg, 0.397 mmol) and 1-(2-aminoethyl)pyrrolidine (65.4 μL, 0.516 mmol).

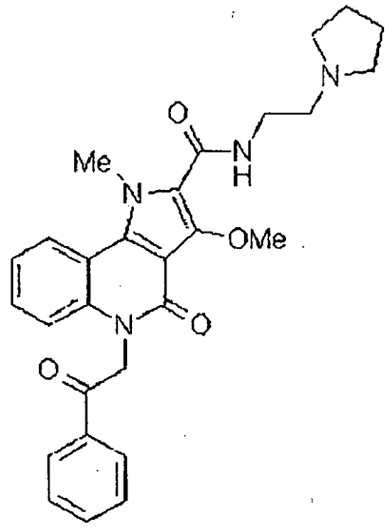
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.69-1.73 (4H, m), 2.49-2.51 (4H, m), 2.61 (2H, t, J = 6.6 Hz), 3.40-3.46 (2H, m), 4.15 (3H, s), 6.00 (2H, s), 7.43 (1H, t, J = 8.1 Hz), 7.54 (1H, d, J = 8.4 Hz), 7.60-7.67 (3H, m), 7.74-7.79 (1H, m), 8.06 (1H, t, J = 8.6 Hz), 8.15-8.19 (3H, m).

[0847]

Example 40

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0848]



[0849]

In the same manner as in Example 25, the title compound (145 mg, 78%) was obtained as a white powder from the compound of Reference Example 28 (150 mg, 0.384 mmol) and 1-(2-aminoethyl)pyrrolidine (63.3 μL, 0.499 mmol).

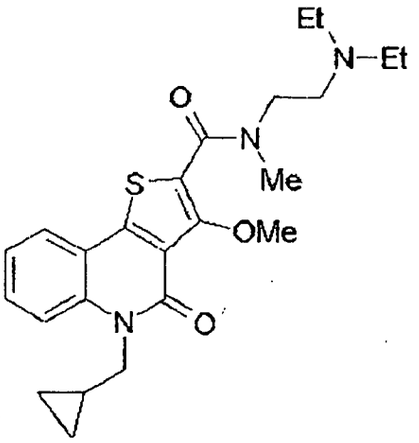
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.65-1.75 (4H, m), 2.48-2.55 (4H, m), 2.62 (2H, t, J = 6.2 Hz), 3.39-3.45 (2H, m), 3.97 (3H, s), 4.37 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.61-7.66 (2H, m), 7.73-7.78 (1H, m), 8.16-8.18 (3H, m), 8.39 (1H, dd, J = 8.1, 1.2 Hz).

[0850]

Example 41

Production of 5-(cyclopropylmethyl)-N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0851]



[0852]

To a solution of the compound of Example 121 (400 mg, 1.03 mmol) in DMF (5 mL) was added sodium hydride (60% in oil, 45.4 mg, 1.14 mmol) under ice-cooling, and the mixture was stirred for 15 min. Cyclopropylmethylbromide (120 μL, 1.24 mmol) was added to the obtained mixture under ice-cooling, and the mixture was stirred for 15 hr. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=3/7) to give the title compound (320 mg, 70%) as a colorless oil.

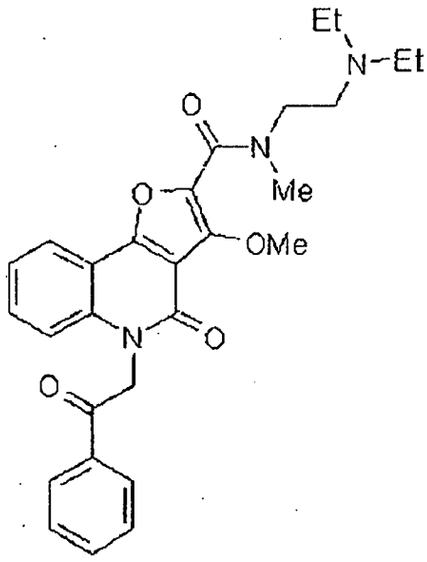
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.45-0.50 (4H, m), 0.70-1.05 (6H, br), 1.23-1.31 (1H, m), 2.25-2.70 (6H, br), 3.06 (3H, s), 3.40-3.60 (2H, br), 3.89 (3H, s), 4.27 (2H, d, J = 6.9 Hz), 7.30-7.35 (1H, m), 7.62-7.68 (1H, m), 7.76 (1H, d, J = 8.4 Hz), 7.91 (1H, dd, J = 7.8, 1.2 Hz).

[0853]

Example 42

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrofuro[3,2-c]quinoline-2-carboxamide

[0854]



[0855]

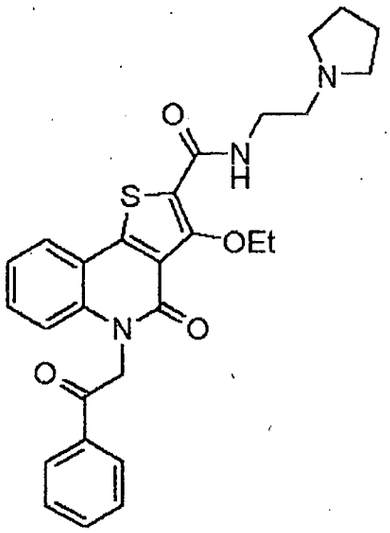
In the same manner as in Example 25, the title compound (130 mg, 80%) was obtained as a colorless oil from the compound of Reference Example 24 (130 mg, 0.344 mmol) and N,N-diethyl-N'-methylethylenediamine (72.3 μL, 0.477 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.75-0.90 (3H, br), 0.90-1.05 (3H, br), 2.25-2.40 (2H, br), 2.45-2.70 (4H, br), 2.95-3.30 (3H, br), 3.52 (2H, t, J = 6.5 Hz), 4.04 (3H, s), 5.99 (2H, s), 7.37-7.42 (1H, m), 7.52 (1H, d, J = 8.7 Hz), 7.57-7.67 (3H, m), 7.74-7.79 (1H, m), 8.04 (1H, d, J = 7.5 Hz), 8.16-8.19 (2H, m).

[0856]

Example 43

Production of 3-ethoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0857]



[0858]

In the same manner as in Example 25, the title compound (126 mg, 67%) was obtained as white crystals from the compound of Reference Example 9 (150 mg, 0.37 mmol) and 1-(2-aminoethyl)pyrrolidine (63 mg,0.55 mmol).

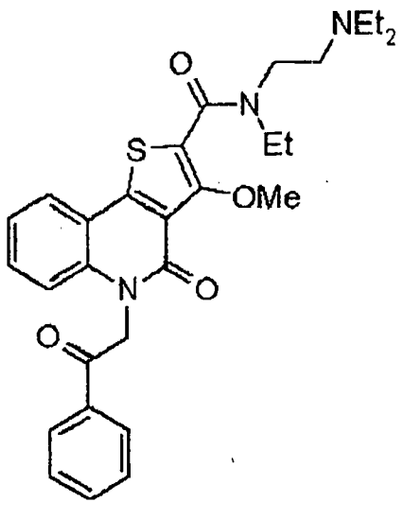
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.39 (3H, t, J = 7.0 Hz), 1.72 (4H, br s), 2.40-2.60 (4H, br), 2.63 (2H, t, J = 6.0 Hz), 3.40-3.47 (2H, m), 4.31 (2H, q, J = 7.0 Hz), 5.99 (2H, s), 7.35 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 8.4 Hz), 7.56 (1H, dd, J = 7.2, 1.5 Hz), 7.64 (2H, t, J = 8.4 Hz), 7.77 (1H, t, J = 7.2 Hz), 8.05 (1H, dd, J = 8.1, 1.5 Hz), 8.10 (1H, br t), 8.16-8.19 (2H, m).

[0859]

Example 44

Production of N-[2-(diethylamino)ethyl]-N-ethyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0860]



[0861]

In the same manner as in Example 25, the title compound (150 mg, 56%) was obtained as white crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and N,N,N'-triethylethylenediamine (110 mg, 0.76 mmol).

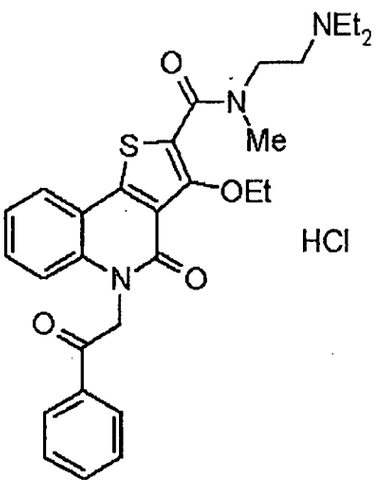
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.10 (6H, br), 1.14 (3H, br t), 2.20-2.70 (6H, br), 3.40-3.60 (4H, br), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 8.1 Hz), 7.55 (1H, td, J = 7.8, 1.5 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 7.95 (1H, dd, J = 7.8, 1.5 Hz), 8.16-8.19 (2H, m).

[0862]

Example 45

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0863]



[0864]

To a solution of the compound of Reference Example 9 (150 mg, 0.37 mmol), N,N-diethyl-N'-methylethylenediamine (72 mg, 0.55 mmol) and HOBt (74 mg, 0.55 mmol) in DMF (5 mL) was added WSCD (105 mg, 0.55 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=1/1) to give a white non-crystalline solid (180 mg).

To a solution of the white non-crystalline solid (180 mg) in ethyl acetate (5 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (173 mg, 83%) as a white powder.

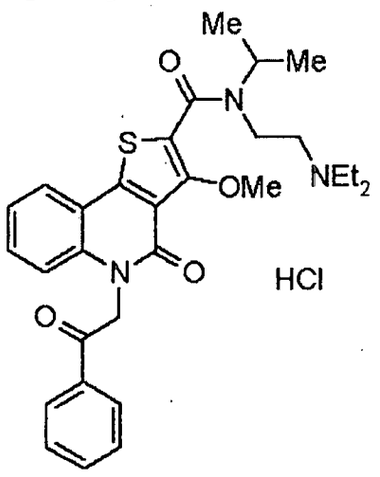
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.35 (9H, m), 3.12-3.40 (9H, br), 3.84 (2H, t, J = 7.2 Hz), 4.14 (2H, q, J = 7.0 Hz), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.1 Hz), 7.55-7.67 (3H, m), 7.75-7.80 (1H, m), 7.98 (1H, dd, J = 8.1, 1.5 Hz), 8.16-8.19 (2H, m), 9.85-10.10 (1H, br).

[0865]

Example 46

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-(1-methylethyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0866]



[0867]

In the same manner as in Example 45, the title compound (164 mg, 56%) was obtained as a white powder from the compound of Reference Example 7 (200 mg, 0.51 mmol) and N,N-diethyl-N'-isopropylethylenediamine (120 mg, 0.76 mmol).

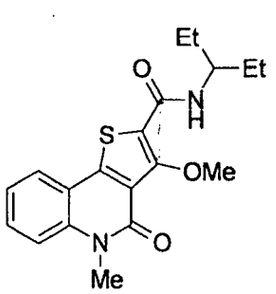
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.35 (12H, m), 3.15-3.40 (6H, br), 3.65-3.80 (2H, m), 3.89 (3H, s), 4.10-4.30 (1H, br), 5.99 (2H, s), 7.33 (1H, t, J = 7.5 Hz), 7.49-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 7.97 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 9.95-10.10 (1H, br).

[0868]

Example 47

Production of N-(1-ethylpropyl)-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0869]



[0870]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and pentan-3-amine.

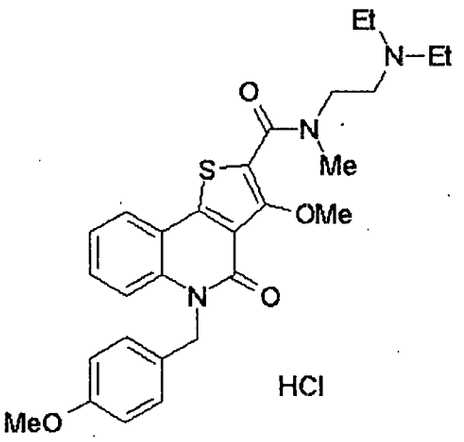
LC/MS 359 (M+H).

[0871]

Example 48

Production of N-[2-(diethylamino)ethyl]-3-methoxy-5-(4-methoxybenzyl)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0872]



[0873]

In the same manner as in Example 25, N-[2-(diethylamino)ethyl]-3-methoxy-5-(4-methoxybenzyl)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (4.90 g, 85%) was obtained as a colorless oil from the compound of Reference Example 13 (4.50 g, 11.4 mmol) and N,N-diethyl-N'-methylethylenediamine (2.40 mL, 14.8 mmol).

The title compound (490 mg, 91%) was obtained as a white powder from the thus-obtained N-[2-(diethylamino)ethyl]-3-methoxy-5-(4-methoxybenzyl)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (500 mg, 0.985 mmol) by a method similar to that in Example 30.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.35 (6H, br), 3.13 (3H, s), 3.10-3.40 (6H, br), 3.70 (3H, s), 3.87 (2H, t, J = 6.6 Hz), 3.96 (3H, s), 5.52 (2H, s), 6.87 (2H, d, J = 8.6 Hz), 7.20 (2H,

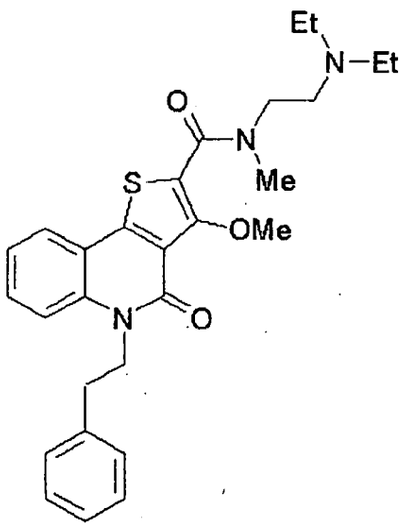
d, J = 8.6 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.49-7.58 (2H, m), 7.92 (1H, d, J = 7.8 Hz), 10.55 (1H, s).

[0874]

Example 49

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0875]



[0876]

In the same manner as in Example 41, the title compound (45.1 mg, 28%) was obtained as a colorless oil from the compound of Example 121 (125 mg, 0.323 mmol) and (2-bromoethyl)benzene (53.5 μL, 0.387 mmol).

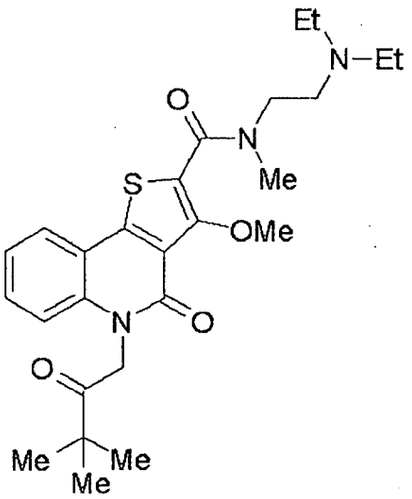
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.75-1.05 (6H, br), 2.25-2.70 (6H, br), 2.92-2.97 (2H, m), 3.05 (3H, s), 3.40-3.55 (2H, br), 3.88 (3H, s), 4.50 (2H, t, J = 6.5 Hz), 7.20-7.26 (1H, m), 7.30-7.36 (5H, m), 7.63-7.75 (2H, m), 7.92 (1H, dd, J = 7.8, 1.5 Hz).

[0877]

Example 50

Production of N-[2-(diethylamino)ethyl]-5-(3,3-dimethyl-2-oxobutyl)-3-methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0878]



[0879]

In the same manner as in Example 41, the title compound (45.1 mg, 28%) was obtained as a colorless oil from the compound of Example 121 (125 mg, 0.323 mmol) and 1-bromo-3,3-dimethylbutan-2-one (57.9 μL, 0.441 mmol).

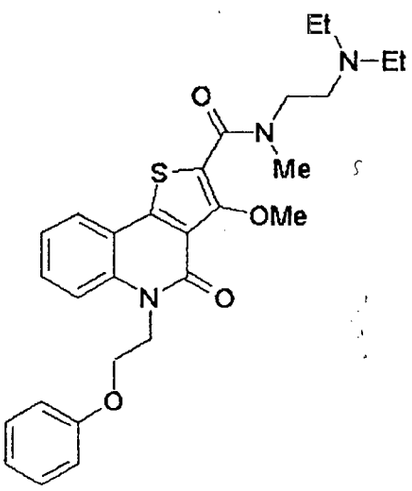
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.10 (6H, br), 1.30 (9H, s), 2.20-2.40 (6H, br), 3.06 (3H, s), 3.40-3.60 (2H, br), 3.87 (3H, s), 5.47 (2H, s), 7.28-7.34 (2H, m), 7.55-7.61 (1H, m), 7.92 (1H, dd, J = 7.8, 1.2 Hz).

[0880]

Example 51

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-phenoxyethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0881]



[0882]

In the same manner as in Example 41, the title compound (75.1 mg, 43%) was obtained as a colorless oil from the compound of Example 121 (135 mg, 0.348 mmol) and (2-bromoethoxy)benzene (105 mg, 0.522 mmol).

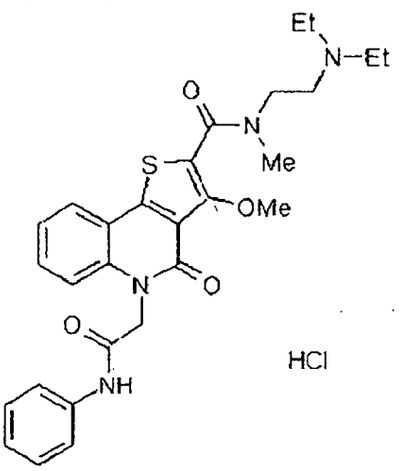
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.10 (6H, br), 2.20-2.70 (6H, br), 3.05 (3H, s), 3.40-3.60 (2H, br), 3.91 (3H, s), 4.30 (2H, t, J = 5.9 Hz), 4.73 (2H, t, J = 5.9 Hz), 6.88-6.93 (3H, m), 7.22-7.36 (3H, m), 7.65 (1H, t, J = 8.0 Hz), 7.83 (1H, d, J = 8.7 Hz), 7.91 (1H, d, J = 7.8 Hz).

[0883]

Example 52

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-[2-oxo-2-(phenylamino)ethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0884]



[0885]

To a solution of the compound of Example 122 (150 mg, 0.336 mmol), aniline (39.8 mg, 0.437 mmol) and HOBt (68.2 mg, 0.505 mmol) in DMF (3 mL) was added WSCD (96.8 mg, 0.505 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified

by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/1) to give N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-[2-oxo-2-(phenylamino)ethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide as a colorless oil.

The title compound (65.2 mg, 35%) was obtained as a white powder from the thus-obtained N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-[2-oxo-2-(phenylamino)ethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide by a method similar to that in Example 30.

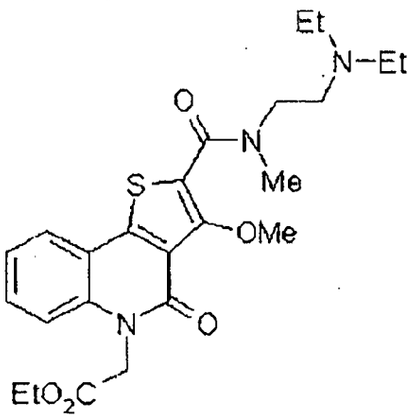
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.35 (6H, br), 3.12 (3H, s), 3.15-3.40 (6H, br), 3.75-3.90 (2H, br), 3.92 (3H, s), 5.22 (2H, s), 7.07 (1H, t, J = 7.5 Hz), 7.29-7.38 (3H, m), 7.53-7.66 (4H, m), 7.96 (1H, dd, J = 7.5, 1.4 Hz), 9.76 (1H, s), 10.51 (1H, s).

[0886]

Example 53

Production of ethyl [2-{[2-(diethylamino)ethyl](methyl)carbamoyl}-3-methoxy-4-oxothieno[3,2-c]quinolin-5(4H)-yl]acetate

[0887]



[0888]

In the same manner as in Example 41, the title compound (680 mg, 83%) was obtained as a colorless oil from the compound of Example 121 (670 mg, 1.73 mmol) and ethyl bromoacetate (229 μL, 2.08 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.10 (6H, br), 1.23 (3H, t, J = 7.1 Hz), 2.25-2.70 (6H, m), 3.06 (3H, s), 3.40-3.60 (2H, br),

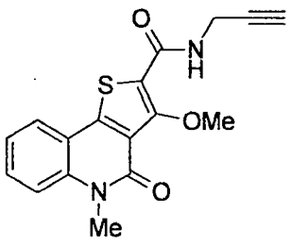
3.89 (3H, s), 4.18 (2H, q, J = 7.1 Hz), 5.16 (2H, s), 7.34 (1H, t, J = 7.7 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.61 (1H, t, J = 8.1 Hz), 7.94 (1H, d, J = 7.7 Hz).

[0889]

Example 54

Production of 3-methoxy-5-methyl-4-oxo-N-prop-2-yn-1-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0890]



[0891]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and prop-2-yn-1-amine.

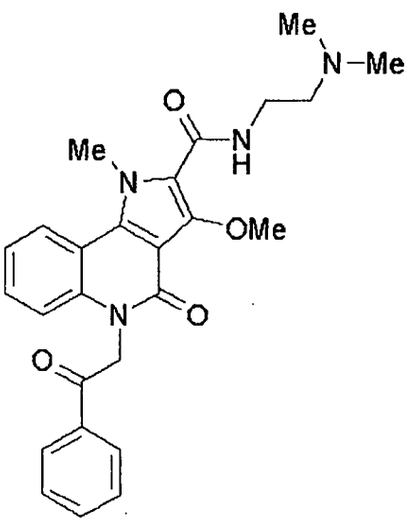
LC/MS 327 (M+H).

[0892]

Example 55

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0893]



[0894]

In the same manner as in Example 25, the title compound (65.0 mg, 61%) was obtained as a white powder from the compound of Reference Example 28 (90.0 mg, 0.231 mmol) and N,N-dimethylethylenediamine (25.2 μL, 0.300 mmol).

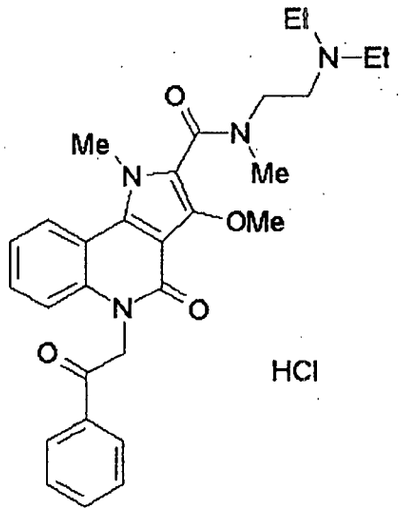
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.22 (6H, s), 2.44 (2H, t, J = 6.2 Hz), 3.37-3.43 (2H, m), 3.98 (3H, s), 4.38 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.7 Hz), 7.73-7.79 (1H, m), 8.11-8.19 (3H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[0895]

Example 56

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N,1-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0896]



[0897]

In the same manner as in Example 25, N-[2-(diethylamino)ethyl]-3-methoxy-N,1-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide was obtained as a colorless oil from the compound of Reference Example 28 (90.0 mg, 0.231 mmol) and N,N-diethyl-N'-methylethylenediamine (48.6 μL, 0.300 mmol).

The title compound (75.1 mg, 60%) was obtained as a white powder from the thus-obtained N-[2-(diethylamino)ethyl]-3-

methoxy-N,1-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide by a method similar to that in Example 30.

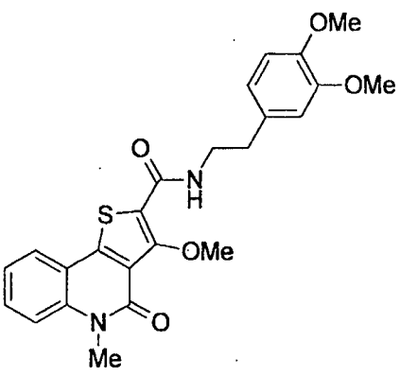
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.31 (6H, br), 2.95-3.40 (9H, br), 3.80-3.95 (5H, m), 4.03 (3H, s), 5.98 (2H, s), 7.29-7.50 (3H, m), 7.64 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.16-8.19 (2H, m), 8.34 (1H, dd, J = 8.3, 1.1 Hz), 9.80-10.15 (1H, br).

[0898]

Example 57

Production of N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0899]



[0900]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 2-(3,4-dimethoxyphenyl)ethanamine.

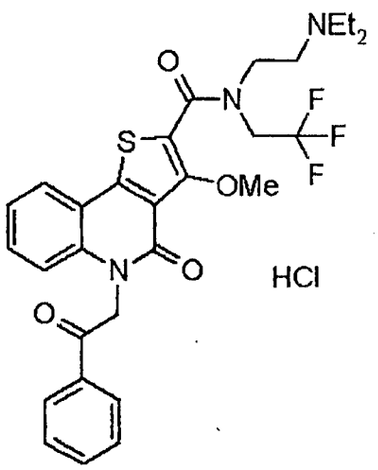
LC/MS 453 (M+H).

[0901]

Example 58

Production of N-[2-(diethylamino)ethyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2,2,2-trifluoroethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0902]



[0903]

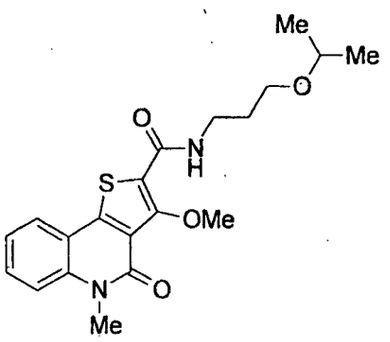
In the same manner as in Example 45, the title compound (12 mg, 7%) was obtained as a white powder from the compound of Reference Example 7 (116 mg, 0.29 mmol) and N,N-diethyl-N'-(2,2,2-trifluoroethyl)ethylenediamine (70 mg, 0.35 mmol). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.80-1.10 (6H, br), 2.30-2.70 (6H, br), 3.75 (2H, t, J = 5.6 Hz), 4.02 (3H, s), 4.44 (2H, br d, J = 7.8 Hz), 5.86 (2H, s), 7.04 (1H, d, J = 8.4 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.47 (1H, td, J = 8.7, 1.5 Hz), 7.56 (2H, t, J = 7.5 Hz), 7.65-7.70 (1H, m), 7.83 (1H, dd, J = 7.8, 1.5 Hz), 8.11 (2H, d, J = 7.2 Hz).

[0904]

Example 59

Production of 3-methoxy-5-methyl-N-[3-(1-methylethoxy)propyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0905]



[0906]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 3-

(1-methylethoxy)propan-1-amine.

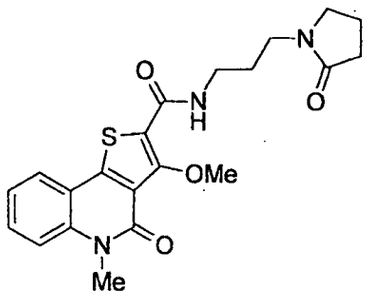
LC/MS 389 (M+H).

[0907]

Example 60

Production of 3-methoxy-5-methyl-4-oxo-N-[3-(2-oxopyrrolidin-1-yl)propyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0908]



[0909]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 1-(3-aminopropyl)pyrrolidin-2-one.

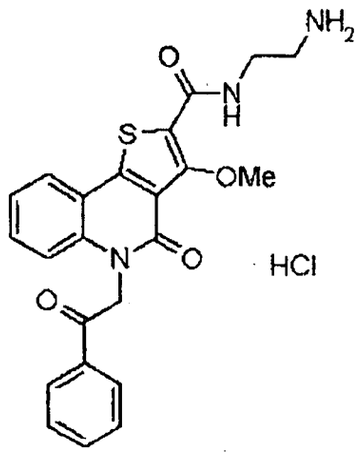
LC/MS 414 (M+H).

[0910]

Example 61

Production of N-(2-aminoethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0911]



[0912]

A solution of the compound of Example 64 (90 mg, 0.17 mmol) and 4N hydrogen chloride ethyl acetate solution (10 mL) in ethyl acetate (20 mL) was stirred at room temperature for 5 hr. The precipitate was collected by filtration, washed with ethyl acetate and diethyl ether, and dried under reduced pressure to give the title compound (78 mg, 97%) as a white powder.

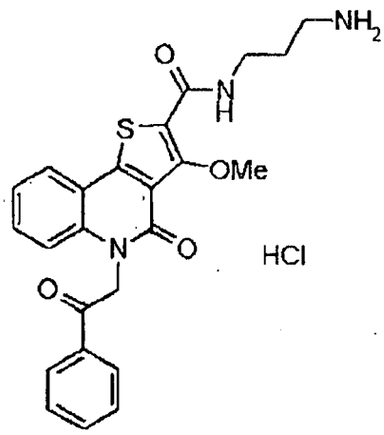
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.02 (2H, t, J = 6.0 Hz), 3.62 (2H, q, J = 6.0 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.4 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.57-7.59 (3H, m), 7.65 (1H, t, J = 7.5 Hz), 7.94 (3H, br s), 8.06 (1H, dd, J = 8.1, 1.5 Hz), 8.16-8.23 (3H, m).

[0913]

Example 62

Production of N-(3-aminopropyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0914]



[0915]

In the same manner as in Example 61, the title compound (121 mg, 100%) was obtained as a white powder from the compound of Example 65 (130 mg, 0.24 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.80-1.90 (2H, m), 2.85 (2H, t, J = 7.4 Hz), 3.33-3.49 (2H, m), 4.04 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.4 Hz), 7.50 (1H, d, J = 8.1 Hz), 7.56-7.67 (3H, m), 7.75-7.80 (4H, m), 8.05 (1H, dd, J = 7.8, 1.2 Hz), 8.16-

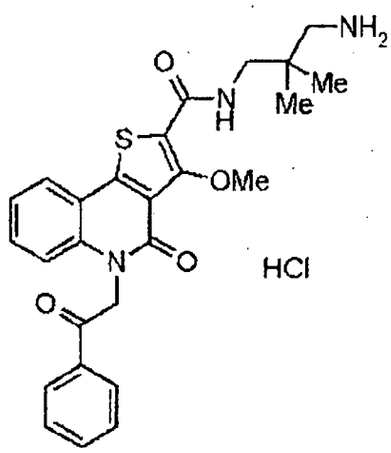
8.23 (3H, m).

[0916]

Example 63

Production of N-(3-amino-2,2-dimethylpropyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0917]



[0918]

In the same manner as in Example 61, the title compound (123 mg, 92%) was obtained as a white powder from the compound of Example 66 (150 mg, 0.26 mmol).

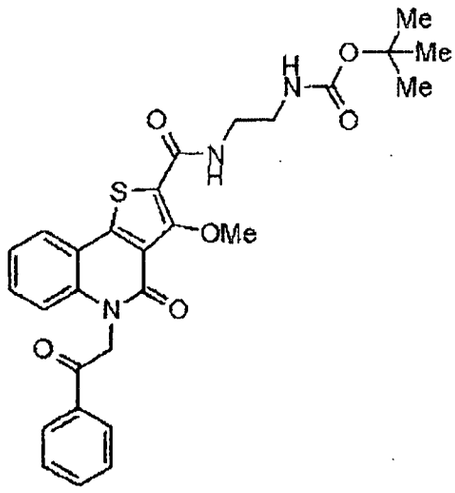
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.01 (6H, s), 2.69 (2H, q, J = 6.0 Hz), 3.32 (2H, d, J = 6.6 Hz), 4.08 (3H, s), 6.01 (2H, s), 7.34 (1H, t, J = 7.8 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.2 Hz), 7.90 (3H, br s), 8.06 (1H, dd, J = 8.1, 1.5 Hz), 8.17-8.19 (3H, m).

[0919]

Example 64

Production of tert-butyl [2-({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)ethyl]carbamate

[0920]



[0921]

In the same manner as in Example 25, the title compound (136 mg, 50%) was obtained as white crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and tert-butyl N-(2-aminoethyl)carbamate (122 mg, 0.76 mmol).

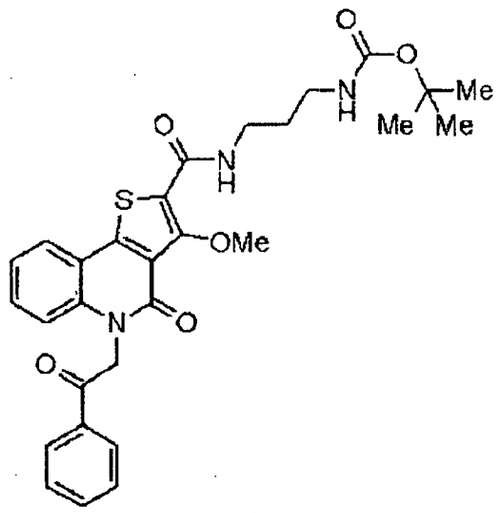
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.37 (9H, s), 3.10-3.20 (2H, m), 3.37-3.41 (2H, m), 4.04 (3H, s), 6.00 (2H, s), 6.99 (1H, br t), 7.35 (1H, t, J = 7.4 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.55-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.04-8.07 (2H, m), 8.16-8.19 (2H, m).

[0922]

Example 65

Production of tert-butyl [3-({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)propyl]carbamate

[0923]



[0924]

In the same manner as in Example 25, the title compound (136 mg, 50%) was obtained as white crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and tert-butyl N-(3-aminopropyl)carbamate (133 mg, 0.76 mmol).

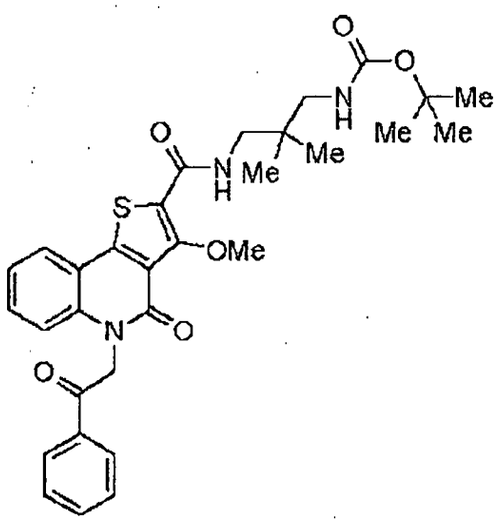
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (9H, s), 1.60-1.70 (2H, m), 2.90-3.00 (2H, m), 3.25-3.35 (2H, m), 4.05 (3H, s), 6.00 (2H, s), 6.91 (1H, br t), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.55-7.67 (3H, m), 7.77 (1H, t, J = 7.2 Hz), 8.05 (1H, dd, J = 7.8, 1.2 Hz), 8.17-8.19 (3H, m).

[0925]

Example 66

Production of tert-butyl [3-({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)-2,2-dimethylpropyl]carbamate

[0926]



[0927]

In the same manner as in Example 25, the title compound (205 mg, 69%) was obtained as white crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and 1-Boc-amino-2,2-dimethyl-1,3-propanediamine (154 mg, 0.76 mmol).

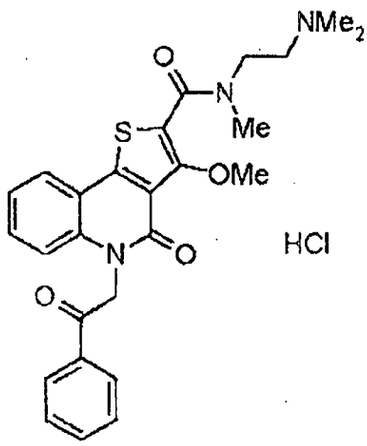
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.42 (9H, s), 2.81 (2H, d, J = 6.3 Hz), 3.13 (2H, d, J = 6.3 Hz), 4.09 (3H, s), 6.00 (2H, s), 7.11 (1H, br t), 7.35 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 8.1, 1.5 Hz), 8.16-8.19 (2H, m), 8.37 (1H, br t).

[0928]

Example 67

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0929]



[0930]

To a solution of the compound of Reference Example 7 (200 mg, 0.51 mmol), N,N,N'-trimethylethylenediamine (78 mg, 0.76 mmol) and HOBt (103 mg, 0.76 mmol) in DMF (5 mL) was added WSCD (145 mg, 0.76 mmol) under ice-cooling, and the mixture was stirred at room temperature for 24 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=2/1) to give N-[2-(dimethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (180 mg) as a colorless amorphous substance.

To a solution of the N-[2-(dimethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (180 mg, 0.38 mmol) in ethyl acetate (10 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL), and the obtained precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (144 mg, 55%) as a white powder.

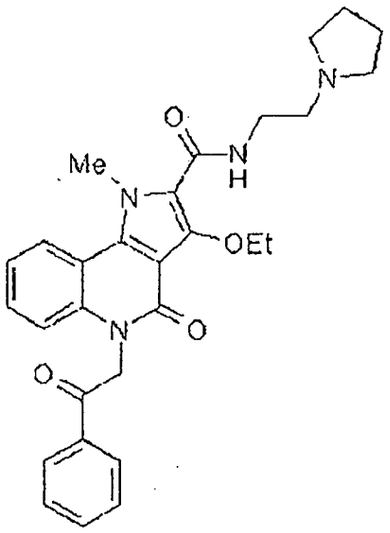
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15 (6H, t, J = 7.1 Hz), 3.10 (3H, s), 3.39-3.50 (4H, m), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, J = 7.5 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.56 (1H, td, J = 8.7, 1.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.96 (1H, dd, J = 7.8, 1.2 Hz), 8.18 (2H, d, J = 7.5 Hz).

[0931]

Example 68

Production of 3-ethoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0932]



[0933]

In the same manner as in Example 25, the title compound (44.0 mg, 18%) was obtained as a white powder from the compound of Reference Example 30 (200 mg, 0.495 mmol) and 1-(2-aminoethyl)pyrrolidine (82.1 μL, 0.644 mmol).

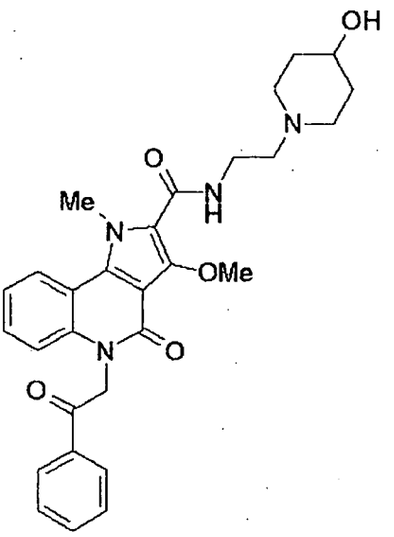
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32 (3H, t, J = 7.0 Hz), 1.65-1.75 (4H, br), 2.40-2.55 (4H, br), 2.62 (2H, t, J = 6.0 Hz), 3.05-3.47 (2H, m), 4.29 (2H, q, J = 7.0 Hz), 4.39 (3H, s), 5.96 (2H, s), 7.29-7.39 (2H, m), 7.48 (1H, t, J = 7.8 Hz), 7.63 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.12-8.19 (3H, m), 8.38 (1H, d, J = 8.4 Hz).

[0934]

Example 69

Production of N-[2-(4-hydroxypiperidin-1-yl)ethyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0935]



[0936]

In the same manner as in Example 25, the title compound (210 mg, 79%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 4-(2-aminoethyl)cyclohexanol (96.0 mg, 0.606 mmol).

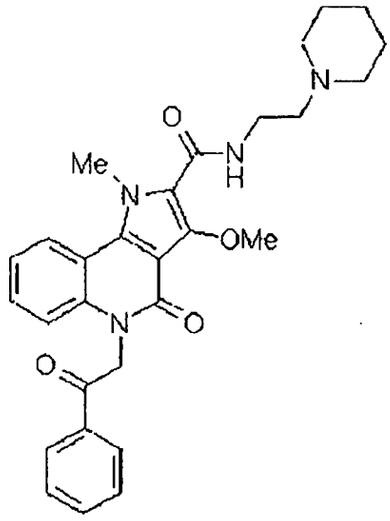
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.50 (2H, br), 1.70-1.80 (2H, br), 2.00-2.15 (2H, br), 2.45-2.55 (2H, br), 2.70-2.85 (2H, br), 3.35-3.50 (3H, m), 4.01 (3H, s), 4.38 (3H, s), 4.56 (1H, d, J = 4.5 Hz), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.48 (1H, t, J = 7.8 Hz), 7.64 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.2 Hz), 8.12-8.19 (3H, m), 8.38 (1H, d, J = 8.4 Hz).

[0937]

Example 70

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-piperidin-1-ylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0938]



[0939]

In the same manner as in Example 25, the title compound (230 mg, 90%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-(2-aminoethyl)piperidine (94.9 μL, 0.666 mmol).

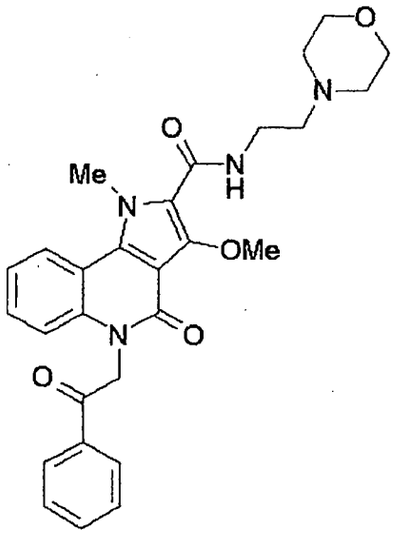
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30-1.65 (6H, br), 2.30-2.60 (6H, br), 3.40-3.45 (2H, m), 4.01 (3H, s), 4.38 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.78 (1H, m), 8.11-8.19 (3H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[0940]

Example 71

Production of 3-methoxy-1-methyl-N-(2-morpholin-4-ylethyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0941]



[0942]

In the same manner as in Example 25, the title compound (210 mg, 82%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-(2-aminoethyl)morpholine (87.4 μL, 0.666 mmol).

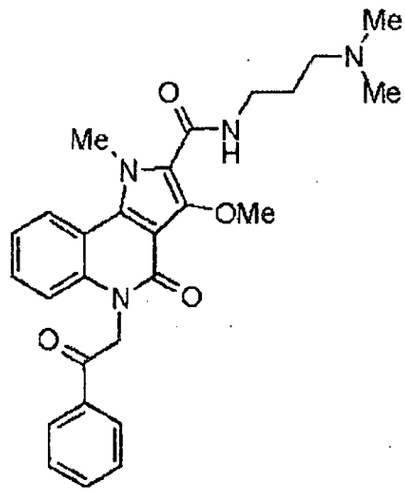
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.40-2.55 (6H, br), 3.40-3.50 (2H, br), 3.61 (4H, t, J = 4.2 Hz), 4.01 (3H, s), 4.37 (3H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.48 (1H, t, J = 7.7 Hz), 7.64 (2H, t, J = 7.4 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.12-8.19 (3H, m), 8.38 (1H, d, J = 8.4 Hz).

[0943]

Example 72

Production of N-[3-(dimethylamino)propyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0944]



[0945]

In the same manner as in Example 25, the title compound (163 mg, 67%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and N,N-dimethylpropane-1,3-diamine (80.0 μL, 0.666 mmol).

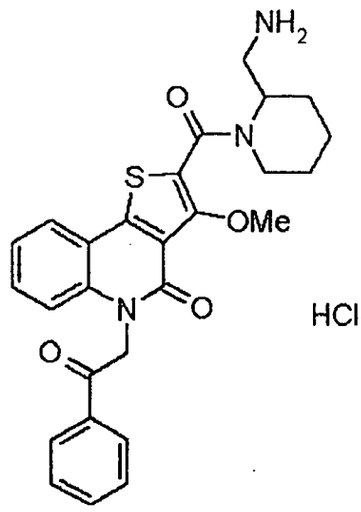
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.75-1.84 (2H, m), 2.43 (6H, s), 2.65 (2H, t, J = 7.2 Hz), 3.34-3.41 (2H, m), 4.00 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.7 Hz), 7.74-7.78 (1H, m), 8.11-8.19 (3H, m), 8.37 (1H, dd, J = 8.4, 1.2 Hz).

[0946]

Example 73

Production of 2-{[2-(aminomethyl)piperidin-1-yl]carbonyl}-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one hydrochloride

[0947]



[0948]

To a solution of the compound of Reference Example 7 (150 mg, 0.38 mmol), 2-(Boc-aminomethyl)piperidine (122 mg, 0.58 mmol) and HOBt (77 mg, 0.58 mmol) in DMF (5 mL) was added WSCD (109 mg, 0.58 mmol) under ice-cooling, and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=1/1 to 2/1) to give tert-butyl [(1-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}piperidin-2-yl)methyl]carbamate (150 mg) as a colorless oil.

A solution of the obtained tert-butyl [(1-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}piperidin-2-yl)methyl]carbamate (150 mg) and 4N hydrogen chloride ethyl acetate solution (8 mL) in ethyl acetate (15 mL) was stirred at room temperature for 18 hr. The obtained precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (133 mg, 67%) as a white powder.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.90 (6H, m), 3.00-3.15 (2H, m), 3.20-3.30 (1H, m), 3.60-3.80 (1H, m), 3.90 (3H, s), 4.75-

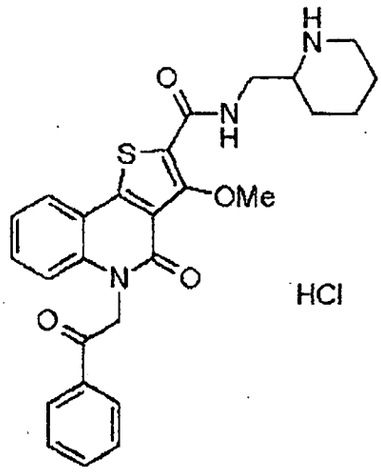
4.90 (1H, br), 5.99 (2H, s), 7.35 (1H, t, J = 7.4 Hz), 7.48-7.67 (4H, m), 7.77 (1H, t, J = 7.4 Hz), 7.85-8.00 (4H, m), 8.16-8.19 (2H, m).

[0949]

Example 74

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(piperidin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0950]



[0951]

In the same manner as in Example 73, the title compound (95 mg, 53%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 2-aminomethyl-N-Boc-piperidine (122 mg, 0.57 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44-1.91 (6H, m), 2.85 (1H, q, J = 12.0 Hz), 3.26 (2H, d, J = 12.0 Hz), 3.47-3.55 (1H, m), 3.62-3.69 (1H, m), 4.06 (3H, s), 6.01 (2H, s), 7.36 (1H, t, J = 7.5 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.4 Hz), 8.07 (1H, dd, J = 7.8, 1.2 Hz), 8.18 (2H, d, J = 8.4 Hz), 8.27 (1H, t, J = 6.2 Hz), 8.50-8.70 (1H, m), 8.70-8.85 (1H, m).

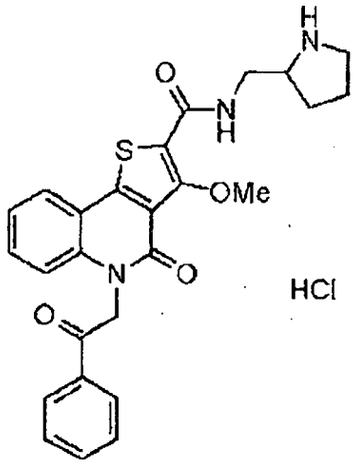
[0952]

Example 75

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyrrolidin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-

carboxamide hydrochloride

[0953]



[0954]

In the same manner as in Example 73, the title compound (126 mg, 65%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 2-aminomethyl-N-Boc-pyrrolidine (122 mg, 0.57 mmol).

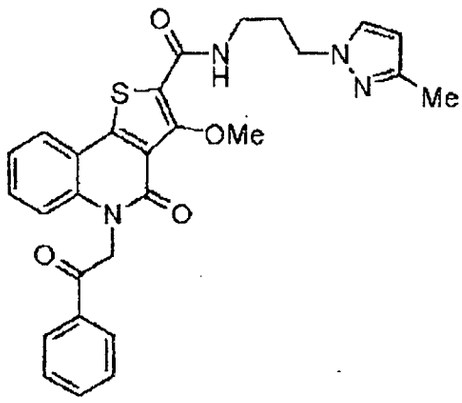
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.63-1.75 (1H, m), 1.83-2.10 (3H, m), 3.11-3.27 (2H, m), 3.61-3.76 (3H, m), 4.08 (3H, s), 6.01 (2H, s), 7.36 (1H, t, J = 7.5 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.5 Hz), 8.07 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H, m), 8.40 (1H, t, J = 5.9 Hz), 8.80-9.20 (2H, br).

[0955]

Example 76

Production of 3-methoxy-N-[3-(3-methyl-1H-pyrazol-1-yl)propyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[0956]



[0957]

In the same manner as in Example 25, the title compound (113 mg, 58%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and (3-methylpyrazol-1-yl)propanamine (79 mg, 0.57 mmol).

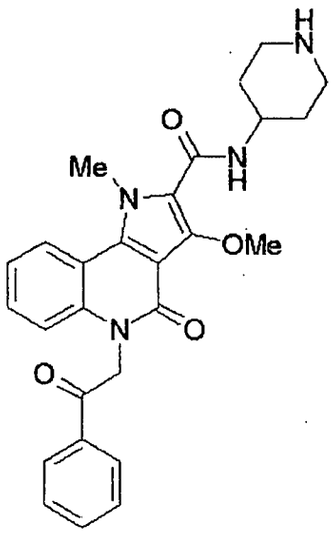
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.02 (2H, t, J = 6.9 Hz), 2.15 (3H, s), 3.26-3.35 (2H, m), 4.04 (3H, s), 4.09 (2H, t, J = 6.9 Hz), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.55-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 8.1, 1.2 Hz), 8.03-8.19 (4H, m).

[0958]

Example 77

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0959]



[0960]

In the same manner as in Example 25, tert-butyl 4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate (615 mg) was obtained as a white powder from the compound of Reference Example 28 (404 mg, 1.00 mmol) and 4-amino-1-Boc-piperidine (260 mg, 1.33 mmol).

The thus-obtained tert-butyl 4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate (610 mg) and trifluoroacetic acid (5 mL) were stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, saturated sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=20/1), and the obtained solid was recrystallized from ethyl acetate-ethanol to give the title compound (430 mg, 85%) as white crystals.

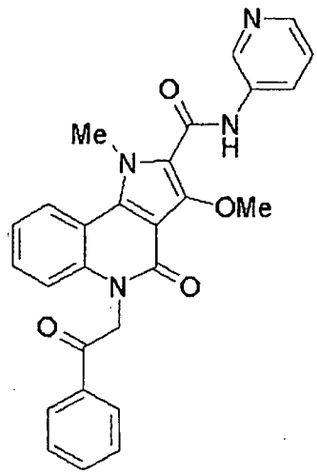
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34-1.46 (2H, m), 1.78-1.84 (2H, m), 1.90-2.20 (1H, br), 2.50-2.60 (2H, m), 2.85-3.00 (2H, br), 3.80-3.95 (1H, m), 3.98 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 7.86 (1H, d, J = 7.8 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.4, 1.2 Hz).

[0961]

Example 78

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-pyridin-3-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0962]



[0963]

A mixture of the compound of Reference Example 28 (200 mg, 0.512 mmol), 3-aminopyridine (60.6 mg, 0.644 mmol), HATU (245 mg, 0.644 mmol), N,N'-diisopropylethylamine (336 μL, 1.93 mmol), and DMF (5 mL) was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from THF to give the title compound (83.0 mg, 36%) as white crystals.

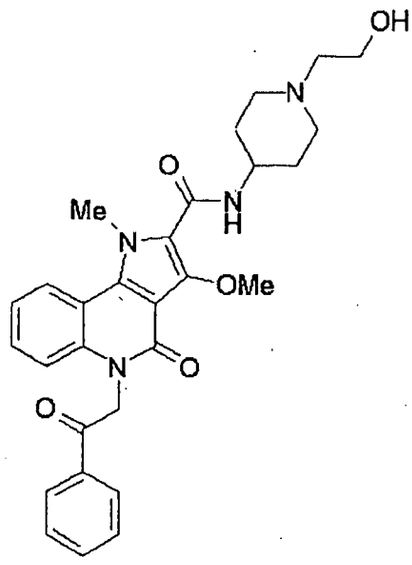
^{1}H-NMR (300 MHz, DMSO-d_6) δ:4.07 (3H, s), 4.33 (3H, s), 6.00 (2H, s), 7.32-7.44 (3H, m), 7.49-7.54 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 8.17-8.22 (3H, m), 8.33 (1H, dd, J = 8.3, 1.1 Hz), 8.41 (1H, dd, J = 8.3, 1.1 Hz), 8.91 (1H, d, J = 2.1 Hz), 10.31 (1H, s).

[0964]

Example 79

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0965]



[0966]

1) A mixture of the compound of Example 77 (200 mg, 0.399 mmol), 2-bromoethanol (42.5 μL, 0.599 mmol), potassium carbonate (248 mg, 1.80 mmol) and DMF (5 mL) was stirred at 100°C for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate-ethanol to give the title compound (68.0 mg, 33%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.51-1.62 (2H, m), 1.75-1.90 (2H, br), 2.18 (2H, t, J = 10. 5 Hz), 2.40 (2H, t, J = 5.9 Hz), 2.70-2.85 (2H, br), 3.47-3.52 (2H, m), 3.75-3.90 (1H, br), 3.98 (3H, s), 4.32-4.38 (4H, m), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.47 (1H, t, J = 7.6 Hz), 7.63 (2H, t, J = 7.6 Hz), 7.76 (1H, t, J = 7.1 Hz), 7.87 (1H, d, J = 7.5 Hz), 8.17 (2H, d, J = 7.6 Hz), 8.37 (1H, d, J = 8.4 Hz).

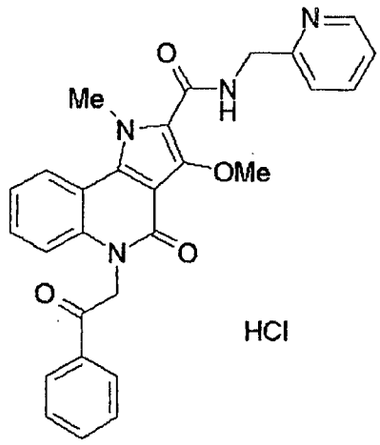
2) The white powder was recrystallized from ethanol-water to give the title compound as white crystals. melting point: 202°C

[0967]

Example 80

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0968]



[0969]

In the same manner as in Example 25, 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 2-(aminomethyl)pyridine (69.6 mg, 0.644 mmol).

The title compound (222 mg, 87%) was obtained as a white powder from the thus-obtained 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide by a method similar to that in Example 30.

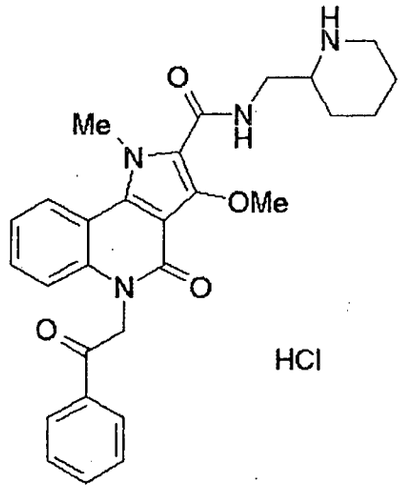
^{1}H-NMR (300 MHz, DMSO-d_6) δ:4.08 (3H, s), 4.34 (3H, s), 4.85 (2H, d, J = 5.7 Hz), 5.98 (2H, s), 7.30-7.42 (2H, m), 7.47-7.52 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.74-7.85 (3H, m), 8.16-8.19 (2H, m), 8.31-8.40 (2H, m), 8.77-8.84 (2H, m).

[0970]

Example 81

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(piperidin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0971]



[0972]

In the same manner as in Example 73, the title compound (230 mg, 89%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 2-(aminomethyl)-1-N-Boc-piperidine (138 mg, 0.644 mmol).

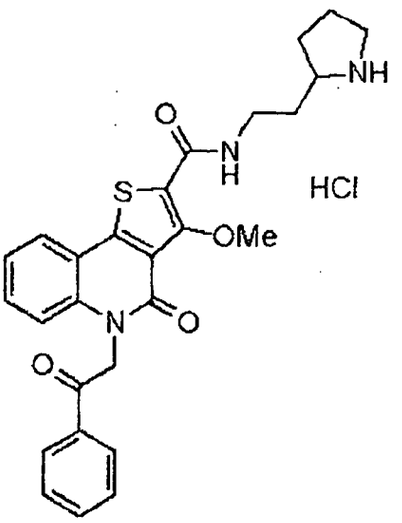
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.95 (6H, br), 2.70-2.95 (1H, br), 3.15-3.35 (2H, br), 3.46-3.69 (2H, m), 4.03 (3H, s), 4.36 (3H, s), 5.98 (2H, s), 7.30-7.41 (2H, m), 7.47-7.52 (1H, m), 7.64 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.16-8.25 (3H, m), 8.39 (1H, dd, J = 8.3, 1.1 Hz), 8.55-8.75 (1H, br), 8.75-8.90 (1H, br).

[0973]

Example 82

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carboxamide hydrochloride

[0974]



[0975]

In the same manner as in Example 73, the title compound (114 mg, 47%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 2-aminoethyl-N-Boc-pyrrolidine (122 mg, 0.57 mmol).

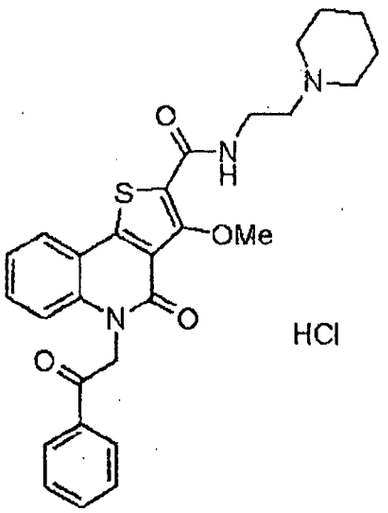
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.65 (1H, m), 1.80-2.10 (5H, m), 2.14-2.25 (1H, m), 3.10-3.20 (2H, m), 3.35-3.60 (2H, m), 4.05 (3H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.7 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.20 (3H, m), 8.50-9.50 (2H, br).

[0976]

Example 83

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[0977]



[0978]

In the same manner as in Example 67, the title compound (147 mg, 53%) was obtained as a white powder from the compound of Reference Example 7 (200 mg, 0.51 mmol) and 1-(2-aminoethyl)piperidine (98 mg, 0.76 mmol).

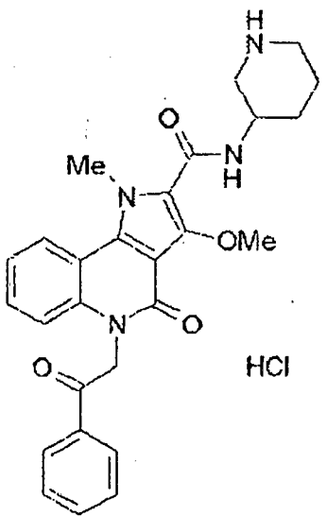
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30-1.50 (1H, m), 1.65-1.80 (5H, m), 2.85-3.00 (2H, m), 3.26 (2H, br d, J = 5.1 Hz), 3.53 (2H, br d, J = 11.1 Hz), 3.73 (2H, q, J = 5.7 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.06 (1H, dd, J = 8.1, 1.5 Hz), 8.16 (1H, d, J = 1.5 Hz), 8.19 (1H, s), 8.40 (1H, t, J = 5.7 Hz), 9.80-9.90 (1H, br).

[0979]

Example 84

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-3-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0980]



[0981]

In the same manner as in Example 73, the title compound (67.1 mg, 27%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 3-amino-1-N-Boc-piperidine (129 mg, 0.644 mmol).

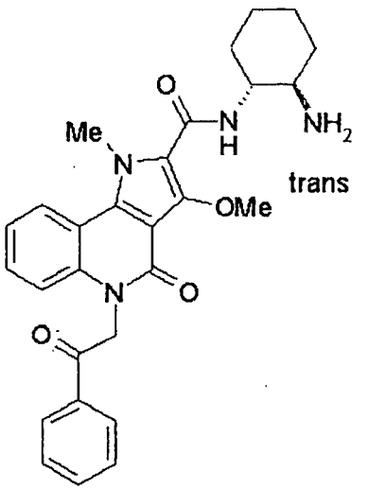
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-2.05 (4H, m), 2.75-3.00 (2H, m), 3.20 (1H, d, J = 13.2 Hz), 3.25-3.40 (1H, br), 3.99 (3H, s), 4.20-4.30 (1H, br), 4.31 (3H, s), 5.98 (2H, s), 7.30-7.41 (2H, m), 7.46-7.52 (1H, m), 7.64 (2H, t, J = 7.7 Hz), 7.73-7.79 (1H, m), 8.05 (1H, d, J = 8.1 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.3, 1.4 Hz), 8.85-9.05 (2H, br).

[0982]

Example 85

Production of N-[trans-2-aminocyclohexyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[0983]



[0984]

In the same manner as in Example 73, N-[trans-2-aminocyclohexyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride was obtained from the compound of Reference Example 28 (200 mg, 0.512 mmol) and N-Boc-trans-1,2-diaminocyclohexane (138 mg, 0.644 mmol).

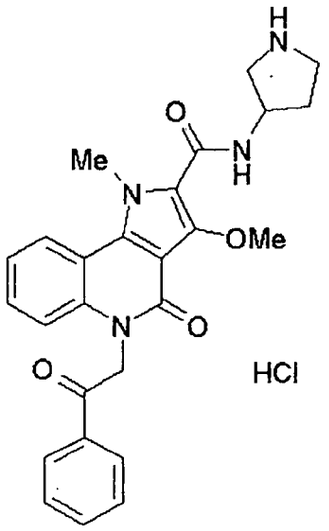
To the thus-obtained N-[trans-2-aminocyclohexyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride was added saturated sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=20/1), and the obtained solid was recrystallized from ethyl acetate-ethanol to give the title compound (80.0 mg, 33%) as white crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.40 (4H, br), 1.50-1.75 (4H, br), 1.70-1.90 (1H, br), 1.90-2.05 (1H, br), 2.45-2.60 (1H, br), 3.45-3.60 (1H, br), 3.97 (3H, s), 4.30 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.47 (1H, t, J = 7.7 Hz), 7.63 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.4 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.17 (2H, d, J = 7.7 Hz), 8.37 (1H, d, J = 8.1 Hz).

[0985]

Example 86

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-pyrrolidin-3-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0986]



[0987]

In the same manner as in Example 73, the title compound (122 mg, 50%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 3-amino-1-N-Boc-pyrrolidine (120 mg, 0.644 mmol).

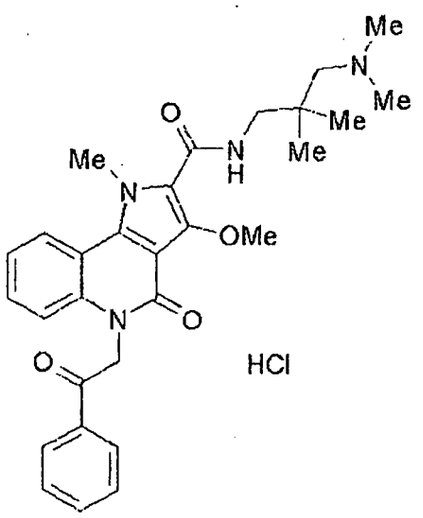
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.94-2.05 (1H, m), 2.20-2.32 (1H, m), 3.17-3.49 (4H, m), 4.00 (3H, s), 4.30 (3H, s), 4.58-4.69 (1H, m), 5.98 (2H, s), 7.30-7.40 (2H, m), 7.46-7.52 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.16-8.19 (2H, m), 8.26 (1H, d, J = 6.9 Hz), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 9.10-9.30 (2H, br).

[0988]

Example 87

Production of N-[3-(dimethylamino)-2,2-dimethylpropyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0989]



[0990]

In the same manner as in Example 25, N-[3-(dimethylamino)-2,2-dimethylpropyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol).

The title compound (203 mg, 76%) was obtained as a white powder from the thus-obtained N-[3-(dimethylamino)-2,2-dimethylpropyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide by a method similar to that in Example 30.

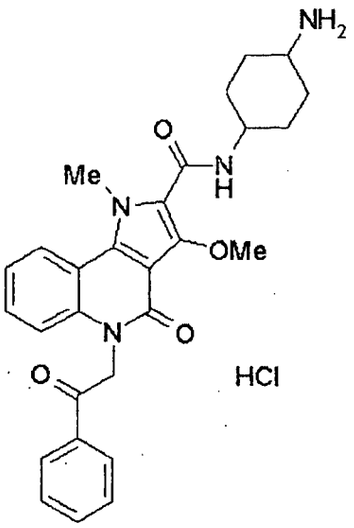
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.12 (6H, s), 2.86 (3H, s), 2.87 (3H, s), 3.03-3.07 (2H, br), 3.33-3.40 (2H, br), 4.04 (3H, s), 4.30 (3H, s), 5.99 (2H, s), 7.30-7.41 (2H, m), 7.46-7.52 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.16-8.21 (3H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 9.50-9.70 (1H, br).

[0991]

Example 88

Production of N-(4-aminocyclohexyl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[0992]



[0993]

In the same manner as in Example 73, the title compound (121 mg, 47%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl (4-aminocyclohexyl)carbamate (138 mg, 0.644 mmol).

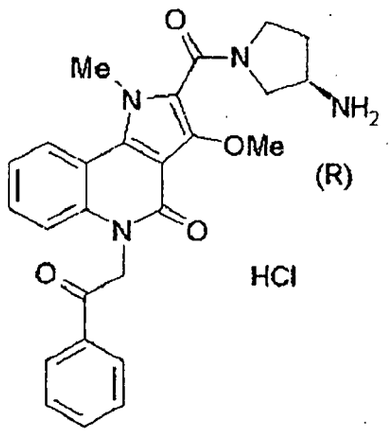
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18-1.34 (1H, br), 1.55-1.75 (1H, br), 1.75-1.90 (2H, br), 1.95-2.20 (1H, br), 2.60-2.81 (2H, m), 3.15-3.45 (3H, m), 4.01 (3H, s), 4.30 (3H, s), 5.98 (2H, s), 7.30-7.40 (2H, m), 7.46-7.51 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.74-7.79 (1H, m), 8.16-8.20 (3H, m), 8.38 (1H, dd, J = 8.3, 1.4 Hz), 8.65-8.95 (2H, br).

[0994]

Example 89

Production of 2-{[(3R)-3-aminopyrrolidin-1-yl]carbonyl}-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one hydrochloride

[0995]



[0996]

In the same manner as in Example 73, the title compound (190 mg, 78%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl (3R)-pyrrolidin-3-ylcarbamate (120 mg, 0.644 mmol).

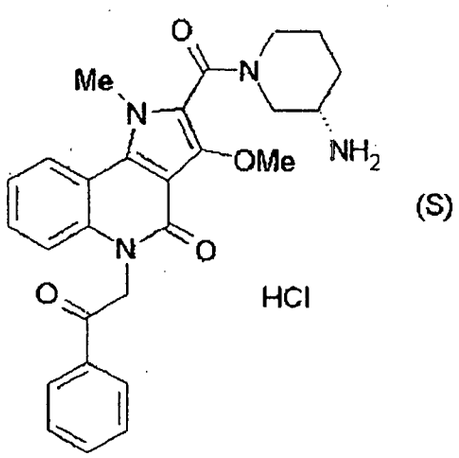
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.95-2.15 (1H, m), 2.15-2.40 (1H, m), 3.57-3.92 (8H, m), 4.03-4.10 (3H, br), 5.98 (2H, s), 7.28-7.40 (2H, m), 7.44-7.49 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.16-8.19 (2H, m), 8.30-8.50 (4H, br).

[0997]

Example 90

Production of 2-{[(3S)-3-aminopiperidin-1-yl]carbonyl}-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one hydrochloride

[0998]



[0999]

In the same manner as in Example 73, the title compound (190 mg, 78%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl (3S)-piperidin-3-ylcarbamate (120 mg, 0.644 mmol).

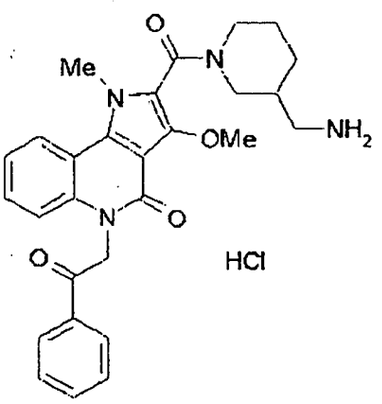
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.45-2.00 (3H, br), 2.00-2.15 (1H, br), 2.75-3.30 (4H, br), 3.65-3.85 (0.5H, br), 3.91 (3H, s), 4.03 (3H, s), 4.40-4.75 (0.5H, br), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.44-7.49 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.10-8.20 (5H, br), 8.34 (1H, d, J = 7.8 Hz).

[1000]

Example 91

Production of 2-{[3-(aminomethyl)piperidin-1-yl]carbonyl}-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one hydrochloride

[1001]



[1002]

In the same manner as in Example 73, the title compound (170 mg, 66%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl (piperidin-3-ylmethyl)carbamate (143 mg, 0.644 mmol).

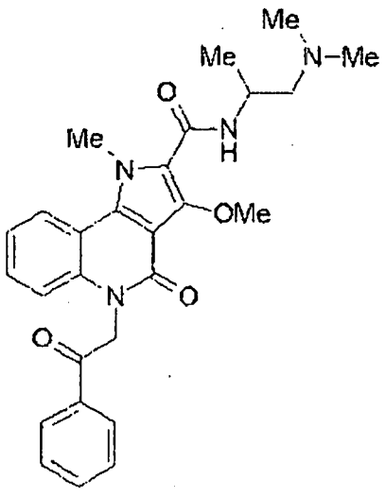
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.60 (2H, br), 1.60-2.00 (3H, br), 2.55-3.05 (3H, br), 3.10-3.30 (1H, br), 3.60-3.80 (1H, br), 3.90 (3H, s), 4.01 (3H, s), 4.25-4.60 (1H, br), 5.98 (2H, s), 7.28-7.39 (2H, m), 7.46 (1H, t, J = 7.7 Hz), 7.64 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.1 Hz), 7.90-8.25 (5H, br), 8.33 (1H, d, J = 8.1 Hz).

[1003]

Example 92

Production of N-[2-(dimethylamino)-1-methylethyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[1004]



[1005]

In the same manner as in Example 25, the title compound (67.0 mg, 29%) was obtained as a white powder from the compound of Reference Example 28 (440 mg, 1.01 mmol) and 1-(dimethylamino)isopropylamine (68.1 mg, 0.666 mmol).

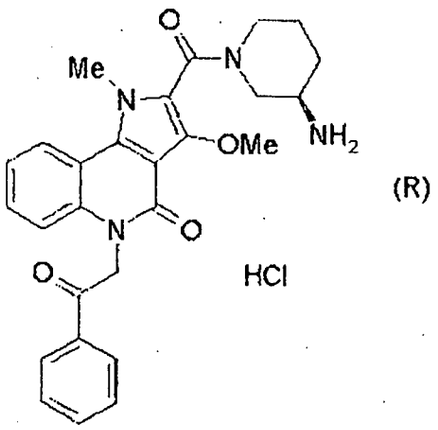
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20 (3H, d, J = 6.0 Hz), 2.20 (6H, s), 2.20-2.27 (1H, m), 2.39-2.46 (1H, m), 3.97 (3H, s), 3.98-4.10 (1H, m), 4.36 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.96 (1H, d, J = 6.6 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.1, 1.2 Hz).

[1006]

Example 93

Production of 2-{[(3R)-3-aminopiperidin-1-yl]carbonyl}-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one hydrochloride

[1007]



[1008]

In the same manner as in Example 73, the title compound (190 mg, 75%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl (3R)-piperidin-3-ylcarbamate (133 mg, 0.666 mmol).

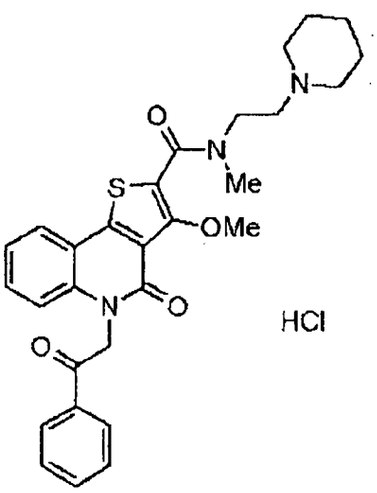
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.45-2.00 (3H, br), 2.00-2.15 (1H, br), 2.75-3.30 (4H, br), 3.65-3.85 (0.5H, br), 3.91 (3H, s), 4.03 (3H, s), 4.40-4.75 (0.5H, br), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.44-7.49 (1H, m), 7.64 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.10-8.30 (5H, br), 8.34 (1H, d, J = 8.1 Hz).

[1009]

Example 94

Production of 3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1010]



[1011]

In the same manner as in Example 67, the title compound (154 mg, 73%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 1-(2-N'-methylaminoethyl)piperidine (108 mg, 0.76 mmol).

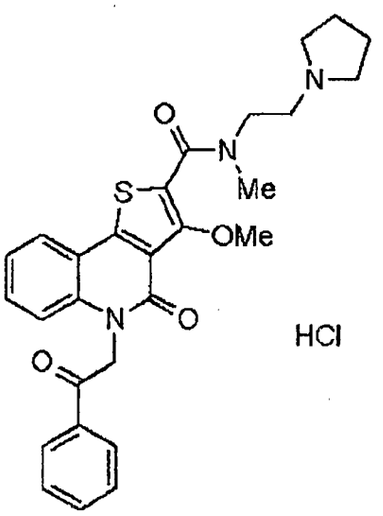
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.25-1.45 (1H, m), 1.60-1.90 (4H, m), 2.80-3.00 (2H, br), 3.11 (3H, s), 3.35-3.40 (2H, m), 3.40-3.65 (2H, br), 3.80-3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.48-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 7.98 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (3H, m), 9.75-9.90 (1H, br).

[1012]

Example 95

Production of 3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1013]



[1014]

In the same manner as in Example 67, the title compound (153 mg, 74%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 1-(2-N'-methylaminoethyl)pyrrolidine (98 mg, 0.76 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.75-2.10 (4H, m), 2.90-3.15 (5H, m), 3.35-3.50 (2H, m), 3.50-3.80 (2H, br), 3.83-3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.48-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 7.97 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2H,

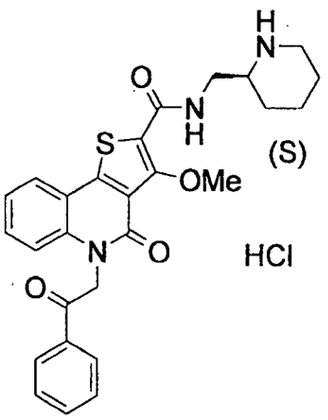
m), 10.35-10.65 (1H, br).

[1015]

Example 96

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-[(2S)-piperidine-2-ylmethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1016]



[1017]

In the same manner as in Example 73, the title compound (80 mg, 57%) was obtained as a white powder from the compound of Reference Example 7 (107 mg, 0.27 mmol) and (S)-2-(Boc-aminomethyl)piperidine (58 mg, 0.27 mmol).

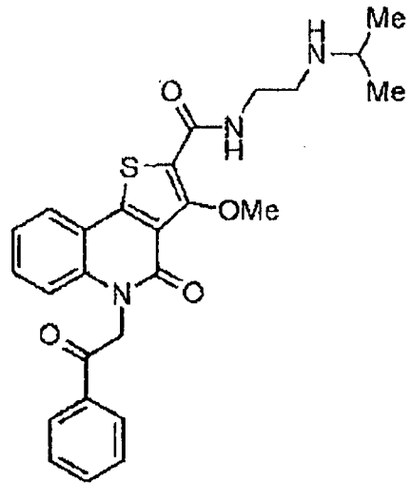
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.35-1.90 (6H, m), 3.00-3.40 (4H, m), 3.90 (3H, s), 4.70-4.90 (1H, br), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.48-7.67 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 7.95-8.19 (6H, m).

[1018]

Example 97

Production of 3-methoxy-N-{2-[(1-methylethyl)amino]ethyl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1019]



[1020]

To a mixed solution of the compound of Example 61 (150 mg, 0.32 mmol) and acetone (0.2 mL) in methanol (5 mL)-DMF (5 mL) was added sodium cyanoborohydride (20 mg, 0.32 mmol), and the mixture was stirred at room temperature for 24 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained white solid was recrystallized from ethyl acetate-hexane to give the title compound (69 mg, 45%) as white crystals.

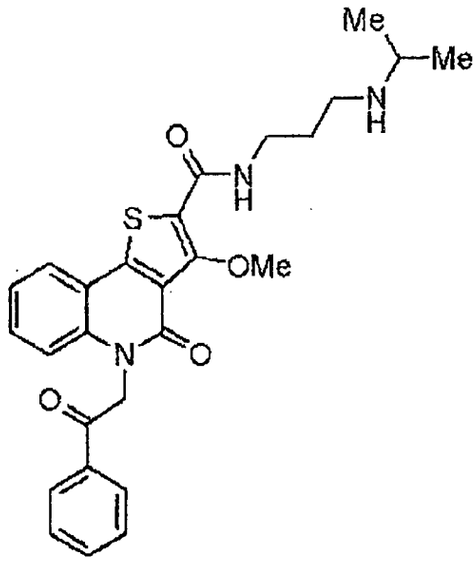
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.09 (6H, d, J = 6.3 Hz), 2.83-2.89 (3H, m), 3.57 (2H, q, J = 5.7 Hz), 4.16 (3H, s), 5.87 (2H, s), 7.02 (1H, d, J = 8.4 Hz), 7.26-7.28 (1H, m), 7.44-7.50 (1H, m), 7.56 (2H, t, J = 7.5 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.91 (1H, dd, J = 8.1, 1.2 Hz), 8.10-8.13 (3H, m).

[1021]

Example 98

Production of 3-methoxy-N-{3-[(1-methylethyl)amino]propyl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1022]



[1023]

In the same manner as in Example 97, the title compound (9 mg, 5%) was obtained as a white powder from the compound of Example 62 (190 mg, 0.38 mmol).

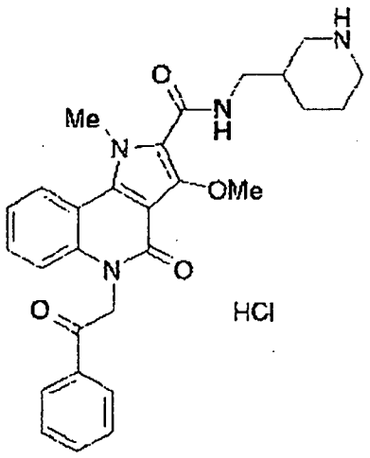
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.08 (6H, d, J = 6.3 Hz), 1.75-1.88 (2H, m), 2.73 (2H, t, J = 6.9 Hz), 2.76-2.85 (1H, m), 3.58 (2H, q, J = 6.4 Hz), 4.14 (3H, s), 5.87 (2H, s), 7.02 (1H, d, J = 8.7 Hz), 7.20-7.28 (1H, m), 7.44-7.50 (1H, m), 7.56 (2H, t, J = 7.5 Hz), 7.65-7.68 (1H, m), 7.80 (1H, br t), 7.91 (1H, dd, J = 7.8, 1.2 Hz), 8.10-8.13 (2H, m).

[1024]

Example 99

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(piperidin-3-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[1025]



[1026]

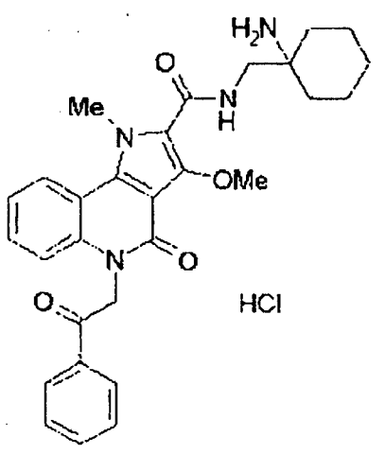
In the same manner as in Example 73, the title compound (190 mg, 75%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (143 mg, 0.666 mmol). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.35 (1H, br), 1.50-1.90 (3H, br), 1.95-2.15 (1H, br), 2.64 (1H, t, J = 6.2 Hz), 2.78 (1H, t, J = 5.7 Hz), 3.15-3.45 (4H, br), 4.01 (3H, s), 4.30 (3H, s), 5.98 (2H, s), 7.29-7.41 (2H, m), 7.48 (1H, t, J = 7.6 Hz), 7.64 (2H, t, J = 7.6 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.16-8.19 (3H, m), 8.37 (1H, d, J = 8.1 Hz), 8.55-8.85 (2H, br).

[1027]

Example 100

Production of N-[(1-aminocyclohexyl)methyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[1028]



[1029]

In the same manner as in Example 73, the title compound (80.0 mg, 30%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and tert-butyl [1-(aminomethyl)cyclohexyl]carbamate (147 mg, 0.644 mmol).

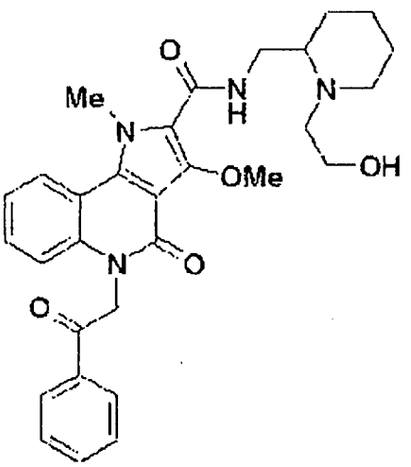
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25-1.70 (10H, br), 3.61 (2H, d, J = 6.3 Hz), 4.04 (3H, s), 4.34 (3H, s), 5.98 (2H, s), 7.31-7.42 (2H, m), 7.50 (1H, t, J = 7.6 Hz), 7.64 (2H, t, J = 7.6 Hz), 7.77 (1H, t, J = 7.5 Hz), 7.80-8.00 (3H, br), 8.16-8.22 (3H, m), 8.39 (1H, d, J = 8.4 Hz).

[1030]

Example 101

Production of N-{[1-(2-hydroxyethyl)piperidin-2-yl]methyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[1031]



[1032]

In the same manner as in Example 79, the title compound (47.1 mg, 39%) was obtained as a white powder from the compound of Example 81 (200 mg, 0.399 mmol) and 2-bromoethanol (24.2 μL, 0.341 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.75 (6H, br), 2.20-3.10 (5H, br), 3.40-3.65 (4H, br), 3.98-4.05 (3H, br), 4.15-4.50 (4H, br), 5.98 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.64 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.00-8.20 (3H,

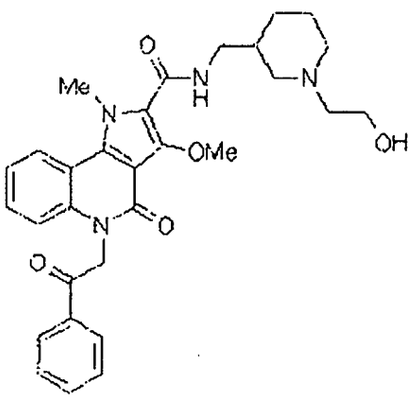
m), 8.39 (1H, dd, J = 8.3, 1.1 Hz).

[1033]

Example 102

Production of N-{[1-(2-hydroxyethyl)piperidin-3-yl]methyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[1034]



[1035]

In the same manner as in Example 79, the title compound (85.2 mg, 50%) was obtained as a white powder from the compound of Example 99 (160 mg, 0.306 mmol) and 2-bromoethanol (65.0 μL, 0.918 mmol).

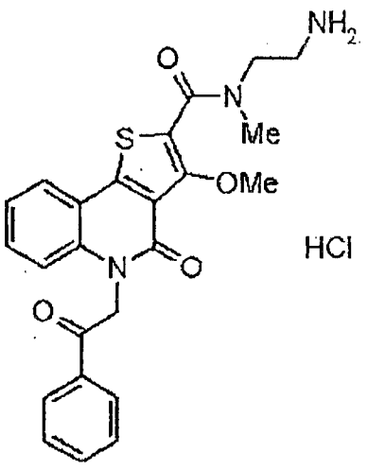
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.90-1.10 (1H, br), 1.35-1.55 (1H, br), 1.55-1.90 (4H, br), 1.96 (1H, t, J = 7.1 Hz), 2.36 (2H, t, J = 6.3 Hz), 2.72 (1H, d, J = 9.9 Hz), 2.83 (1H, d, J = 7.5 Hz), 3.15-3.30 (2H, br), 3.45-3.51 (2H, m), 3.99 (3H, s), 4.30-4.34 (4H, m), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.47 (1H, t, J = 7.7 Hz), 7.63 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.02 (1H, t, J = 6.0 Hz), 8.17 (2H, d, J = 7.7 Hz), 8.37 (1H, d, J = 8.1 Hz).

[1036]

Example 103

Production of N-(2-aminoethyl)-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1037]



[1038]

To a solution of the compound of Reference Example 7 (300 mg, 0.760 mmol), 1-Boc-amino-2-methylaminoethane hydrochloride (321 mg, 1.52 mmol), triethylamine (154 mg, 1.52 mmol) and HOBt (206 mg, 1.52 mmol) in DMF (10 mL) was added WSCD (290 mg, 1.52 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=2/1) to give tert-butyl {2-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]ethyl}carbamate (230 mg) as a colorless oil.

A solution of the obtained tert-butyl {2-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]ethyl}carbamate (230 mg) and 4N hydrogen chloride ethyl acetate solution (8 mL) in ethyl acetate (15 mL) was stirred at room temperature for 2 hr. The obtained precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (178 mg, 48%) as a white powder.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.00-3.10 (5H, m), 3.60-3.75 (2H, m), 3.89 (3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49

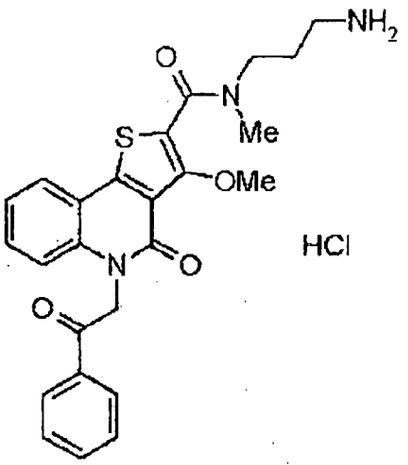
(1H, d, J = 8.7 Hz), 7.56 (1H, d, J=7.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.2 Hz), 7.80-7.98 (4H, m), 8.17 (2H, d, J = 7.5 Hz).

[1039]

Example 104

Production of N-(3-aminopropyl)-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1040]



[1041]

To a solution of the compound of Reference Example 7 (300 mg, 0.760 mmol), 1-Boc-amino-3-methylaminopropane (286 mg, 1.52 mmol) and HOBt (206 mg, 1.52 mmol) in DMF (10 mL) was added WSCD (290 mg, 1.52 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=2/1) to give tert-butyl {3-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]propyl}carbamate (230 mg) as a white non-crystalline solid.

A solution of the obtained tert-butyl {3-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-

2-yl]carbonyl}(methyl)amino]propyl}carbamate (230 mg) and 4N hydrogen chloride ethyl acetate solution (8 mL) in ethyl acetate (15 mL) was stirred at room temperature for 2 hr. The obtained precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (216 mg, 54%) as a white powder.

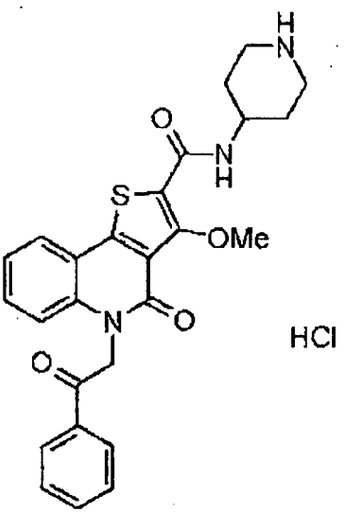
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.80-2.00 (2H, m), 2.70-2.90 (2H, br), 3.06 (3H, s), 3.45-3.60 (2H, m), 3.89 (3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.48-7.67 (4H, m), 7.75-7.79 (4H, m), 7.97 (1H, d, J = 7.8 Hz), 8.17-8.19 (2H, m).

[1042]

Example 105

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1043]



[1044]

In the same manner as in Example 73, the title compound (222 mg, 57%) was obtained as a white powder from the compound of Reference Example 7 (300 mg, 0.760 mmol) and 4-amino-1-Boc-piperidine (305 mg, 1.52 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.70-1.95 (2H, m), 2.05 (2H, d, J = 11.1 Hz), 3.04 (2H, t, J = 11.1 Hz), 3.29 (2H, d, J = 14.7 Hz), 4.03-4.12 (4H, m), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.59-7.67 (3H, m), 7.77 (1H, t, J =

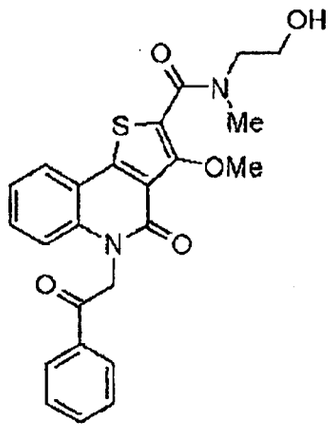
7.5 Hz), 7.90 (1H, d, J = 7.2 Hz), 8.05 (1H, dd, J = 8.1, 1.2 Hz), 8.18 (2H, d, J = 7.5 Hz), 8.70-8.85 (2H, br).

[1045]

Example 106

Production of N-(2-hydroxyethyl)-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1046]



[1047]

In the same manner as in Example 25, the title compound (1.16 g, 68%) was obtained as white crystals from the compound of Reference Example 7 (1.50 g, 3.80 mmol) and N-methyl-2-aminoethanol (428 mg, 5.70 mmol).

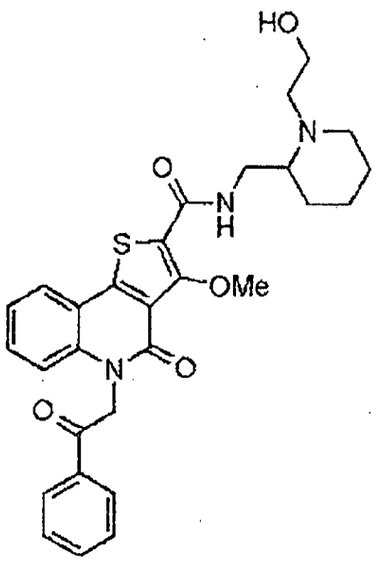
^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.00-3.10 (1H, br), 3.21 (3H, s), 3.65-3.80 (2H, br), 3.80-4.00 (2H, br), 4.04 (3H, s), 5.86 (2H, s), 7.03 (1H, d, J = 8.4 Hz), 7.26 (1H, t, J = 7.5 Hz), 7.47 (1H, td, J = 7.8, 1.5 Hz), 7.53-7.59 (2H, m), 7.65-7.71 (1H, m), 7.83 (1H, dd, J = 9.0, 1.2 Hz), 8.10-8.13 (2H, m).

[1048]

Example 107

Production of N-{[1-(2-hydroxyethyl)piperidin-2-yl]methyl}-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1049]



[1050]

In the same manner as in Example 101, the title compound (29 mg, 29%) was obtained as a white powder from the compound of Example 74 (100 mg, 0.19 mmol).

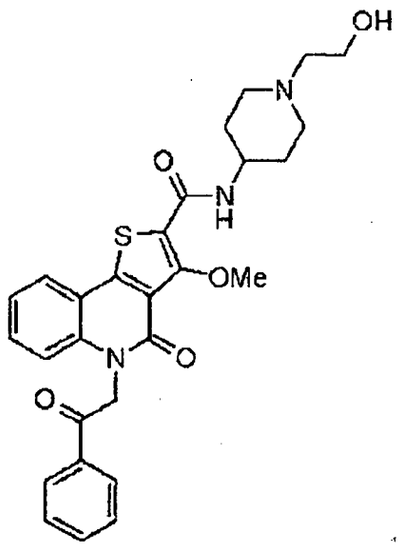
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.50 (3H, m), 1.50-1.80 (3H, m), 2.27 (1H, t, J = 9.5 Hz), 2.35-2.60 (3H, m), 2.75-2.90 (1H, m), 2.95 (2H, d, J = 12.0 Hz), 3.45-3.60 (4H, m), 4.44 (1H, t, J = 5.4 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 7.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, d, J = 7.2 Hz), 8.10 (1H, t, J = 4.2 Hz), 8.18 (2H, d, J = 7.2 Hz).

[1051]

Example 108

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1052]



[1053]

In the same manner as in Example 101, the title compound (41 mg, 27%) was obtained as a white powder from the compound of Example 105 (150 mg, 0.29 mmol).

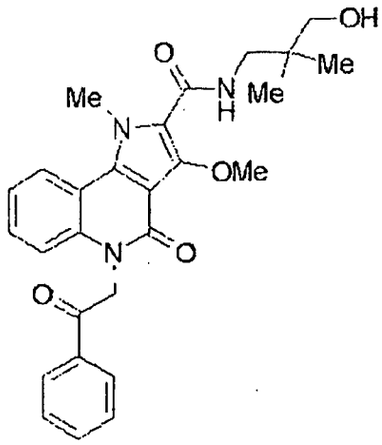
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-1.75 (2H, m), 1.84 (2H, d, J = 9.6 Hz), 2.18 (2H, t, J = 10.2 Hz), 2.37-2.44 (2H, m), 2.77 (2H, d, J = 10.8 Hz), 3.46-3.52 (2H, m), 3.75-3.85 (1H, m), 4.04 (3H, s), 4.38 (1H, t, J = 5.4 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 7.2, 1.5 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.71-7.80 (2H, m), 8.05 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m).

[1054]

Example 109

Production of N-(3-hydroxy-2,2-dimethylpropyl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[1055]



[1056]

In the same manner as in Example 25, the title compound (190 mg, 62%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 3-amino-2,2-dimethyl-1-propanol (66.4 mg, 0.644 mmol).

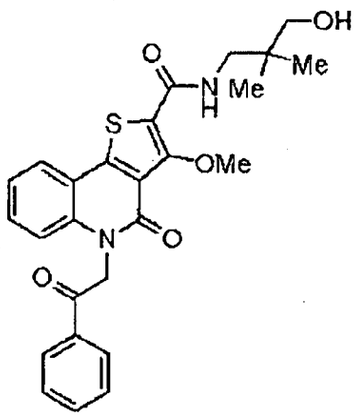
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.88 (6H, s), 3.22-3.24 (4H, m), 4.02 (3H, s), 4.34 (3H, s), 4.78 (1H, t, J = 8.3 Hz), 5.98 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.10-8.19 (3H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[1057]

Example 110

Production of N-(3-hydroxy-2,2-dimethylpropyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1058]



[1059]

In the same manner as in Example 25, the title compound

(251 mg, 69%) was obtained as white crystals from the compound of Reference Example 7 (300 mg, 0.76 mmol) and 3-amino-2,2-dimethyl-1-propanol (118 mg, 1.14 mmol).

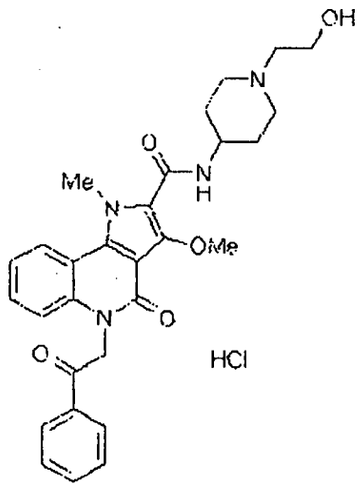
^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.89 (6H, s), 3.25-3.35 (4H, m), 4.04 (3H, s), 4.99 (1H, t, J = 4.8 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57 (1H, dd, J = 7.2, 1.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 8.29 (1H, t, J = 5.7 Hz).

[1060]

Example 111

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[1061]



[1062]

To a solution of the compound of Example 79 (150 mg, 0.290 mmol) in ethyl acetate (4 mL)/ethanol (6 mL) was added 4N hydrogen chloride ethyl acetate solution (80.0 μL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (72 mg, 45%) as a white powder.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.88-2.20 (4H, br), 3.05-3.65 (6H, br), 3.74-3.82 (2H, br), 3.90-4.15 (4H, br), 4.28 (3H, s), 5.30-5.45 (1H, m), 5.98 (2H, s), 7.29-7.40 (2H, m), 7.46-7.51

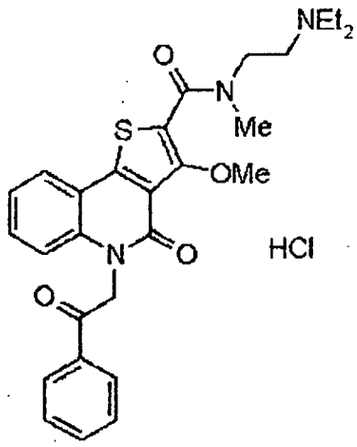
(1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.4 Hz), 8.09-8.19 (3H, m), 8.37 (1H, d, J = 7.5 Hz), 9.75-10.10 (1H, br).

[1063]

Example 112

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1064]



[1065]

In the same manner as in Example 30, the title compound (289 mg, 82%) was obtained as a white powder from the compound of Reference Example 7 (330 mg, 0.65 mmol) and N,N-diethyl-N'-methylethylenediamine (149 mg, 1.14 mmol).

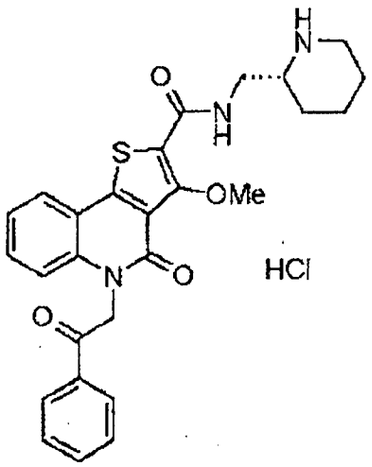
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.40 (6H, br), 3.10-3.40 (6H, m), 3.58 (3H, s), 3.84-3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.56 (1H, dd, J = 7.2, 1.2 Hz), 7.60-7.67 (2H, m), 7.77 (1H, t, J = 7.5 Hz), 7.97 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 10.35-10.60 (1H, br).

[1066]

Example 113

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-[(2R)-piperidin-2-ylmethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1067]



[1068]

In the same manner as in Example 73, the title compound (166 mg, 60%) was obtained as a white powder from the compound of Reference Example 7 (200 mg, 0.51 mmol) and (R)-2-aminomethyl-1-N-Boc-piperidine (163 mg, 0.76 mmol).

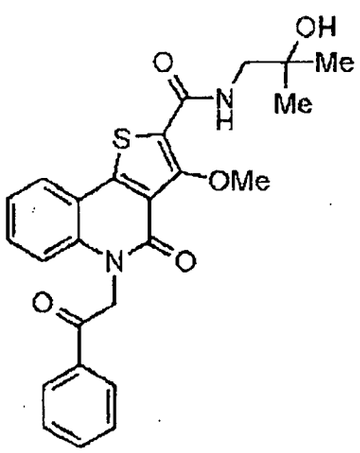
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.95 (6H, m), 2.75-3.00 (1H, m), 3.25 (2H, d, J = 10.8 Hz), 3.49-3.57 (1H, m), 3.63-3.70 (1H, m), 4.07 (3H, s), 6.01 (2H, s), 7.36 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.7 Hz), 7.57-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.06 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 8.27 (1H, t, J = 6.0 Hz), 8.70-8.90 (2H, m).

[1069]

Example 114

Production of N-(2-hydroxy-2-methylpropyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1070]



[1071]

In the same manner as in Example 73, the title compound (108 mg, 47%) was obtained as white crystals from the compound of Reference Example 7 (200 mg, 0.51 mmol) and 1-amino-2-methyl-2-propanol (68 mg, 0.76 mmol).

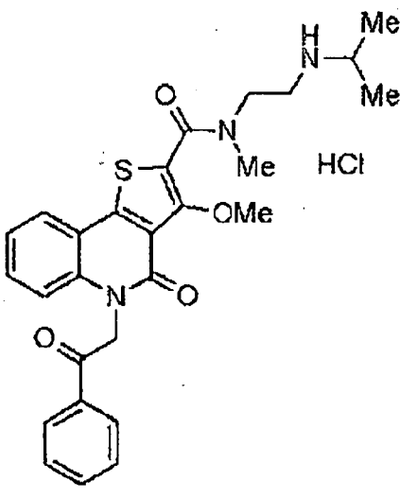
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (6H, s), 3.31 (2H, s), 4.06 (3H, s), 4.77 (1H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 7.98 (1H, t, J = 2.4 Hz), 8.05 (1H, d, J = 7.8 Hz), 8.18 (2H, d, J = 7.2 Hz).

[1072]

Example 115

Production of 3-methoxy-N-methyl-N-{2-[(1-methylethyl)amino]ethyl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1073]



[1074]

To a solution of the compound of Example 103 (130 mg, 0.27 mmol), acetone (155 mg, 2.67 mmol) and acetic acid (0.1 mL) in THF (5 mL) was added sodium triacetoxyborohydride (113 mg, 0.54 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated

under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate) to give a colorless oil (0.09 g). To a solution of the obtained colorless oil in ethyl acetate (5 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (73.0 mg, 52%) as a white powder.

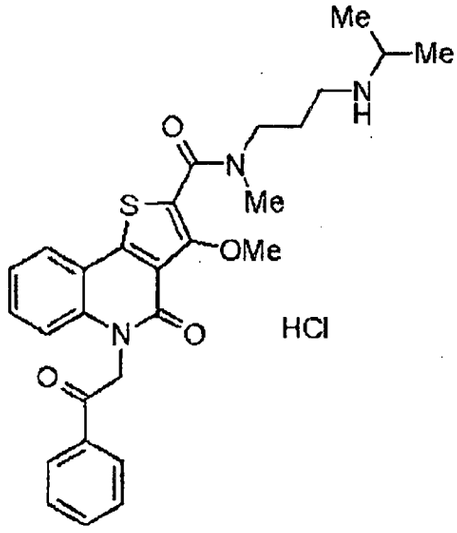
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.35 (6H, br), 3.05-3.25 (5H, m), 3.30-3.40 (1H, m), 3.76 (2H, br t, J = 6.6 Hz), 3.90 (3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, t, J = 8.1 Hz), 7.56 (1H, dd, J =7.2, 1.2 Hz), 7.60-7.67 (2H, m), 7.77 (1H, t, J = 7.5 Hz), 7.98 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 8.50-8.80 (2H, br).

[1075]

Example 116

Production of 3-methoxy-N-methyl-N-{3-[(1-methylethyl)amino]propyl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1076]



[1077]

In the same manner as in Example 115, the title compound (118 mg, 73%) was obtained as a white powder from the compound of Example 104 (150 mg, 0.30 mmol).

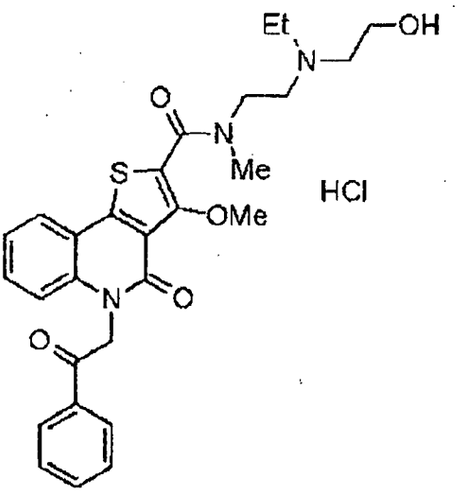
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.35 (6H, br), 1.85-2.05 (2H, br), 2.70-3.00 (2H, br), 3.07 (3H, s), 3.20-3.40 (1H, m), 3.45-3.60 (2H, m), 3.90 (3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.56 (1H, dd, J = 6.9, 1.2 Hz), 7.62-7.67 (2H, m), 7.77 (1H, t, J = 7.5 Hz), 7.97 (1H, dd, J = 7.2, 1.2 Hz), 8.16-8.19 (2H, m), 8.65-8.80 (2H, br).

[1078]

Example 117

Production of N-{2-[ethyl(2-hydroxyethyl)amino]ethyl}-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[1079]



[1080]

To a solution of the compound of Example 106 (1.0 g, 2.21 mmol) and triethylamine (269 mg, 2.66 mmol) in dichloromethane (20 mL) was added methanesulfonyl chloride (279 mg, 2.44 mmol) under ice-cooling, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give N-(2-chloroethyl)-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (1.01 g) as a white non-crystalline solid.

A solution of the obtained N-(2-chloroethyl)-3-methoxy-N-

methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (200 mg, 0.43 mmol), N-ethylaminoethanol (228 mg, 2.55 mmol), diisopropylethylamine (330 mg, 2.55 mmol) and sodium iodide (64 mg, 0.43 mmol) in 1-butanol (5 mL) was stirred at 110°C for 18 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate to ethyl acetate/methanol=20/1) to give N-{2-[ethyl(2-hydroxyethyl)amino]ethyl}-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide (0.08 g) as a white non-crystalline solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.00-1.15 (0.75H, br), 1.20-1.35 (2.25H, m), 2.20-2.9 0 (4H, m), 3.16 (0.75H, s), 3.20 (2.25H, s), 3.50-3.95 (6H, m), 4.02-4.04 (3H, m), 5.85 (2H, s), 7.03 (1H, d, J = 8.4 Hz), 7.23-7.28 (1H, m), 7.45 (1H, t, J = 7.5 Hz), 7.55 (2H, t, J =7.5 Hz), 7.64-7.69 (1H, m), 7.80-7.84 (1H, m), 8.09-8.12 (2H, m).

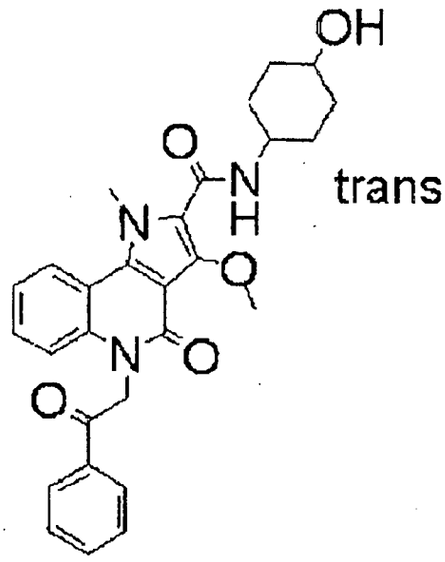
To a solution of the obtained white non-crystalline solid in ethyl acetate (5 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL). The precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (7 mg, 5%) as a white powder.

[1081]

Example 118

Production of N-(trans-4-hydroxycyclohexyl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[1082]



[1083]

In the same manner as in Example 25, the title compound (230 mg, 95%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and trans-4-aminocyclohexanol (74.2 mg, 0.644 mmol).

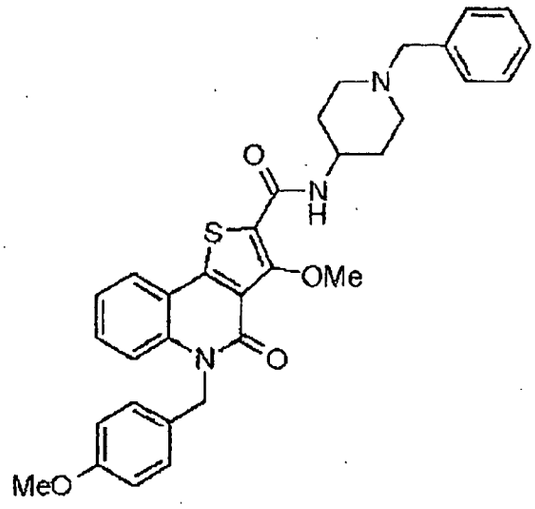
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.22-1.44 (4H, m), 1.83-1.92 (4H, m), 3.40-3.55 (1H, br), 3.68-3.85 (1H, br), 3.96 (3H, s), 4.30 (3H, s), 4.57 (1H, d, J = 4.2 Hz), 5.96 (2H, s), 7.28-7.38 (2H, m), 7.44-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (2H, m), 8.15-8.18 (2H, m), 8.36 (1H, dd, J = 8.3, 1.1 Hz).

[1084]

Example 119

Production of N-(1-benzylpiperidin-4-yl)-3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1085]



[1086]

In the same manner as in Example 25, the title compound (1.17 g, 82%) was obtained as white crystals from the compound of Reference Example 13 (1.0 g, 2.52 mmol) and 4-amino-1-benzylpiperidine (720 mg, 3.78 mmol).

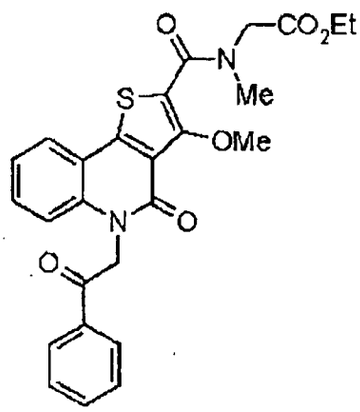
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-1.75 (2H, m), 1.80-1.95 (2H, br d), 2.17 (2H, t, J = 10.2 Hz), 2.65-2.80 (2H, br d), 3.50 (2H, s), 3.70 (3H, s), 3.80-3.90 (1H, br), 4.08 (3H, s), 5.53 (2H, br s), 6.85-6.88 (2H, m), 7.20 (2H, d, J = 8.7 Hz), 7.25-7.34 (5H, m), 7.49-7.56 (2H, m), 7.74 (1H, d, J = 7.8 Hz), 8.00 (1H, dd, J = 8.1, 1.2 Hz).

[1087]

Example 120

Production of N-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}-N-methylglycine ethyl ester

[1088]



[1089]

In the same manner as in Example 25, the title compound (400 mg, 91%) was obtained as a white solid from the compound of Example 7 (350 mg, 0.89 mmol) and sarcosine ethyl ester hydrochloride (204 mg, 1.33 mmol).

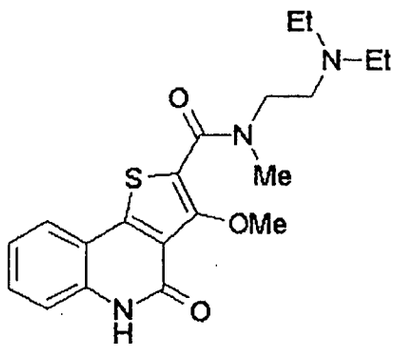
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.24-1.35 (3H, m), 3.19 (1.2H, br s), 3.24 (1.8H, s), 3.98 (1.2H, br s), 4.08 (1.8H, s), 4.15-4.30 (4H, m), 5.86 (2H, s), 7.03 (1H, d, J = 8.7 Hz), 7.24-7.29 (1H, m), 7.43-7.49 (1H, m), 7.53-7.58 (2H, m), 7.65-7.70 (1H, m), 7.83 (1H, dd, J = 7.8, 1.2 Hz), 8.10-8.13 (2H, m).

[1090]

Example 121

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1091]



[1092]

A mixture of the compound of Example 48 (4.10 g, 8.08 mol), trifluoroacetic acid (34 mL) and trifluoromethanesulfonic acid (6.6 mL) was stirred at room temperature for 5 hr and at 80°C for 2.5 hr. After cooling, the reaction mixture was concentrated under reduced pressure, and ethyl acetate and 1N aqueous sodium hydroxide solution were added to the residue. The mixture was extracted with ethyl acetate and the extract was washed successively with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/2) to give the title compound (1.50 g, 48%)

as a white powder.

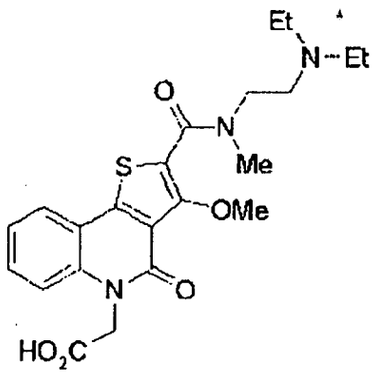
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.10 (6H, br), 2.20-2.70 (6H, br), 3.05 (3H, s), 3.40-3.60 (2H, br), 3.91 (3H, s), 7.21-7.26 (1H, m), 7.38-7.41 (1H, m), 7.49-7.55 (1H, m), 7.82-7.85 (1H, m), 11.75 (1H, s).

[1093]

Example 122

Production of [2-{[2-(diethylamino)ethyl](methyl)carbamoyl}-3-methoxy-4-oxothieno[3,2-c]quinolin-5(4H)-yl]acetic acid

[1094]



[1095]

A solution of the compound of Example 53 (670 mg, 1.41 mmol) and 8N aqueous sodium hydroxide solution (1.0 mL) in ethanol (7.0 mL) was stirred at room temperature for 15 hr. The reaction mixture was neutralized with 1N hydrochloric acid, and concentrated under reduced pressure. THF was added to the residue and, after filtration, the filtrate was concentrated under reduced pressure to give the title compound (580 mg, 92%) as a pale-yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.35 (6H, br), 2.70-3.30 (9H, m), 3.70-3.85 (2H, br), 3.91 (3H, s), 5.06 (2H, s), 7.34 (1H, t, J = 7.7 Hz), 7.48 (1H, d, J = 8.2 Hz), 7.62 (1H, t, J = 8.2 Hz), 7.94 (1H, d, J = 7.7 Hz).

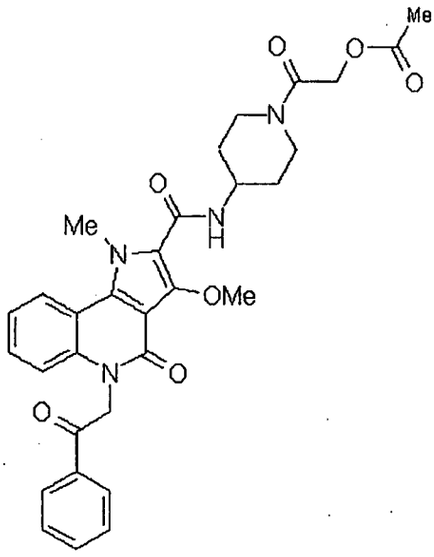
[1096]

Example 123

Production of 2-[4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-

yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[1097]



[1098]

To a mixture of the compound of Example 77 (200 mg, 0.423 mmol), triethylamine (122 μL, 0.880 mmol) and THF (10 mL) was added acetoxyacetyl chloride (47.3 μL, 0.440 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate-THF to give the title compound (171 mg, 75%) as a white powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.70 (2H, m), 1.80-2.00 (2H, m), 2.08 (3H, s), 2.80-3.00 (1H, m), 3.10-3.25 (1H, m), 3.60-3.80 (1H, m), 3.97 (3H, s), 4.00-4.25 (2H, m), 4.31 (3H, s), 4.80 (2H, d, J = 1.8 Hz), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.4, 1.2 Hz).

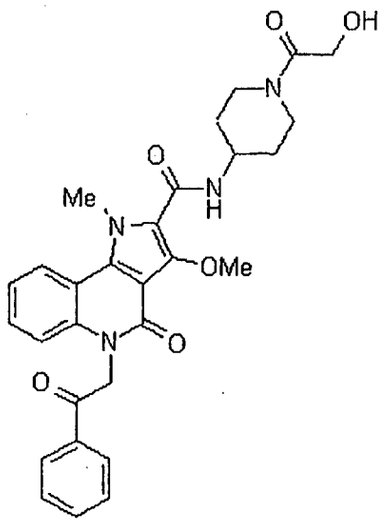
[1099]

Example 124

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-

pyrrolo[3,2-c]quinoline-2-carboxamide

[1100]



[1101]

1) A mixed solution of the compound of Example 123 (125 mg, 0.218 mmol) and 8N aqueous sodium hydroxide solution (1 mL) in THF (2 mL)-ethanol (7 mL) was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid (1.5 mL), and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate-THF to give the title compound (59.2 mg, 51%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.65 (2H, m), 1.80-2.00 (2H, m), 2.85-3.00 (1H, m), 3.05-3.25 (1H, m), 3.60-3.75 (1H, m), 3.97 (3H, s), 4.00-4.30 (4H, m), 4.31 (3H, s), 4.51 (1H, t, J = 5.3 Hz), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.48 (1H, t, J = 7.6 Hz), 7.63 (2H, t, J = 7.6 Hz), 7.76 (1H, t, J = 7.4 Hz), 7.95 (1H, d, J = 8.4 Hz), 8.17 (2H, d, J = 7.6 Hz), 8.37 (1H, d, J = 8.1 Hz).

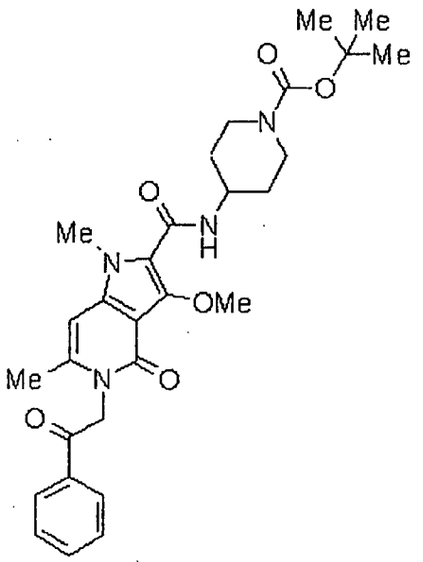
2) The white powder was recrystallized from ethanol-water to give the title compound as white crystals. melting point: 224°C

[1102]

Example 125

Production of tert-butyl 4-({[3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[1103]



[1104]

In the same manner as in Example 25, the title compound (315 mg, 72%) was obtained as a white powder from the compound of Reference Example 35 (290 mg, 0.818 mmol) and 4-amino-1-Boc-piperidine (212 mg, 1.06 mmol).

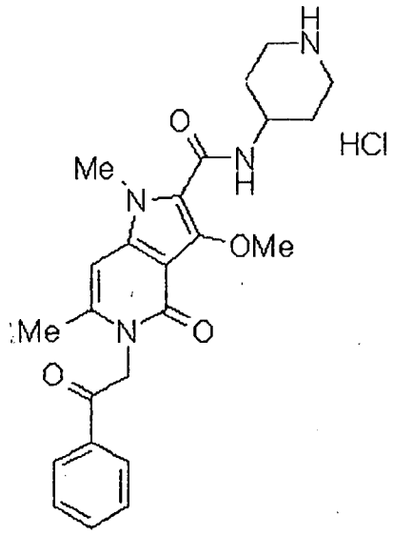
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.29-1.51 (11H, m), 1.75-1.90 (2H, m), 2.28 (3H, s), 2.86-3.05 (2H, m), 3.77-3.90 (5H, m), 3.92-4.04 (4H, m), 5.62 (2H, s), 6.58 (1H, s), 7.55-7.66 (3H, m), 7.73 (1H, d, J = 6.6 Hz), 8.11 (2H, d, J = 7.7 Hz).

[1105]

Example 126

Production of 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide hydrochloride

[1106]



[1107]

To a mixture of the compound of Example 125 (300 mg, 0.559 mmol) and ethyl acetate (4 mL) was added 4N hydrogen chloride ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 2 hr. The precipitated solid was collected by filtration, and washed with ethyl acetate to give the title compound (240 mg, 91%) as a white powder.

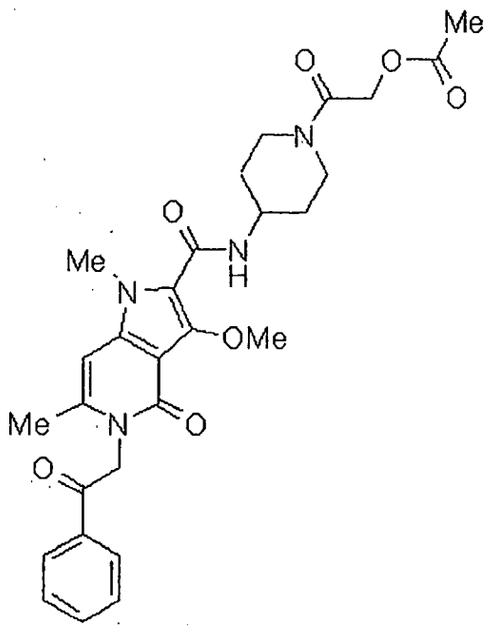
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.61-1.84 (2H, m), 1.95-2.11 (2H, m), 2.28 (3H, s), 2.92-3.12 (2H, m), 3.20-3.32 (2H, m), 3.83 (3H, s), 3.94-4.15 (4H, m), 5.62 (2H, s), 6.59 (1H, s), 7.61 (2H, t, J = 7.6 Hz), 7.68-7.81 (2H, m), 8.04-8.19 (2H, m), 8.64 (1H, br s), 8.87 (1H, br s).

[1108]

Example 127

Production of 2-[4-({[3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[1109]



[1110]

In the same manner as in Example 123, the title compound (210 mg, 82%) was obtained as a white powder from the compound of Example 126 (225 mg, 0.476 mmol) and acetoxyacetyl chloride (61.4 μL, 0.571 mmol).

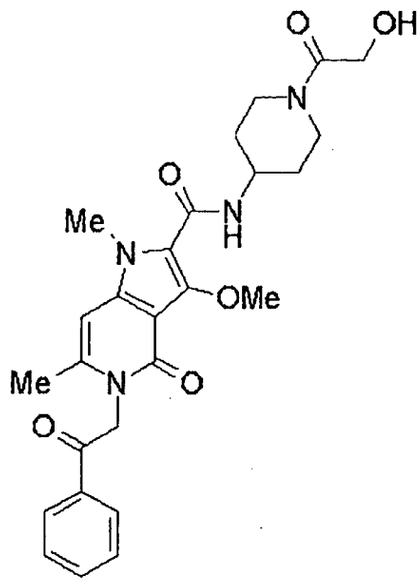
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.26-1.64 (2H, m), 1.78-1.97 (2H, m), 2.09 (3H, s), 2.28 (3H, s), 2.79-2.97 (1H, m), 3.09-3.25 (1H, m), 3.58-3.74 (1H, m), 3.86 (3H, s), 3.95-4.20 (5H, m), 4.79 (2H, s), 5.62 (2H, s), 6.58 (1H, s), 7.55-7.68 (3H, m), 7.69-7.78 (1H, m), 8.06-8.15 (2H, m).

[1111]

Example 128

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1112]



[1113]

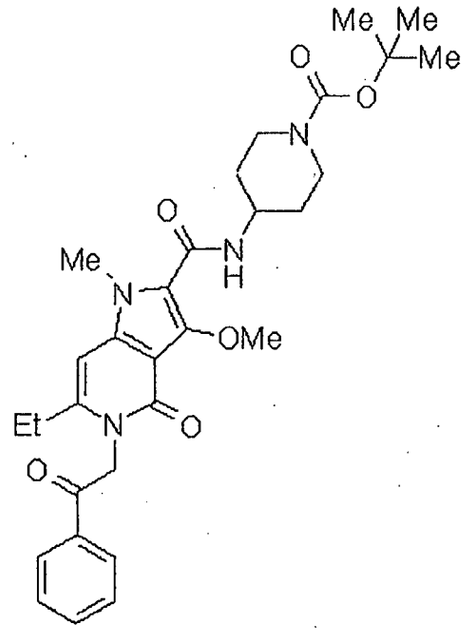
In the same manner as in Example 124, the title compound (156 mg, 85%) was obtained as a white powder from the compound of Example 127 (200 mg, 0.373 mmol), 8N aqueous sodium hydroxide solution (0.5 mL), THF (2.5 mL) and ethanol (5 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32-1.61 (2H, m), 1.79-1.93 (2H, m), 2.28 (3H, s), 2.82-2.98 (1H, m), 3.04-3.20 (1H, m), 3.57-3.71 (1H, m), 3.86 (3H, s), 3.96-4.25 (7H, m), 4.50 (1H, d, J = 5.3 Hz), 5.61 (2H, s), 6.58 (1H, s), 7.55-7.67 (3H, m), 7.69-7.78 (1H, m), 8.07-8.16 (2H, m).

[1114]

Example 129

Production of tert-butyl 4-({[6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[1115]



[1116]

In the same manner as in Example 25, the title compound (126 mg, 84%) was obtained as a white powder from the compound of Reference Example 42 (100 mg, 0.271 mmol) and 4-amino-1-Boc-piperidine (70.7 mg, 0.353 mmol).

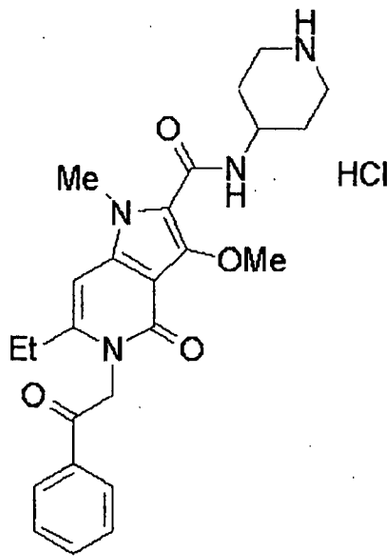
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.3 Hz), 1.32-1.51 (11H, m), 1.74-1.89 (2H, m), 2.58 (2H, q, J = 7.5 Hz), 2.85-3.04 (2H, m), 3.77-3.91 (5H, m), 3.91-4.05 (4H, m), 5.59 (2H, s), 6.49 (1H, s), 7.55-7.67 (3H, m), 7.69-7.79 (1H, m), 8.06-8.16 (2H, m).

[1117]

Example 130

Production of 6-ethyl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide hydrochloride

[1118]



[1119]

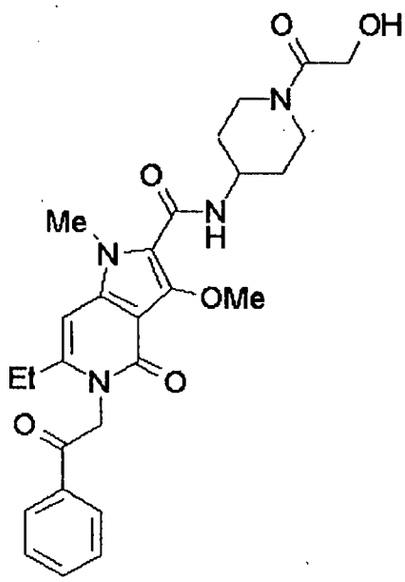
A solution of the compound of Example 129 (115 mg, 0.209 mmol) and 4N hydrogen chloride ethyl acetate solution (4 mL) in ethyl acetate (4 mL) was stirred at room temperature for 3 hr. The precipitated solid was collected by filtration, and washed with ethyl acetate to give the title compound.

[1120]

Example 131

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1121]



[1122]

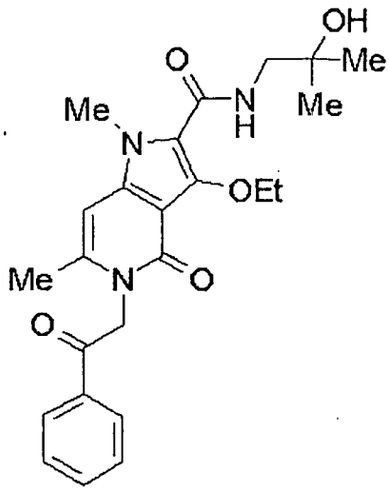
To a mixture of the compound of Example 130 (90.0 mg, 0.185 mmol), triethylamine (76.9 μL, 0.555 mmol) and THF (5 mL) was added acetoxyacetyl chloride (23.8 μL, 0.221 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was dissolved in THF (1.2 mL)-ethanol (2.5 mL). 8N Aqueous sodium hydroxide solution (250 μL) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid (0.5 mL), and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=10/0 - 9/1), and the obtained solid was recrystallized from ethyl acetate to give the title compound (61.2 mg, 65%) as white crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.23 (3H, m), 1.31-1.59 (2H, m), 1.80-1.94 (2H, m), 2.58 (2H, q, J = 7.4 Hz), 2.83-2.99 (1H, m), 3.04-3.21 (1H, m), 3.59-3.70 (1H, m), 3.89 (3H, s), 3.97-4.26 (7H, m), 4.49 (1H, t, J = 5.4 Hz), 5.59 (2H, s), 6.49 (1H, s), 7.56-7.67 (3H, m), 7.70-7.78 (1H, m), 8.06-8.15 (2H, m).

[1123]

Example 132

Production of 3-ethoxy-N-(2-hydroxy-2-methylpropyl)-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1124]



[1125]

In the same manner as in Example 25, the title compound (65.8 mg, 67%) was obtained as a white powder from the compound of Reference Example 44 (100 mg, 0.271 mmol) and 1-amino-2-methylpropan-2-ol (31.5 mg, 0.353 mmol).

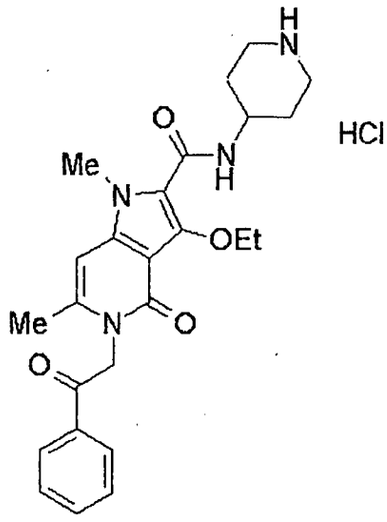
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13 (6H, s), 1.31 (3H, t, J = 7.0 Hz), 2.28 (3H, s), 3.24 (2H, d, J = 5.5 Hz), 3.90 (3H, s), 4.35 (2H, q, J = 7.0 Hz), 4.66 (1H, s), 5.61 (2H, s), 6.59 (1H, s), 7.61 (2H, t, J = 7.6 Hz), 7.69-7.79 (1H, m), 7.93 (1H, t, J = 5.6 Hz), 8.06-8.15 (2H, m).

[1126]

Example 133

Production of 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide hydrochloride

[1127]



[1128]

In the same manner as in Example 73, the title compound (303 mg, 95%) was obtained as a white powder from the compound of Reference Example 44 (250 mg, 0.679 mmol) and 4-amino-1-Boc-piperidine (177 mg, 0.882 mmol).

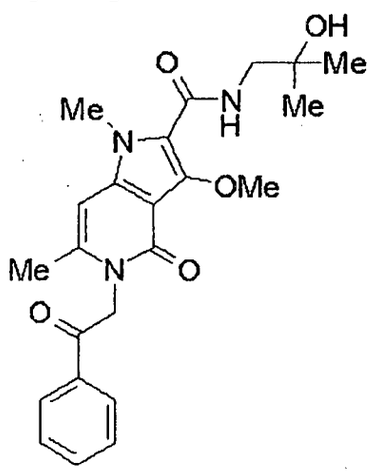
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3H, t, J = 7.1 Hz), 1.61-1.81 (2H, m), 1.97-2.12 (2H, m), 2.28 (3H, s), 2.94-3.10 (2H, m), 3.21-3.32 (2H, m), 3.85 (3H, s), 3.97-4.14 (1H, m), 4.34 (2H, q, J = 7.0 Hz), 5.62 (2H, s), 6.59 (1H, s), 7.61 (2H, t, J = 7.6 Hz), 7.69-7.81 (2H, m), 8.04-8.17 (2H, m), 8.85 (2H, br s).

[1129]

Example 134

Production of N-(2-hydroxy-2-methylpropyl)-3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1130]



[1131]

In the same manner as in Example 25, the title compound (201 mg, 84%) was obtained as a white powder from the compound of Reference Example 35 (200 mg, 0.564 mmol) and 1-amino-2-methylpropan-2-ol (65.4 mg, 0.734 mmol).

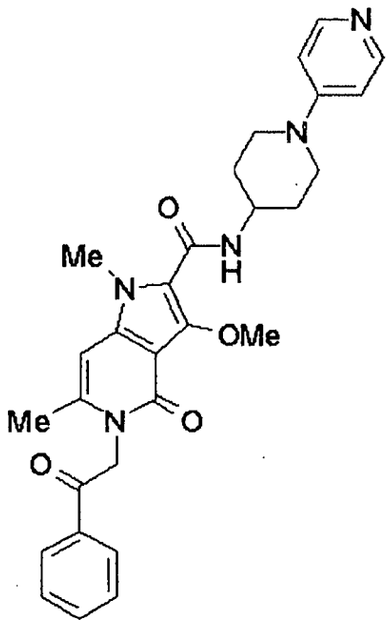
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13 (6H, s), 2.29 (3H, s), 3.24 (2H, d, J = 5.7 Hz), 3.89 (3H, s), 4.02 (3H, s), 4.65 (1H, s), 5.62 (2H, s), 6.59 (1H, s), 7.56-7.66 (2H, m), 7.69-7.78 (1H, m), 7.85 (1H, t, J = 5.7 Hz), 8.06-8.15 (2H, m).

[1132]

Example 135

Production of 3-methoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyridin-4-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1133]



[1134]

In the same manner as in Example 25, the title compound (656 mg, 91%) was obtained as a white powder from the compound of Reference Example 35 (500 mg, 1.41 mmol) and 1-pyridin-4-ylpiperidin-4-amine (388 mg, 1.55 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.48-1.65 (2H, m), 1.85-1.97 (2H, m), 2.28 (3H, s), 2.98-3.14 (2H, m), 3.77-3.90 (5H, m), 3.98

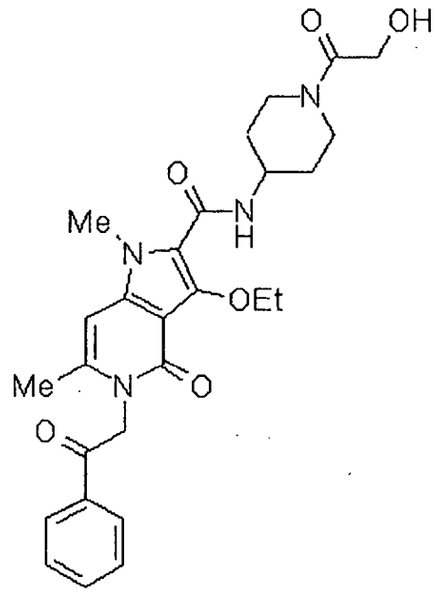
(3H, s), 4.01-4.15 (1H, m), 5.61 (2H, s), 6.58 (1H, s), 6.82 (2H, d, J = 1.5 Hz), 7.56-7.68 (3H, m), 7.70-7.78 (1H, m), 8.05-8.20 (4H, m).

[1135]

Example 136

Production of 3-ethoxy-N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1136]



[1137]

To a mixture of the compound of Example 133 (200 mg, 0.423 mmol), triethylamine (122 μL, 0.880 mmol) and THF (10 mL) was added acetoxyacetyl chloride (47.3 μL, 0.440 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethanol (7 mL) and THF (2 mL), 8N aqueous sodium hydroxide solution (1 mL) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with water, acidified with 6N hydrochloric acid (1.5 mL), and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate and

concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate-hexane to give the title compound (102 mg, 65%) as white crystals.

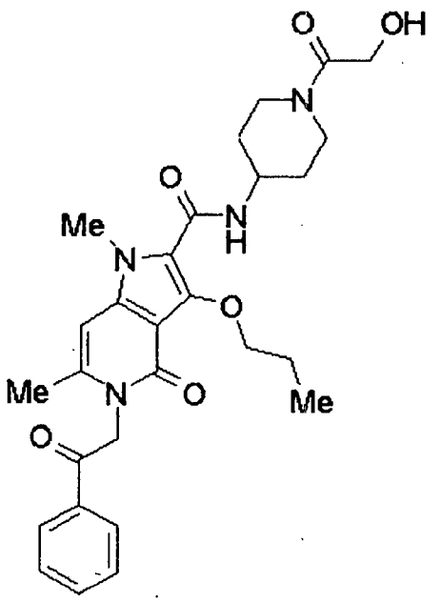
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (3H, t, J = 7.1 Hz), 1.31-1.57 (2H, m), 1.82-1.96 (2H, m), 2.28 (3H, s), 2.80-2.95 (1H, m), 3.03-3.19 (1H, m), 3.87 (3H, s), 3.95-4.13 (3H, m), 4.18-4.28 (1H, m), 4.34 (2H, q, J = 7.0 Hz), 4.50 (1H, t, J = 5.4 Hz), 5.61 (2H, s), 6.58 (1H, s), 7.55-7.78 (4H, m), 8.06-8.14 (2H, m).

[1138]

Example 137

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1139]



[1140]

In the same manner as in Example 25, the title compound (45.2 mg, 33%) was obtained as a white powder from the compound of Reference Example 46 (100 mg, 0.262 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (61.1 mg, 0.314 mmol) and triethylamine (43.5 μL, 0.314 mmol).

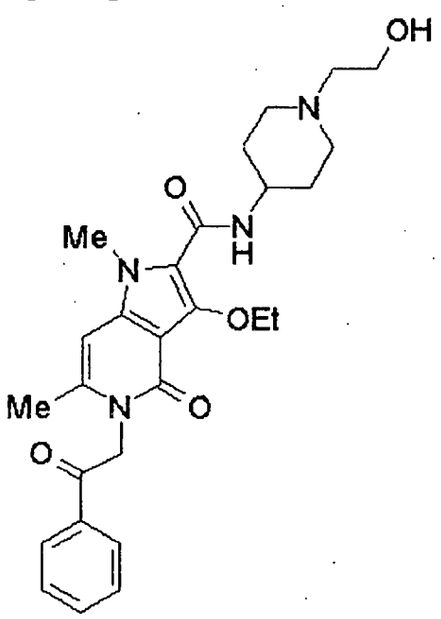
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.92 (3H, t, J = 7.4 Hz), 1.22-1.53 (2H, m), 1.60-1.75 (2H, m), 1.85-1.95 (2H, m), 2.27 (3H, s), 2.77-2.92 (1H, m), 3.00-3.17 (1H, m), 3.60-3.74 (1H, m), 3.86 (3H, s), 3.95-4.13 (3H, m), 4.25 (3H, t, J = 6.7 Hz), 4.50 (1H, t, J = 5.4 Hz), 5.62 (2H, s), 6.57 (1H, s), 7.55-7.67 (3H, m), 7.69-7.78 (1H, m), 8.05-8.16 (2H, m).

[1141]

Example 138

Production of 3-ethoxy-N-[1-(2-hydroxyethyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1142]



[1143]

In the same manner as in Example 79, the title compound (78.5 mg, 57%) was obtained as a white powder from the compound of Example 133 (135 mg, 0.277 mmol) and 2-bromoethanol (58.9 μL, 0.832 mmol).

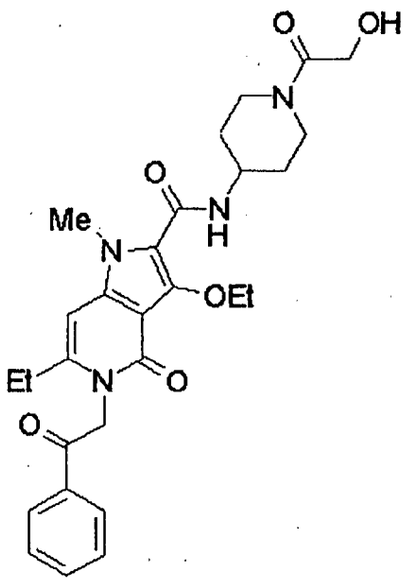
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3H, t, J = 7.1 Hz), 1.39-1.57 (2H, m), 1.78-1.91 (2H, m), 2.09-2.22 (2H, m), 2.28 (3H, s), 2.38 (2H, t, J = 6.3 Hz), 2.67-2.81 (2H, m,), 3.48 (2H, q, J = 6.2 Hz), 3.70-3.83 (1H, m), 3.87 (3H, s), 4.29-4.41 (3H, m), 5.61 (2H, s), 6.58 (1H, s), 7.56-7.68 (3H, m), 7.70-7.78 (1H, m), 8.06-8.15 (2H, m).

[1144]

Example 139

Production of 3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1145]



[1146]

1) To a solution of the compound of Reference Example 48 (74.0 mg, 0.194 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (49.1 mg, 0.252 mmol), HOBt (39.2 mg, 0.290 mmol) and triethylamine (34.9 μL, 0.252 mmol) in DMF (3 mL) was added WSCD (55.6 mg, 0.290 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate to give the title compound (61.2 mg, 60%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.29 (6H, m), 1.32-1.56 (2H, m), 1.83-1.96 (2H, m), 2.57 (2H, q, J = 7.4 Hz), 2.80-2.94 (1H, m), 3.04-3.19 (1H, m), 3.59-3.72 (1H, m), 3.90 (3H, s), 3.95-

4.14 (3H, m), 4.17-4.27 (1H, m), 4.34 (2H, q, J = 7.2 Hz), 4.51 (1H, t, J = 5.4 Hz), 5.59 (2H, s), 6.49 (1H, s), 7.56-7.65 (2H, m), 7.66-7.77 (2H, m), 8.07-8.14 (2H, m).

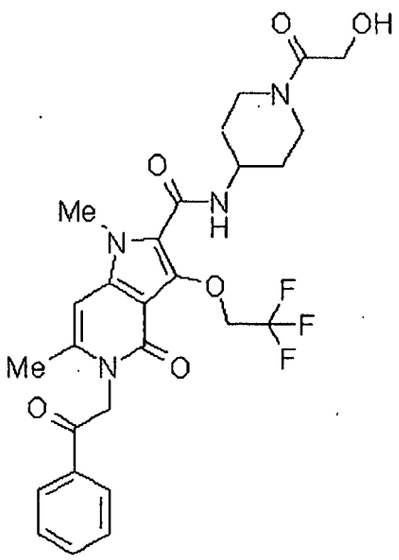
2) The white crystals were recrystallized from ethanol-water to give the title compound as white crystals. melting point: 204°C

[1147]

Example 140

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1148]



[1149]

1) To a solution of the compound of Reference Example 50 (70.0 mg, 0.166 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (42.0 mg, 0.216 mmol), HOBt (33.6 mg, 0.249 mmol) and triethylamine (29.9 μL, 0.216 mmol) in DMF (3 mL) was added WSCD (55.6 mg, 0.290 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified

by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from ethyl acetate to give the title compound (51.3 mg, 55%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.22-1.50 (2H, m), 1.81-1.94 (2H, m), 2.29 (3H, s), 2.74-2.91 (1H, m), 3.01-3.16 (1H, m), 3.63-3.75 (1H, m), 3.83 (3H, s), 3.95-4.13 (3H, m), 4.20-4.32 (1H, m), 4.53 (1H, t, J = 5.5 Hz), 5.06 (2H, q, J = 9.3 Hz), 5.65 (2H, s), 6.64 (1H, s), 7.51 (1H, d, J = 7.7 Hz), 7.57-7.66 (2H, m), 7.70-7.79 (1H, m), 8.07-8.15 (2H, m).

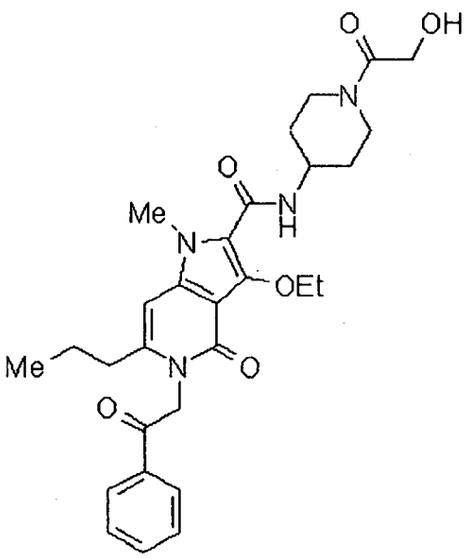
2) The white crystals were recrystallized from ethanol-water to give the title compound as white crystals. melting point: 132°C

[1150]

Example 141

Production of 3-ethoxy-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-6-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1151]



[1152]

To a solution of the compound of Reference Example 57 (200 mg, 0.504 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (128 mg, 0.656 mmol), HOBt (102 mg, 0.757 mmol) and triethylamine (90.8 μL, 0.656 mmol) in DMF (5 mL) was added WSCD (145 mg, 0.757 mmol) under ice-cooling, and the mixture

was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from THF-ethyl acetate to give the title compound (224 mg, 83%) as white crystals.

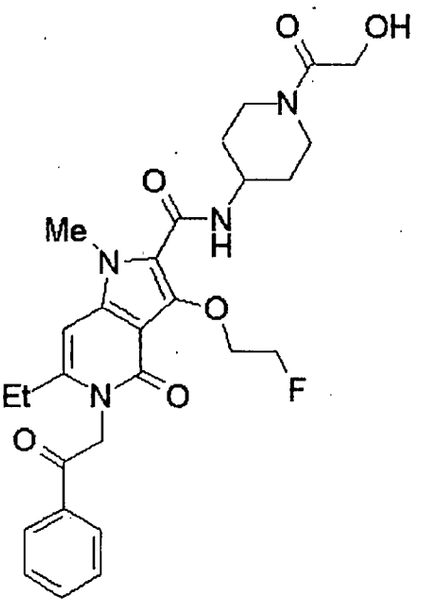
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.93 (3H, t, J = 7.3 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.31-1.66 (4H, m), 1.84-1.95 (2H, m), 2.51-2.59 (2H, m), 2.81-2.95 (1H, m), 3.04-3.18 (1H, m), 3.61-3.71 (1H, m), 3.89 (3H, s), 3.96-4.14 (3H, m), 4.18-4.27 (1H, m), 4.33 (2H, q, J = 7.0 Hz), 4.51 (1H, t, J = 5.1 Hz), 5.55 (2H, s), 6.51 (1H, s), 7.56-7.77 (4H, m), 8.08-8.14 (2H, m).

[1153]

Example 142

Production of 6-ethyl-3-(2-fluoroethoxy)-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1154]



[1155]

To a solution of the compound of Reference Example 59

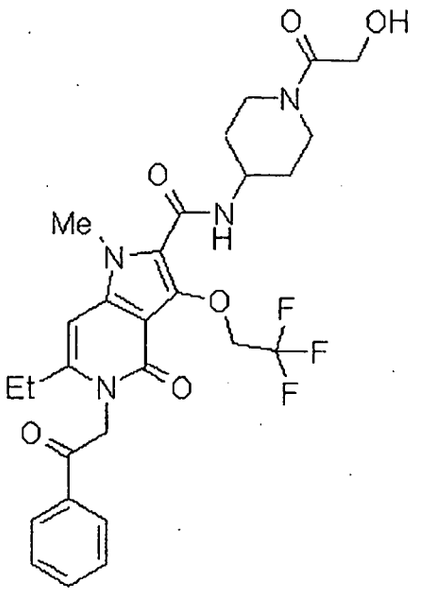
(202 mg, 0.504 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (128 mg, 0.656 mmol), HOBt (102 mg, 0.757 mmol) and triethylamine (90.8 μL, 0.656 mmol) in DMF (5 mL) was added WSCD (145 mg, 0.757 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate), and the obtained solid was recrystallized from THF-ethyl acetate to give the title compound (219 mg, 80%) as white crystals.
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.4 Hz), 1.26-1.48 (2H, m), 1.87 (2H, s), 2.59 (2H, q, J = 7.4 Hz), 2.76-2.91 (1H, m), 3.01-3.17 (1H, m), 3.57-3.73 (1H, m), 3.92 (3H, s), 3.97-4.13 (3H, m), 4.18-4.32 (1H, m), 4.45-4.81 (5H, m), 5.59 (2H, s), 6.49-6.56 (1H, m), 7.55-7.66 (3H, m), 7.69-7.78 (1H, m), 8.06-8.16 (2H, m).

[1156]

Example 143

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[1157]



[1158]

1) To a solution of the compound of Reference Example 61 (230 mg, 0.527 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (133 mg, 0.685 mmol), HOBt (107 mg, 0.791 mmol) and triethylamine (95.0 μL, 0.685 mmol) in DMF (4 mL) was added WSCD (152 mg, 0.791 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=1/3 - 1/0), and the obtained solid was recrystallized from ethyl acetate-hexane to give the title compound (146 mg, 48%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.13-1.49 (5H, m), 1.82-1.94 (2H, m), 2.59 (2H, q, J = 7.2 Hz), 2.76-2.88 (1H, m), 3.023.15 (1H, m), 3.64-3.75 (1H, m), 3.86 (3H, s), 3.96-4.16 (3H, m), 4.20-4.33 (1H, m), 4.53 (1H, t, J = 5.4 Hz), 5.05 (2H, q, J = 9.3 Hz), 5.63 (2H, s), 6.54 (1H, s), 7.51 (1H, d, J = 7.7 Hz), 7.61 (2H, t, J = 7.6 Hz), 7.70-7.78 (1H, m), 8.08-8.14 (2H, m).

2) The white crystals were recrystallized from ethanol-water to give the title compound as white crystals. melting

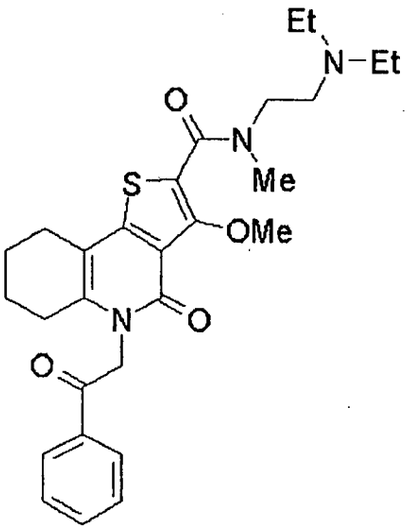
point:159°C

[1159]

Example 144

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5,6,7,8,9-hexahydrothieno[3,2-c]quinoline-2-carboxamide

[1160]



[1161]

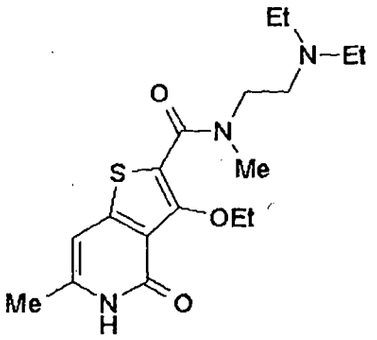
In the same manner as in Example 25, the title compound (54.0 mg, 28%) was obtained as a colorless oil from the compound of Reference Example 66 (150 mg, 0.377 mmol) and N,N-diethyl-N'-methylethane-1,2-diamine (79.3 μL, 0.490 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.74-1.05 (6H, m), 1.67-1.85 (4H, m), 2.19-2.65 (10H, m), 3.03 (3H, s), 3.40-3.56 (2H, m), 3.82 (3H, s), 5.65 (2H, s), 7.61 (2H, t, J = 7.6 Hz), 7.70-7.78 (1H, m), 8.07-8.16 (2H, m).

[1162]

Example 145

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N,6-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1163]



[1164]

A mixture of the compound of Reference Example 70 (2.50 g, 6.51 mmol), 6N hydrochloric acid (15 mL) and DMF (15 mL) was stirred for 15 hr under refluxing conditions. After cooling, the reaction mixture was concentrated under reduced pressure, and water (20 mL) was added to the residue. The mixture was neutralized with saturated sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate) to give the title compound (568 mg, 24%) as a colorless oil.

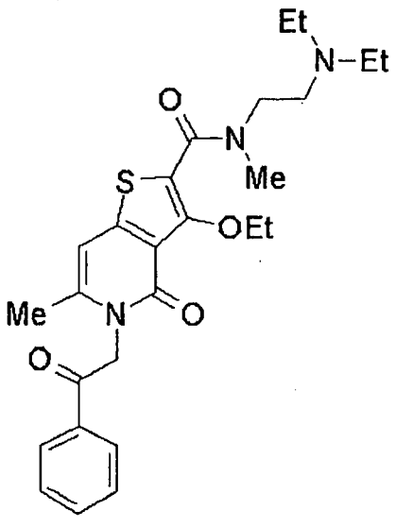
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.05 (6H, m), 1.21 (3H, t, J = 7.0 Hz), 2.21 (3H, s), 2.25-2.65 (6H, m), 3.01 (3H, s), 3.40-3.55 (2H, m), 4.13 (2H, q, J = 7.0 Hz), 6.54 (1H, s), 11.41 (1H, s).

[1165]

Example 146

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1166]



[1167]

A mixture of the compound of Example 145 (300 mg, 0.821 mmol), phenacyl bromide (196 mg, 0.985 mmol), potassium carbonate (272 mg, 1.97 mmol) and DMF (5 mL) was stirred at 60°C for 15 hr. After cooling, the mixture was diluted with water (10 mL), and extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane = 1/9 to 10/0) to give the title compound (51.2 mg, 13%) as a colorless oil.

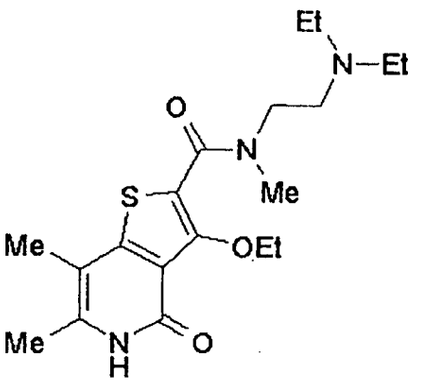
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70-1.05 (6H, m), 1.15-1.20 (3H, m), 2.25-2.65 (9H, m), 3.02 (3H, br s), 3.40-3.55 (2H, m), 4.05 (2H, q, J = 6.9 Hz), 5.66 (2H, s), 6.80-6.81 (1H, m), 7.62 (2H, t, J = 7.7 Hz), 7.72-7.78 (1H, m), 8.10-8.13 (2H, m).

[1168]

Example 147

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N,6,7-trimethyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1169]



[1170]

In the same manner as in Example 145, the title compound (60 mg, 29%) was obtained as a white solid from the compound of Reference Example 74 (220 mg, 0.55 mmol).

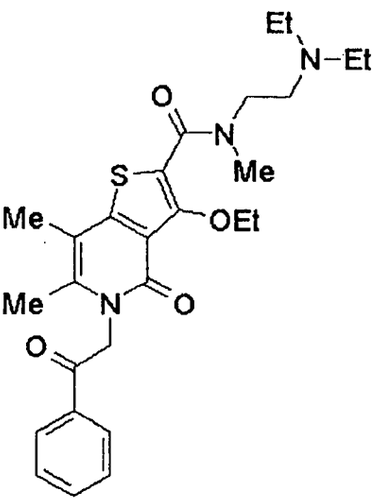
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.80-1.10 (6H, m), 1.37 (3H, t, J = 6.9 Hz), 2.17 (3H, s), 2.41 (3H, s), 2.48-2.73 (6H, m), 3.17 (3H, s), 3.61 (2H, br s), 4.27 (2H, q, J = 7.1 Hz), 12.31 (1H, br s).

[1171]

Example 148

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N,6,7-trimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1172]



[1173]

In the same manner as in Example 146, the title compound (10 mg, 12%) was obtained as a pale-yellow oil from the

compound of Example 147 (60 mg, 0.16 mmol) and phenacyl bromide (196 mg, 0.985 mmol).

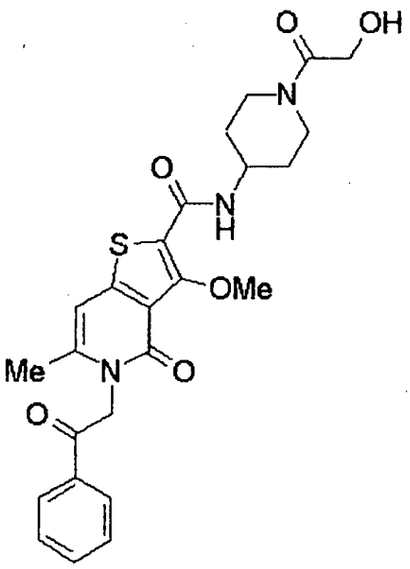
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.80-1.15 (6H, m), 1.34 (3H, t, J = 7.1 Hz), 2.21-2.80 (12H, m), 3.16 (3H, s), 3.62 (2H, br s), 4.22 (2H, q, J= 7.1 Hz), 5.67 (2H, s), 7.54 (2H, t, J = 7.5 Hz), 7.66 (1H, t, J = 7.5 Hz), 8.08 (2H, dd, J = 8.1, 1.5 Hz).

[1174]

Example 149

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1175]



[1176]

In the same manner as in Example 25, the title compound (224 mg, 80%) was obtained as a white powder from the compound of Reference Example 78 (200 mg, 0.560 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (142 mg, 0.727 mmol) and triethylamine (101 μL, 0.727 mmol).

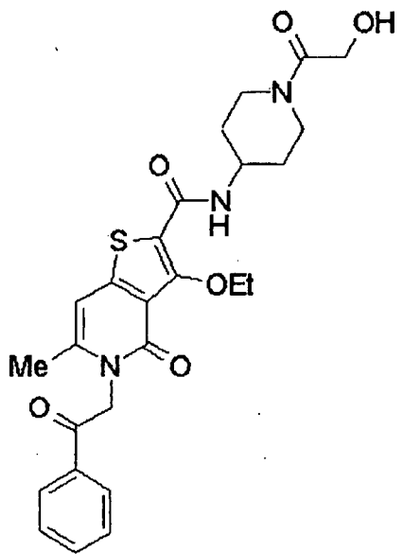
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.38-1.66 (2H, m), 1.79-1.92 (2H, m), 2.26-2.35 (3H, m), 2.78-2.94 (1H, m), 3.03-3.18 (1H, m), 3.58-3.71 (1H, m), 3.94-4.14 (6H, m), 4.18-4.30 (1H, m), 4.51 (1H, t, J = 5.3 Hz), 5.68 (2H, s), 6.86 (1H, s), 7.56-7.69 (3H, m), 7.71-7.80 (1H, m), 8.07-8.16 (2H, m).

[1177]

Example 150

Production of 3-ethoxy-N-[1-(hydroxyacetyl)piperidin-4-yl]-6-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[1178]



[1179]

In the same manner as in Example 25, the title compound (178 mg, 65%) was obtained as a white powder from the compound of Reference Example 79 (200 mg, 0.538 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (142 mg, 0.727 mmol) and triethylamine (101 μL, 0.727 mmol).

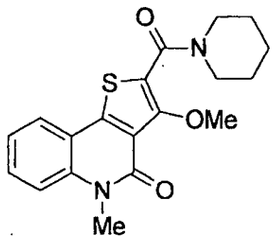
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.30 (3 H, t, J=7.1 Hz), 1.37-1.61 (2 H, m), 1.84-1.95 (2 H, m), 2.30 (3 H, s), 2.76-2.91 (1 H, m), 3.02-3.18 (1 H, m), 3.59-3.73 (1 H, m), 3.95-4.13 (3 H, m), 4.21-4.33 (3 H, m), 4.51 (1 H, t, J=5.4 Hz), 5.68 (2 H, s), 6.86 (1 H, s), 7.57-7.70 (3 H, m), 7.71-7.79 (1 H, m), 8.07-8.17 (2 H, m).

[1180]

Example 151

Production of 3-methoxy-5-methyl-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1181]



[1182]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and piperidine.

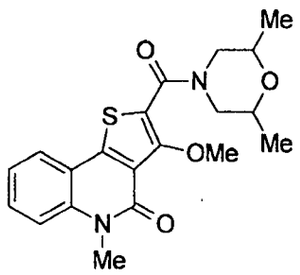
LC/MS 357 (M+H).

[1183]

Example 152

Production of 2-[(2,6-dimethylmorpholin-4-yl)carbonyl]-3-methoxy-5-methylthieno[3,2-c]quinolin-4(5H)-one

[1184]



[1185]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 2,6-dimethylmorpholine.

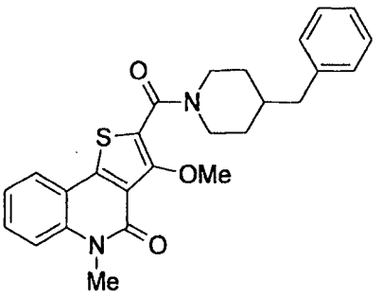
LC/MS 387 (M+H).

[1186]

Example 153

Production of 2-[(4-benzylpiperidin-1-yl)carbonyl]-3-methoxy-5-methylthieno[3,2-c]quinolin-4(5H)-one

[1187]



[1188]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 4-benzylpiperidine.

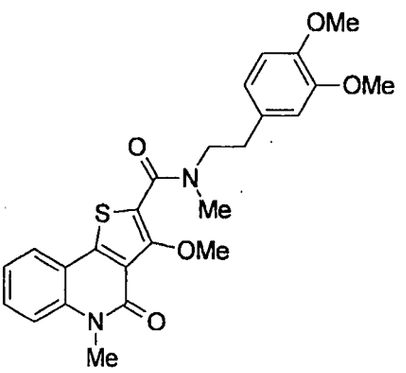
LC/MS 447 (M+H).

[1189]

Example 154

Production of N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1190]



[1191]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 2-(3,4-dimethoxyphenyl)-N-methylethanamine.

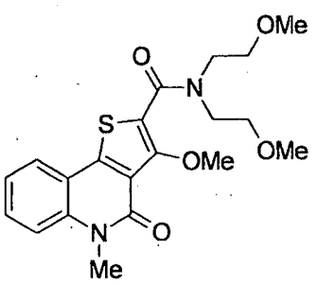
LC/MS 467 (M+H).

[1192]

Example 155

Production of 3-methoxy-N,N-bis(2-methoxyethyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1193]



[1194]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and 2-methoxy-N-(2-methoxyethyl)ethanamine.

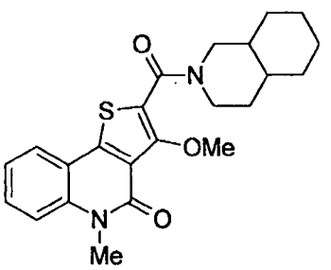
LC/MS 405 (M+H).

[1195]

Example 156

Production of 3-methoxy-5-methyl-2-(octahydroisoquinoline-2(1H)-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1196]



[1197]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and decahydroisoquinoline.

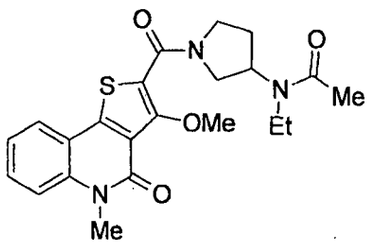
LC/MS 411 (M+H).

[1198]

Example 157

Production of N-ethyl-N-{1-[(3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinolin-2-yl)carbonyl]pyrrolidin-3-yl}acetamide

[1199]



[1200]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and N-ethyl-N-pyrrolidin-3-ylacetamide.

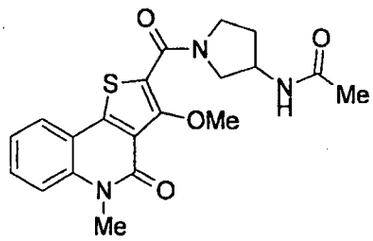
LC/MS 428 (M+H).

[1201]

Example 158

Production of N-{1-[(3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinolin-2-yl)carbonyl]pyrrolidin-3-yl}acetamide

[1202]



[1203]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and N-pyrrolidin-3-ylacetamide.

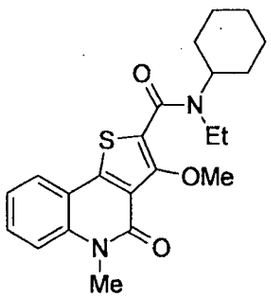
LC/MS 400 (M+H).

[1204]

Example 159

Production of N-cyclohexyl-N-ethyl-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1205]



[1206]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 84 and N-ethylcyclohexanamine.

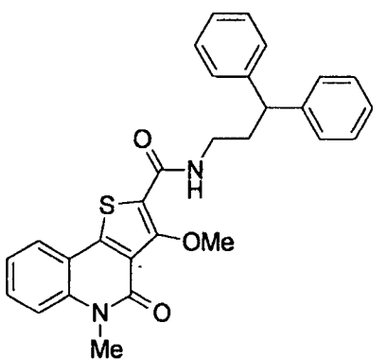
LC/MS 399 (M+H).

[1207]

Example 160

Production of N-(3,3-diphenylpropyl)-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1208]



[1209]

A solution of the compound of Reference Example 84 in DMF (0.10 M, 0.601 mL, 60 μmol) was diluted with DMF (0.200 mL), and a solution of 3,3-diphenylpropan-1-amine in DMF (1.0 M, 0.062 mL, 62 μmol) and a solution of HOBt and WSCD in 1:1 mixture in DMF (0.50 M, 0.134 mL, 67 μmol) were added. The obtained mixture was agitated at room temperature for 16 hr. Dichloromethane (2 mL) and water (1 mL) were added to the reaction mixture. After agitating for 2.5 hr, sodium hydrogen carbonate (7 mg) was added and the mixture was agitated. The

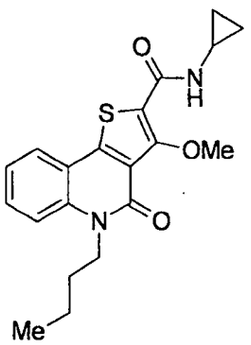
organic layer was filtered through a Teflon (registered trade mark) filter to separate the aqueous layer, and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (21.9 mg, 76%).
LC/MS 483 (M+H).

[1210]

Example 161

Production of 5-butyl-N-cyclopropyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1211]



[1212]

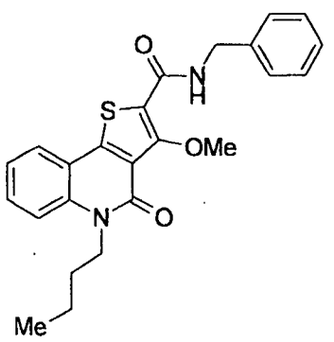
In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and cyclopropanamine.
LC/MS 371 (M+H).

[1213]

Example 162

Production of N-benzyl-5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1214]



[1215]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 1-phenylmethanamine.

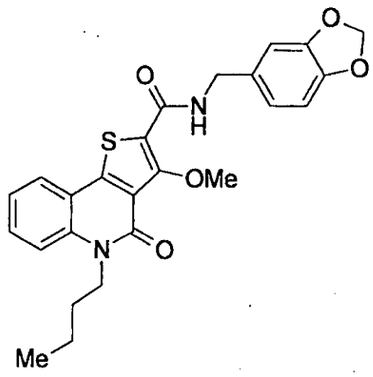
LC/MS 421 (M+H).

[1216]

Example 163

Production of N-(1,3-benzodioxol-5-ylmethyl)-5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1217]



[1218]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 1-(1,3-benzodioxol-5-yl)methanamine.

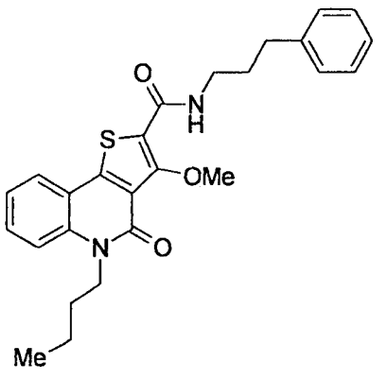
LC/MS 465 (M+H).

[1219]

Example 164

Production of 5-butyl-3-methoxy-4-oxo-N-(3-phenylpropyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1220]



[1221]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 3-phenylpropan-1-amine.

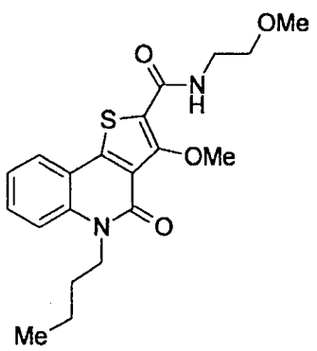
LC/MS 449 (M+H).

[1222]

Example 165

Production of 5-butyl-3-methoxy-N-(2-methoxyethyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1223]



[1224]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 2-methoxyethanamine.

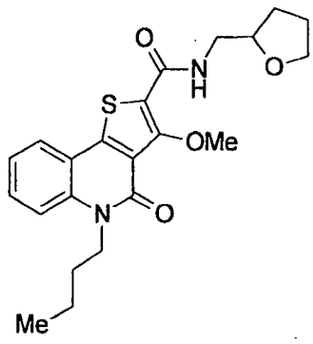
LC/MS 389 (M+H).

[1225]

Example 166

Production of 5-butyl-3-methoxy-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1226]



[1227]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 1-(tetrahydrofuran-2-yl)methanamine.

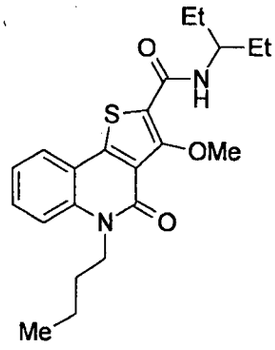
LC/MS 415 (M+H).

[1228]

Example 167

Production of 5-butyl-N-(1-ethylpropyl)-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1229]



[1230]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and pentan-3-amine.

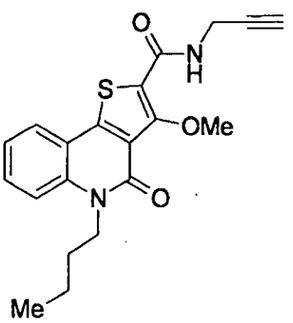
LC/MS 401 (M+H).

[1231]

Example 168

Production of 5-butyl-3-methoxy-4-oxo-N-prop-2-yn-1-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1232]



[1233]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and prop-2-yn-1-amine.

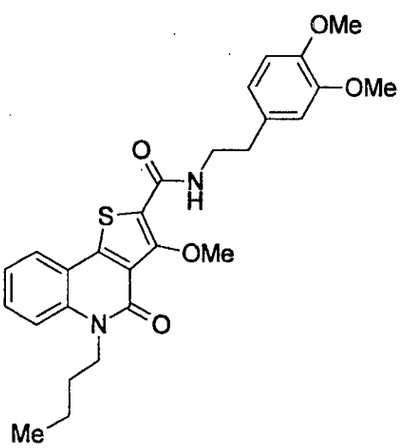
LC/MS 369 (M+H).

[1234]

Example 169

Production of 5-butyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1235]



[1236]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 2-(3,4-dimethoxyphenyl)ethanamine.

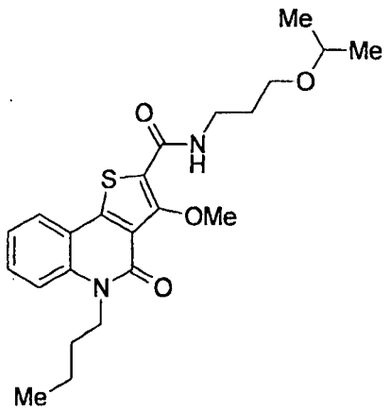
LC/MS 495 (M+H).

[1237]

Example 170

Production of 5-butyl-3-methoxy-N-[3-(1-methylethoxy)propyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1238]



[1239]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 3-(1-methylethoxy)propan-1-amine.

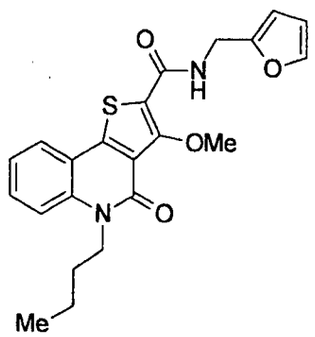
LC/MS 431 (M+H).

[1240]

Example 171

Production of 5-butyl-N-(furan-2-ylmethyl)-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1241]



[1242]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 1-furan-2-ylmethanamine.

LC/MS 411 (M+H).

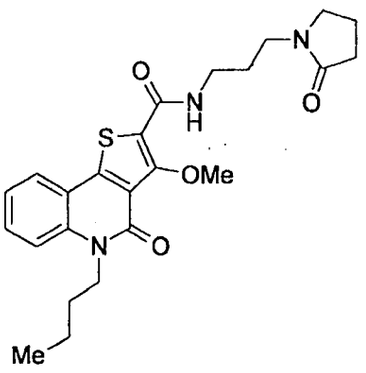
[1243]

Example 172

Production of 5-butyl-3-methoxy-4-oxo-N-[3-(2-oxopyrrolidin-1-

yl)propyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1244]



[1245]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 1-(3-aminopropyl)pyrrolidin-2-one.

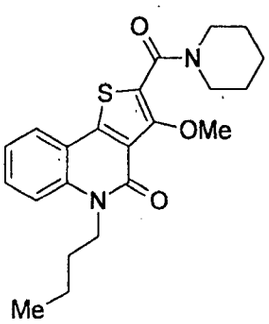
LC/MS 456 (M+H).

[1246]

Example 173

Production of 5-butyl-3-methoxy-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1247]



[1248]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and piperidine.

LC/MS 399 (M+H).

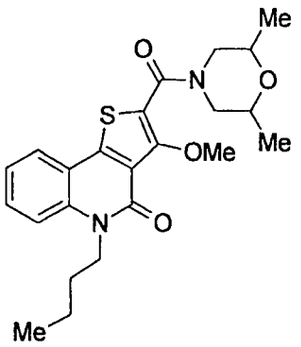
[1249]

Example 174

Production of 5-butyl-2-[(2,6-dimethylmorpholin-4-

yl)carbonyl]-3-methoxythieno[3,2-c]quinolin-4(5H)-one

[1250]



[1251]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 2,6-dimethylmorpholine.

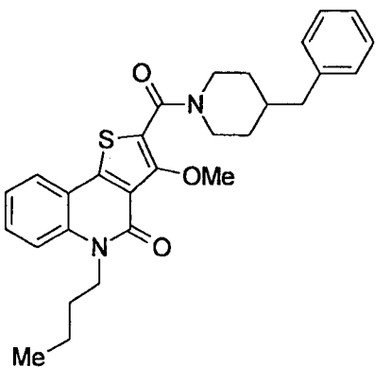
LC/MS 429 (M+H).

[1252]

Example 175

Production of 2-[(4-benzylpiperidin-1-yl)carbonyl]-5-butyl-3-methoxythieno[3,2-c]quinolin-4(5H)-one

[1253]



[1254]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 4-benzylpiperidine.

LC/MS 489 (M+H).

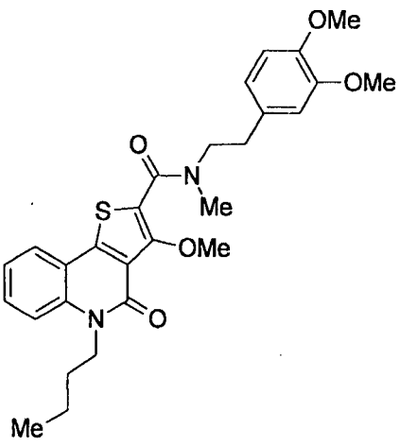
[1255]

Example 176

Production of 5-butyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-

methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1256]



[1257]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 2-(3,4-dimethoxyphenyl)-N-methylethanamine.

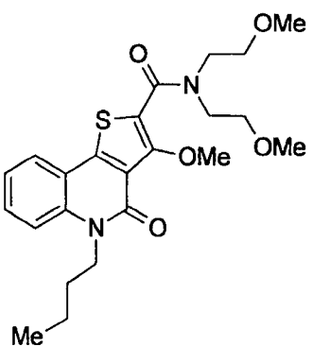
LC/MS 509 (M+H).

[1258]

Example 177

Production of 5-butyl-3-methoxy-N,N-bis(2-methoxyethyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1259]



[1260]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and 2-methoxy-N-(2-methoxyethyl)ethanamine.

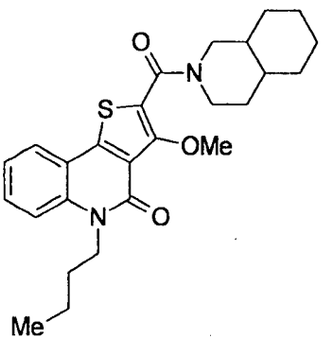
LC/MS 447 (M+H).

[1261]

Example 178

Production of 5-butyl-3-methoxy-2-(octahydroisoquinoline-2(1H)-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1262]



[1263]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and decahydroisoquinoline.

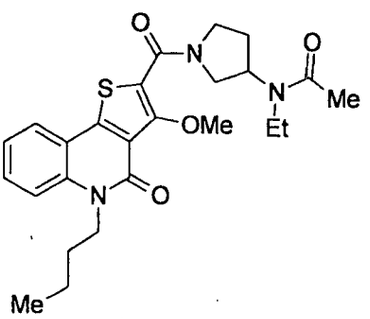
LC/MS 453 (M+H).

[1264]

Example 179

Production of N-{1-[(5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinolin-2-yl)carbonyl]pyrrolidin-3-yl}-N-ethylacetamide

[1265]



[1266]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and N-ethyl-N-pyrrolidin-3-ylacetamide.

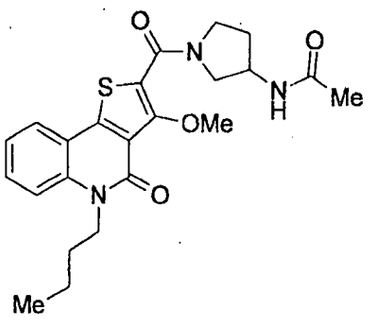
LC/MS 470 (M+H).

[1267]

Example 180

Production of N-{1-[(5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinolin-2-yl)carbonyl]pyrrolidin-3-yl}acetamide

[1268]



[1269]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and N-pyrrolidin-3-ylacetamide.

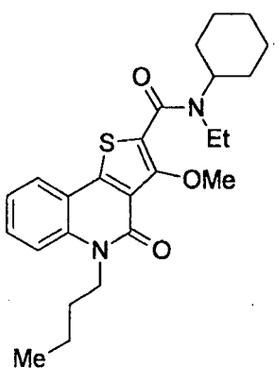
LC/MS 442 (M+H).

[1270]

Example 181

Production of 5-butyl-N-cyclohexyl-N-ethyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1271]



[1272]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 103 and N-ethylcyclohexanamine.

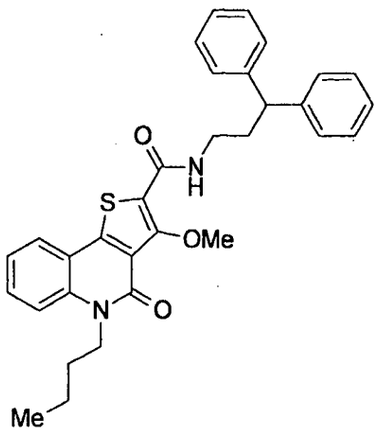
LC/MS 441 (M+H).

[1273]

Example 182

Production of 5-butyl-N-(3,3-diphenylpropyl)-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1274]



[1275]

In the same manner as in Example 160, the title compound was obtained from the compound of Reference Example 103 and 3,3-diphenylpropan-1-amine.

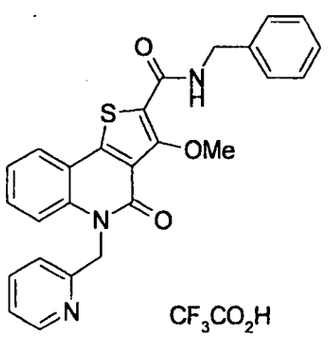
LC/MS 525 (M+H).

[1276]

Example 183

Production of N-benzyl-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1277]



[1278]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 1-

phenylmethanamine.

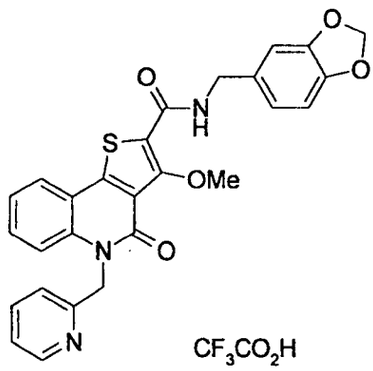
LC/MS 456 (M+H).

[1279]

Example 184

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1280]



[1281]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 1-(1,3-benzodioxol-5-yl)methanamine.

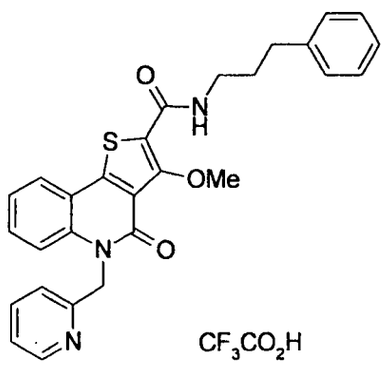
LC/MS 500 (M+H).

[1282]

Example 185

Production of 3-methoxy-4-oxo-N-(3-phenylpropyl)-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1283]



[1284]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 3-phenylpropan-1-amine.

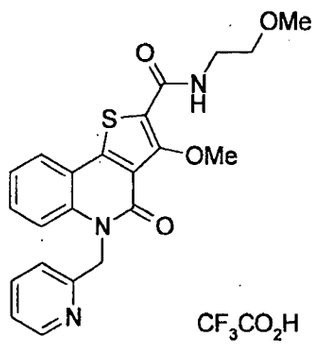
LC/MS 484 (M+H).

[1285]

Example 186

Production of 3-methoxy-N-(2-methoxyethyl)-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1286]



[1287]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 2-methoxyethanamine.

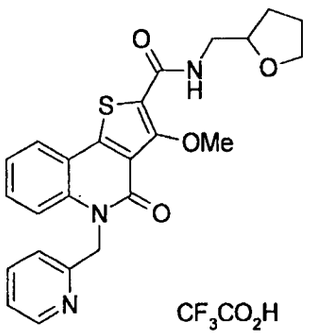
LC/MS 424 (M+H).

[1288]

Example 187

Production of 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1289]



[1290]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 1-(tetrahydrofuran-2-yl)methanamine.

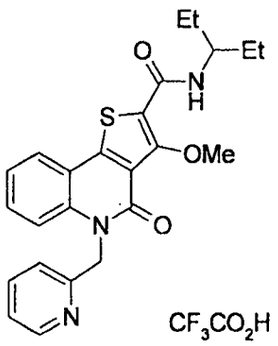
LC/MS 450 (M+H).

[1291]

Example 188

Production of N-(1-ethylpropyl)-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1292]



[1293]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and pentan-3-amine.

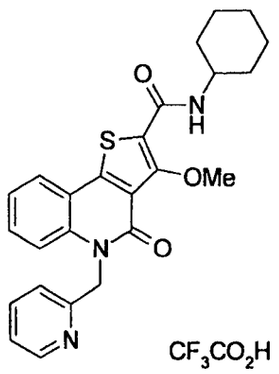
LC/MS 436 (M+H).

[1294]

Example 189

Production of N-cyclohexyl-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1295]



[1296]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and cyclohexanamine.

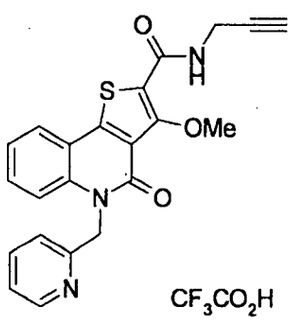
LC/MS 448 (M+H).

[1297]

Example 190

Production of 3-methoxy-4-oxo-N-prop-2-yn-1-yl-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1298]



[1299]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and prop-2-yn-1-amine.

LC/MS 404 (M+H).

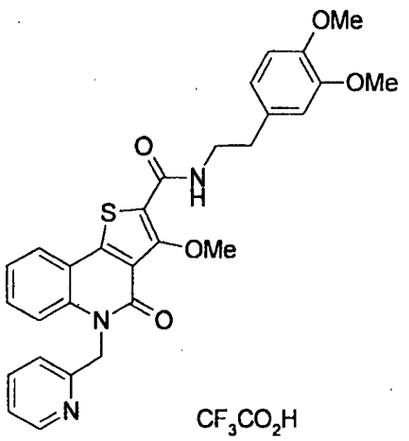
[1300]

Example 191

Production of N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-4-

oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1301]



[1302]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 2-(3,4-dimethoxyphenyl)ethanamine.

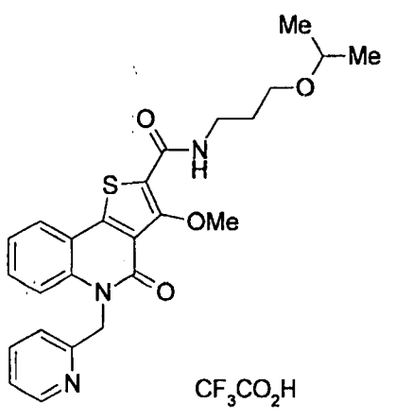
LC/MS 530 (M+H).

[1303]

Example 192

Production of 3-methoxy-N-[3-(1-methylethoxy)propyl]-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1304]



[1305]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 3-

(1-methylethoxy)propan-1-amine.

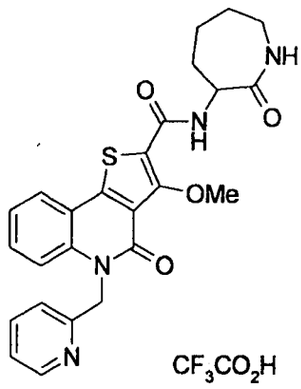
LC/MS 466 (M+H).

[1306]

Example 193

Production of 3-methoxy-4-oxo-N-(2-oxoazepan-3-yl)-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1307]



[1308]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 3-aminoazepan-2-one.

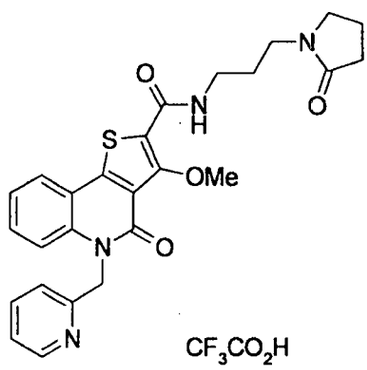
LC/MS 477 (M+H).

[1309]

Example 194

Production of 3-methoxy-4-oxo-N-[3-(2-oxopyrrolidin-1-yl)propyl]-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1310]



[1311]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 1-(3-aminopropyl)pyrrolidin-2-one.

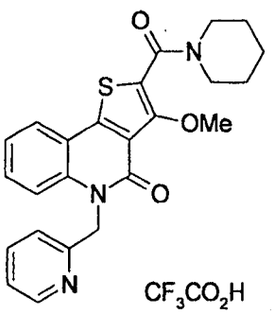
LC/MS 491 (M+H).

[1312]

Example 195

Production of 3-methoxy-2-(piperidin-1-ylcarbonyl)-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1313]



[1314]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and piperidine.

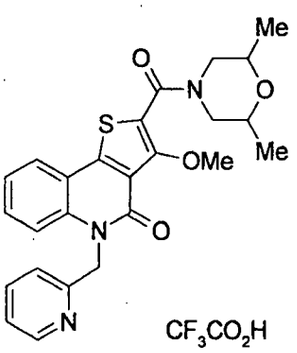
LC/MS 434 (M+H).

[1315]

Example 196

Production of 2-[(2,6-dimethylmorpholin-4-yl)carbonyl]-3-methoxy-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1316]



[1317]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 2,6-dimethylmorpholine.

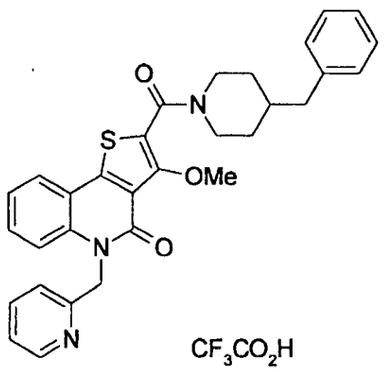
LC/MS 464 (M+H).

[1318]

Example 197

Production of 2-[(4-benzylpiperidin-1-yl)carbonyl]-3-methoxy-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1319]



[1320]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 4-benzylpiperidine.

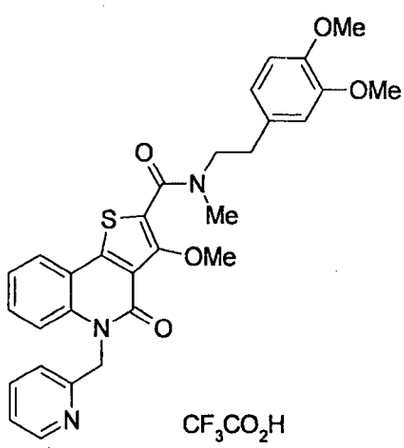
LC/MS 524 (M+H).

[1321]

Example 198

Production of N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-N-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1322]



[1323]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 2-(3,4-dimethoxyphenyl)-N-methylethanamine.

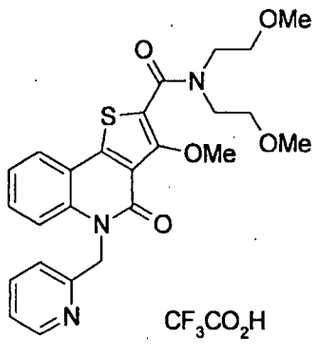
LC/MS 544 (M+H).

[1324]

Example 199

Production of 3-methoxy-N,N-bis(2-methoxyethyl)-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1325]



[1326]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and 2-methoxy-N-(2-methoxyethyl)ethanamine.

LC/MS 482 (M+H).

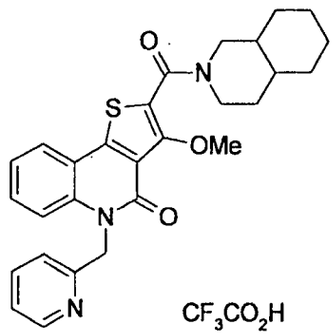
[1327]

Example 200

Production of 3-methoxy-2-(octahydroisoquinolin-2(1H)-

ylcarbonyl)-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1328]



[1329]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and decahydroisoquinoline.

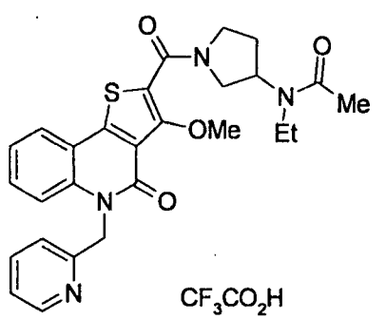
LC/MS 488 (M+H).

[1330]

Example 201

Production of N-ethyl-N-(1-{[3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}pyrrolidin-3-yl)acetamide trifluoroacetate

[1331]



[1332]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and N-ethyl-N-pyrrolidin-3-ylacetamide.

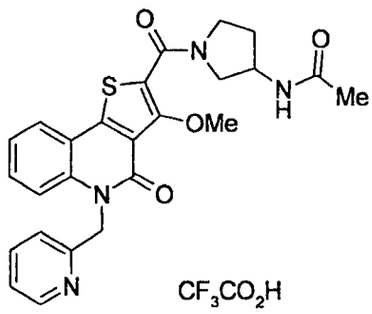
LC/MS 505 (M+H).

[1333]

Example 202

Production of N-(1-{[3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}pyrrolidin-3-yl)acetamide trifluoroacetate

[1334]



[1335]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and N-pyrrolidin-3-ylacetamide.

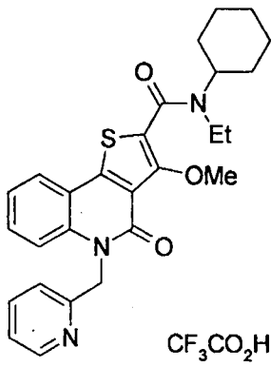
LC/MS 477 (M+H).

[1336]

Example 203

Production of N-cyclohexyl-N-ethyl-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1337]



[1338]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 19 and N-ethylcyclohexanamine.

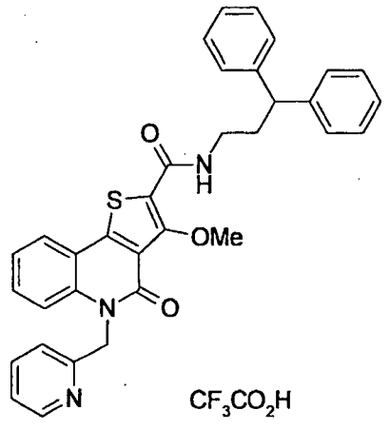
LC/MS 476 (M+H).

[1339]

Example 204

Production of N-(3,3-diphenylpropyl)-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1340]



[1341]

In the same manner as in Example 160, the title compound was obtained from the compound of Reference Example 19 and 3,3-diphenylpropan-1-amine.

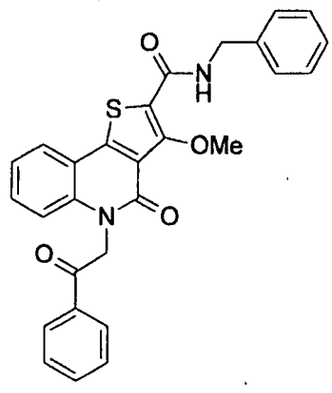
LC/MS 560 (M+H).

[1342]

Example 205

Production of N-benzyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1343]



[1344]

In the same manner as in Example 1, the title compound

was obtained from the compound of Reference Example 7 and 1-phenylmethanamine.

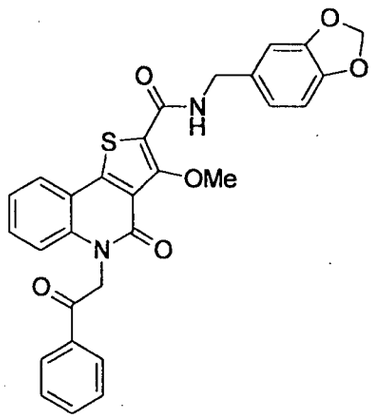
LC/MS 483 (M+H).

[1345]

Example 206

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1346]



[1347]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 1-(1,3-benzodioxol-5-yl)methanamine.

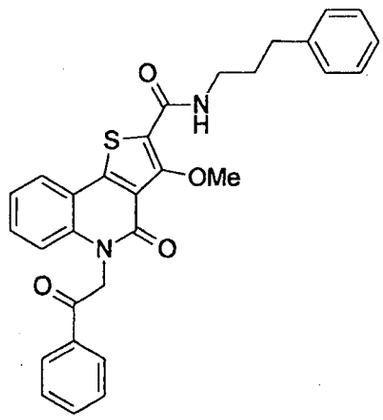
LC/MS 527 (M+H).

[1348]

Example 207

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(3-phenylpropyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1349]



[1350]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 3-phenylpropan-1-amine.

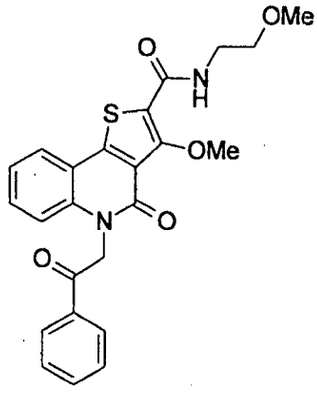
LC/MS 511 (M+H).

[1351]

Example 208

Production of 3-methoxy-N-(2-methoxyethyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1352]



[1353]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 2-methoxyethanamine.

LC/MS 451 (M+H).

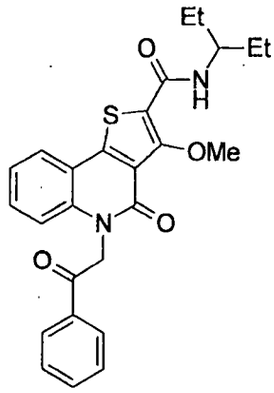
[1354]

Example 209

Production of N-(1-ethylpropyl)-3-methoxy-4-oxo-5-(2-oxo-2-

phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1355]



[1356]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and pentan-3-amine.

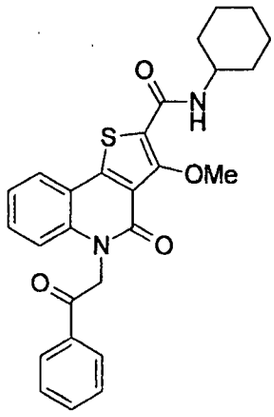
LC/MS 463 (M+H).

[1357]

Example 210

Production of N-cyclohexyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1358]



[1359]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and cyclohexanamine.

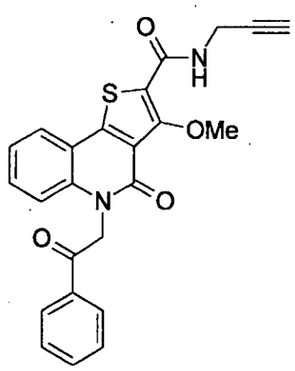
LC/MS 475 (M+H).

[1360]

Example 211

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-prop-2-yn-1-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1361]



[1362]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and prop-2-yn-1-amine.

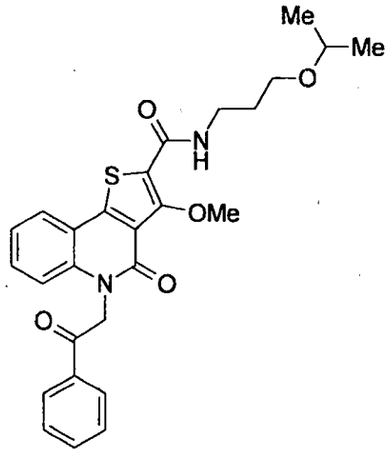
LC/MS 431 (M+H).

[1363]

Example 212

Production of 3-methoxy-N-[3-(1-methylethoxy)propyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1364]



[1365]

In the same manner as in Example 1, the title compound

was obtained from the compound of Reference Example 7 and 3-(1-methylethoxy)propan-1-amine.

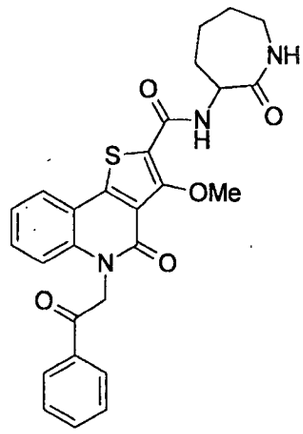
LC/MS 493 (M+H).

[1366]

Example 213

Production of 3-methoxy-4-oxo-N-(2-oxoazepan-3-yl)-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1367]



[1368]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 3-aminoazepan-2-one.

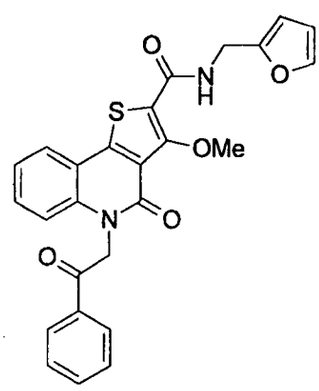
LC/MS 504 (M+H).

[1369]

Example 214

Production of N-(furan-2-ylmethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1370]



[1371]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 1-furan-2-ylmethanamine.

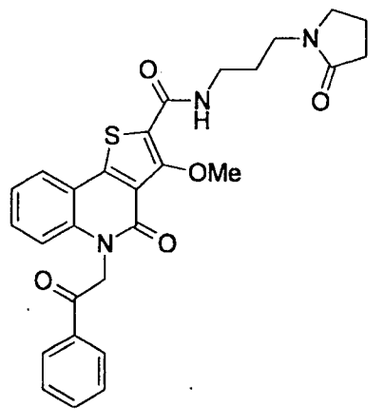
LC/MS 473 (M+H).

[1372]

Example 215

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-[3-(2-oxopyrrolidin-1-yl)propyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1373]



[1374]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 1-(3-aminopropyl)pyrrolidin-2-one.

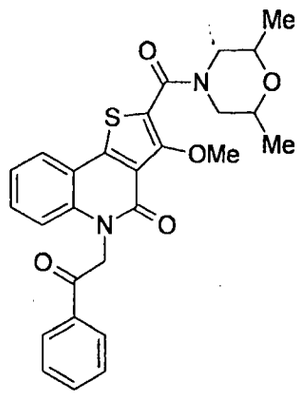
LC/MS 518 (M+H).

[1375]

Example 216

Production of 2-[(2,6-dimethylmorpholin-4-yl)carbonyl]-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one

[1376]



[1377]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 2,6-dimethylmorpholine.

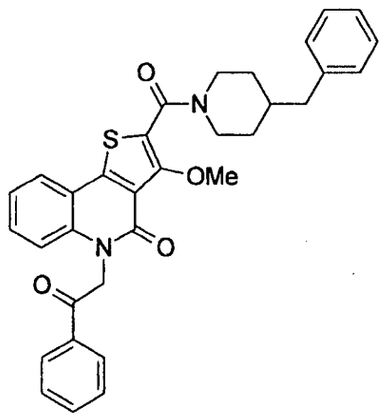
LC/MS 491 (M+H).

[1378]

Example 217

Production of 2-[(4-benzylpiperidin-1-yl)carbonyl]-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one

[1379]



[1380]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 4-benzylpiperidine.

LC/MS 551 (M+H).

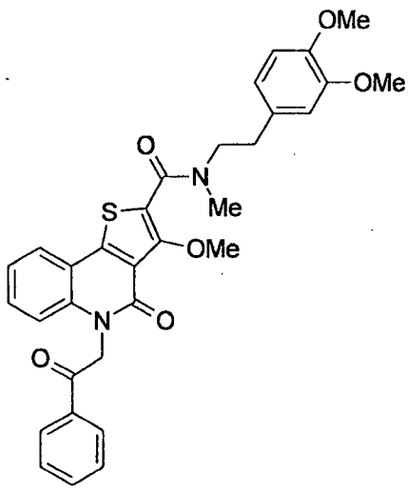
[1381]

Example 218

Production of N-[2-(3,4-dimethoxyphenyl)ethyl]-3-methoxy-N-

methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1382]



[1383]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 2-(3,4-dimethoxyphenyl)-N-methylethanamine.

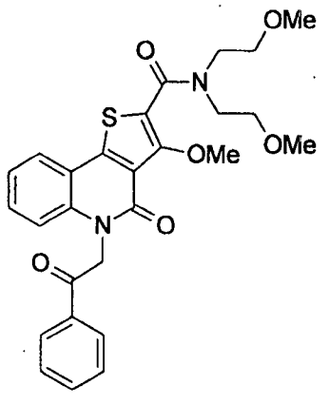
LC/MS 571 (M+H).

[1384]

Example 219

Production of 3-methoxy-N,N-bis(2-methoxyethyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1385]



[1386]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 2-

methoxy-N-(2-methoxyethyl)ethanamine.

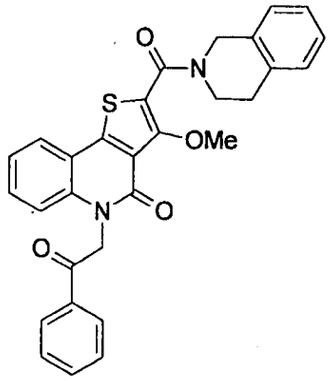
LC/MS 509 (M+H).

[1387]

Example 220

Production of 2-(3,4-dihydroisoquinolin-2(1H)-ylcarbonyl)-3-methoxy-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one

[1388]



[1389]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and 1,2,3,4-tetrahydroisoquinoline.

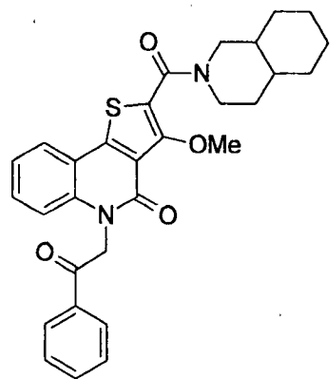
LC/MS 509 (M+H).

[1390]

Example 221

Production of 3-methoxy-2-(octahydroisoquinolin-2(1H)-ylcarbonyl)-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one

[1391]



[1392]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and decahydroisoquinoline.

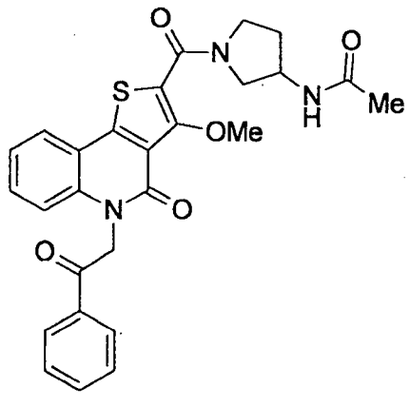
LC/MS 515 (M+H).

[1393]

Example 222

Production of N-(1-{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}pyrrolidin-3-yl)acetamide

[1394]



[1395]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and N-pyrrolidin-3-ylacetamide.

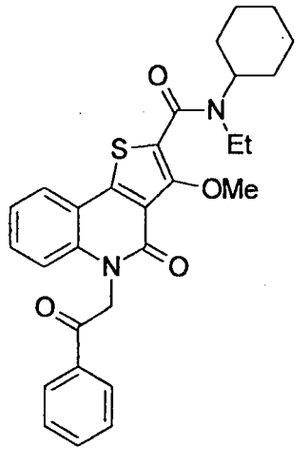
LC/MS 504 (M+H).

[1396]

Example 223

Production of N-cyclohexyl-N-ethyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1397]



[1398]

In the same manner as in Example 1, the title compound was obtained from the compound of Reference Example 7 and N-ethylcyclohexanamine.

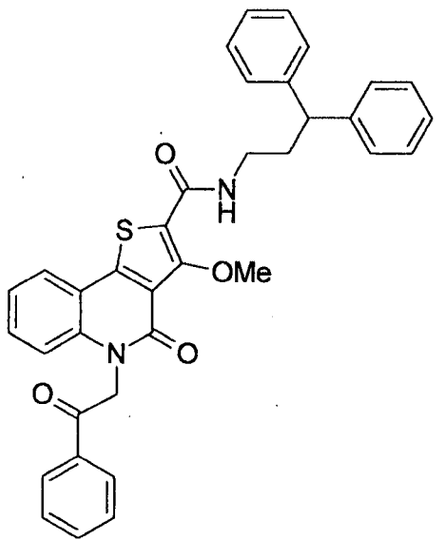
LC/MS 503 (M+H).

[1399]

Example 224

Production of N-(3,3-diphenylpropyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1400]



[1401]

In the same manner as in Example 160, the title compound was obtained from the compound of Reference Example 7 and 3,3-

diphenylpropan-1-amine.

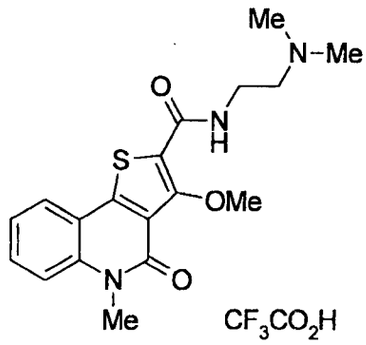
LC/MS 587 (M+H).

[1402]

Example 225

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1403]



[1404]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and N,N-dimethylethane-1,2-diamine.

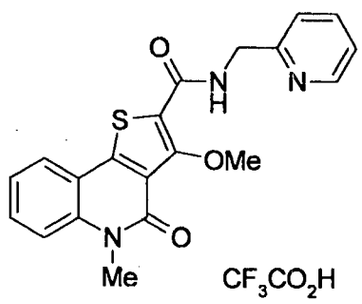
LC/MS 360 (M+H).

[1405]

Example 226

Production of 3-methoxy-5-methyl-4-oxo-N-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1406]



[1407]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 84 and 1-pyridin-2-ylmethanamine.

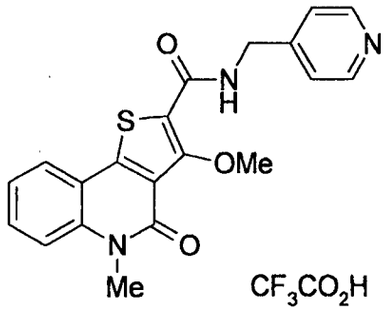
LC/MS 380 (M+H).

[1408]

Example 227

Production of 3-methoxy-5-methyl-4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1409]



[1410]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-pyridin-4-ylmethanamine.

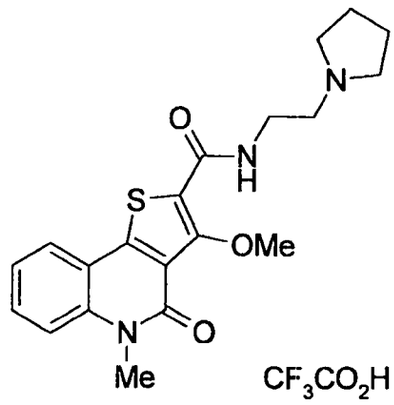
LC/MS 380 (M+H).

[1411]

Example 228

Production of 3-methoxy-5-methyl-4-oxo-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1412]



[1413]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 2-pyrrolidin-1-ylethanamine.

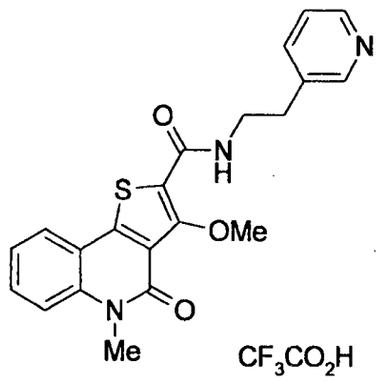
LC/MS 386 (M+H).

[1414]

Example 229

Production of 3-methoxy-5-methyl-4-oxo-N-(2-pyridin-3-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1415]



[1416]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 2-pyridin-3-ylethanamine.

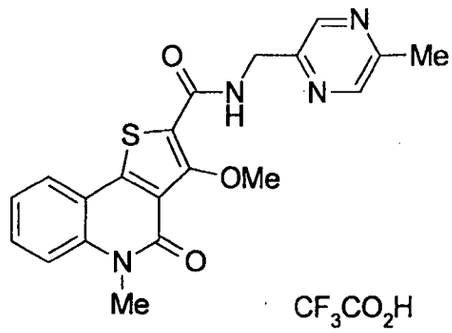
LC/MS 394 (M+H).

[1417]

Example 230

Production of 3-methoxy-5-methyl-N-[(5-methylpyrazin-2-yl)methyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1418]



[1419]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-(5-methylpyrazin-2-yl)methanamine.

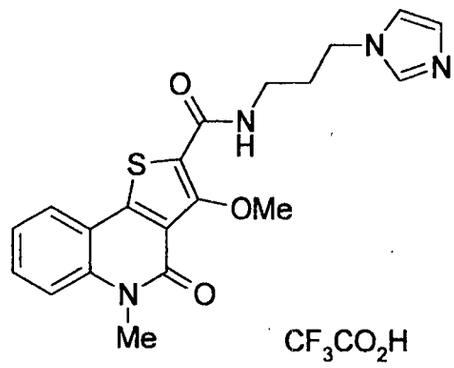
LC/MS 395 (M+H).

[1420]

Example 231

Production of N-[3-(1H-imidazol-1-yl)propyl]-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1421]



[1422]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 3-(1H-imidazol-1-yl)propan-1-amine.

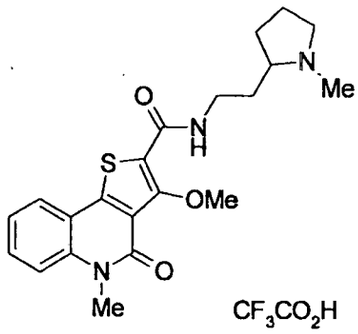
LC/MS 397 (M+H).

[1423]

Example 232

Production of 3-methoxy-5-methyl-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1424]



[1425]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 2-(1-methylpyrrolidin-2-yl)ethanamine.

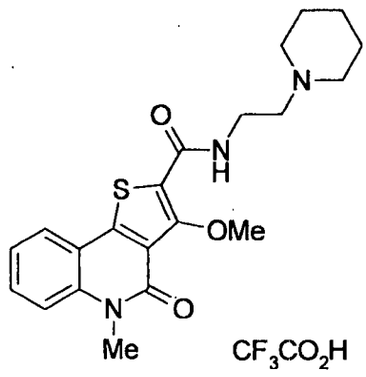
LC/MS 400 (M+H).

[1426]

Example 233

Production of 3-methoxy-5-methyl-4-oxo-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1427]



[1428]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 2-

piperidin-1-ylethanamine.

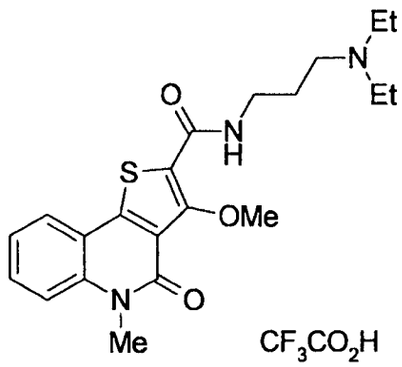
LC/MS 400 (M+H).

[1429]

Example 234

Production of N-[3-(diethylamino)propyl]-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1430]



[1431]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and N,N-diethylpropane-1,3-diamine.

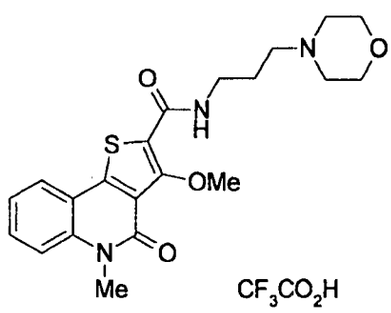
LC/MS 402 (M+H).

[1432]

Example 235

Production of 3-methoxy-5-methyl-N-(3-morpholin-4-ylpropyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1433]



[1434]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 3-morpholin-4-ylpropan-1-amine.

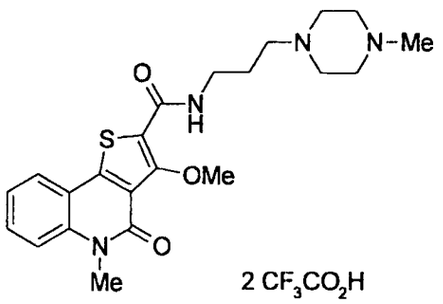
LC/MS 416 (M+H).

[1435]

Example 236

Production of 3-methoxy-5-methyl-N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1436]



[1437]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 3-(4-methylpiperazin-1-yl)propan-1-amine.

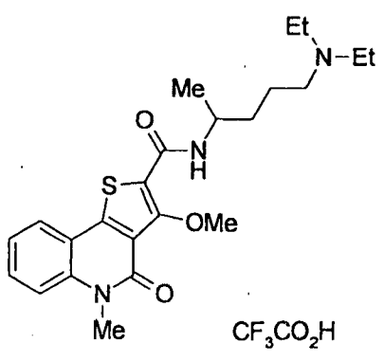
LC/MS 429 (M+H).

[1438]

Example 237

Production of N-[4-(diethylamino)-1-methylbutyl]-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1439]



[1440]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and N^1,N^1-diethylpentane-1,4-diamine.

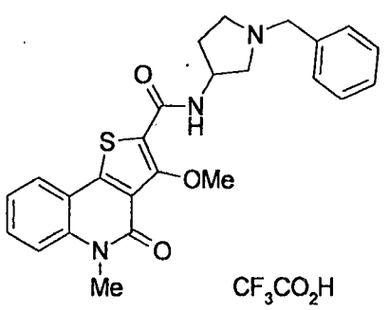
LC/MS 430 (M+H).

[1441]

Example 238

Production of N-(1-benzylpyrrolidin-3-yl)-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1442]



[1443]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-benzylpyrrolidin-3-amine.

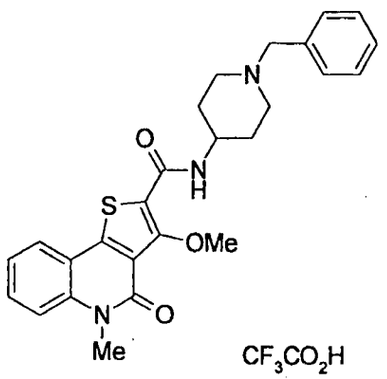
LC/MS 448 (M+H).

[1444]

Example 239

Production of N-(1-benzylpiperidin-4-yl)-3-methoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1445]



[1446]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-benzylpiperidin-4-amine.

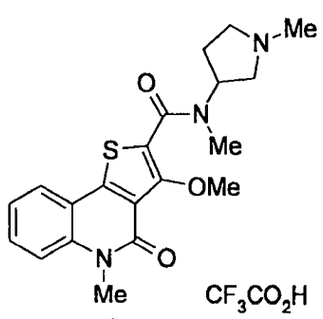
LC/MS 462 (M+H).

[1447]

Example 240

Production of 3-methoxy-N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1448]



[1449]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and N,1-dimethylpyrrolidin-3-amine.

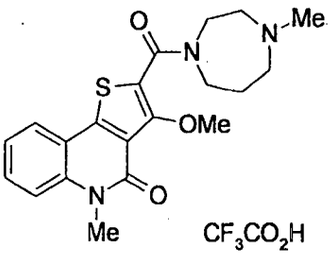
LC/MS 386 (M+H).

[1450]

Example 241

Production of 3-methoxy-5-methyl-2-[(4-methyl-1,4-diazepan-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1451]



[1452]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-methyl-1,4-diazepane.

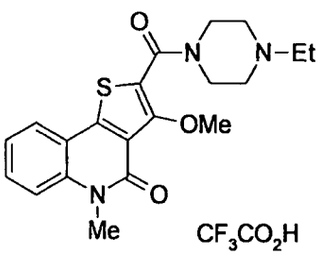
LC/MS 386 (M+H).

[1453]

Example 242

Production of 2-[(4-ethylpiperazin-1-yl)carbonyl]-3-methoxy-5-methylthieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1454]



[1455]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-ethylpiperazine.

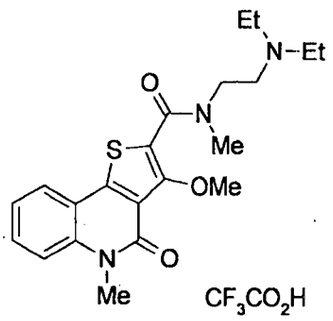
LC/MS 386 (M+H).

[1456]

Example 243

Production of N-[2-(diethylamino)ethyl]-3-methoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1457]



[1458]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and N,N-diethyl-N'-methylethane-1,2-diamine.

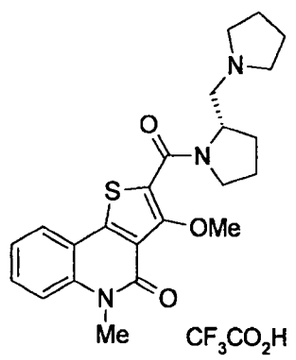
LC/MS 402 (M+H).

[1459]

Example 244

Production of 3-methoxy-5-methyl-2-{[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1460]



[1461]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-[(2S)-pyrrolidin-2-ylmethyl]pyrrolidine.

LC/MS 426 (M+H).

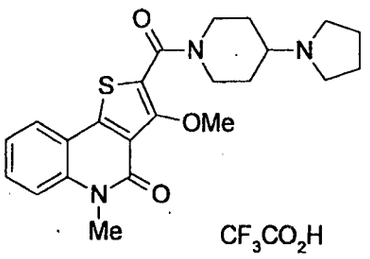
[1462]

Example 245

Production of 3-methoxy-5-methyl-2-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one

trifluoroacetate

[1463]



[1464]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 4-pyrrolidin-1-ylpiperidine.

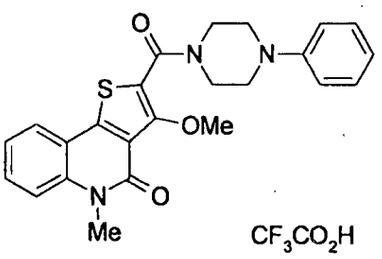
LC/MS 426 (M+H).

[1465]

Example 246

Production of 3-methoxy-5-methyl-2-[(4-phenylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1466]



[1467]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-phenylpiperazine.

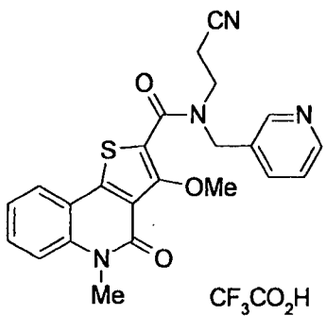
LC/MS 434 (M+H).

[1468]

Example 247

Production of N-(2-cyanoethyl)-3-methoxy-5-methyl-4-oxo-N-(pyridin-3-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1469]



[1470]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 3-[(pyridin-3-ylmethyl)amino]propanenitrile.

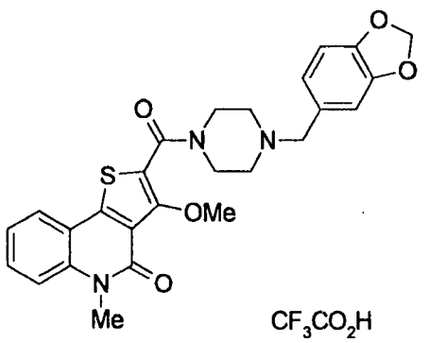
LC/MS 433 (M+H).

[1471]

Example 248

Production of 2-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}-3-methoxy-5-methylthieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1472]



[1473]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 84 and 1-(1,3-benzodioxol-5-ylmethyl)piperazine.

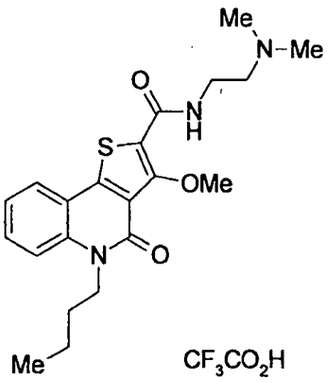
LC/MS 492 (M+H).

[1474]

Example 249

Production of 5-butyl-N-[2-(dimethylamino)ethyl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1475]



[1476]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and N,N-dimethylethane-1,2-diamine.

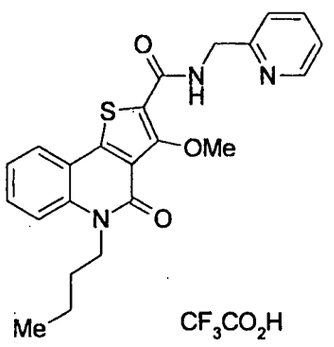
LC/MS 402 (M+H).

[1477]

Example 250

Production of 5-butyl-3-methoxy-4-oxo-N-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1478]



[1479]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-pyridin-2-ylmethanamine.

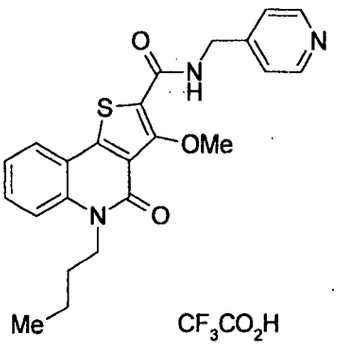
LC/MS 422 (M+H).

[1480]

Example 251

Production of 5-butyl-3-methoxy-4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1481]



[1482]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-pyridin-4-ylmethanamine.

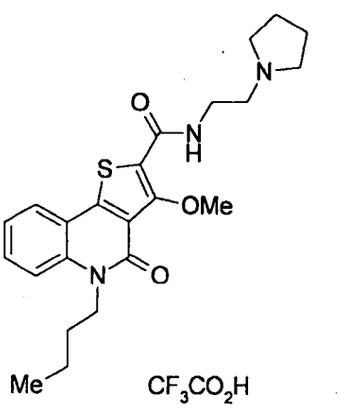
LC/MS 422 (M+H).

[1483]

Example 252

Production of 5-butyl-3-methoxy-4-oxo-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1484]



[1485]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 2-

pyrrolidin-1-ylethanamine.

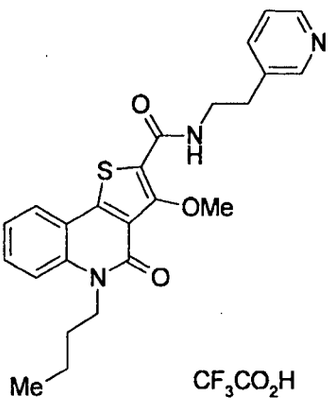
LC/MS 428 (M+H).

[1486]

Example 253

Production of 5-butyl-3-methoxy-4-oxo-N-(2-pyridin-3-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1487]



[1488]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 2-pyridin-3-ylethanamine.

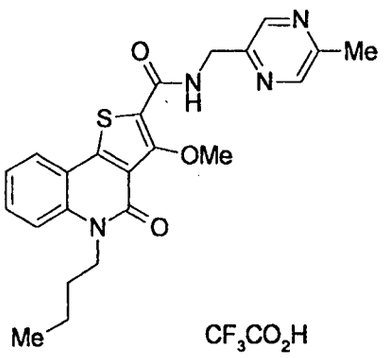
LC/MS 436 (M+H).

[1489]

Example 254

Production of 5-butyl-3-methoxy-N-[(5-methylpyrazin-2-yl)methyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1490]



[1491]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-(5-methylpyrazin-2-yl)methanamine.

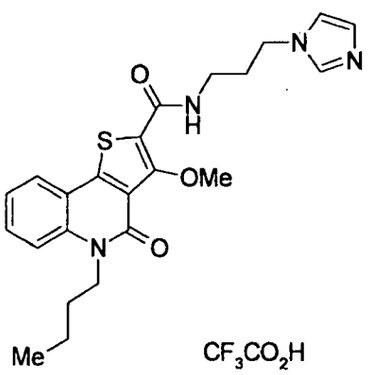
LC/MS 437 (M+H).

[1492]

Example 255

Production of 5-butyl-N-[3-(1H-imidazol-1-yl)propyl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1493]



[1494]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 3-(1H-imidazol-1-yl)propan-1-amine.

LC/MS 439 (M+H).

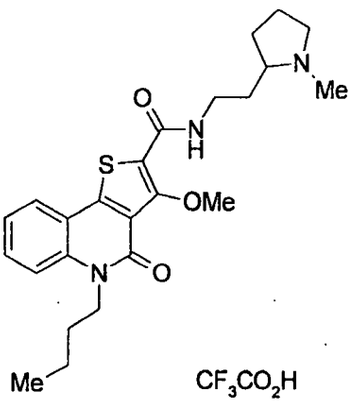
[1495]

Example 256

Production of 5-butyl-3-methoxy-N-[2-(1-methylpyrrolidin-2-

yl)ethyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1496]



[1497]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 2-(1-methylpyrrolidin-2-yl)ethanamine.

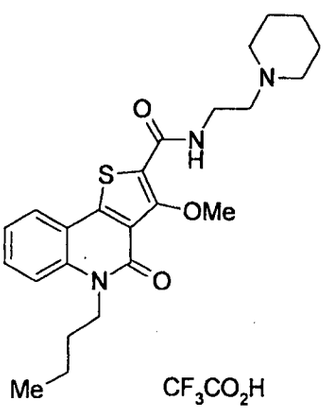
LC/MS 442 (M+H).

[1498]

Example 257

Production of 5-butyl-3-methoxy-4-oxo-N-(2-piperidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1499]



[1500]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 2-

piperidin-1-ylethanamine.

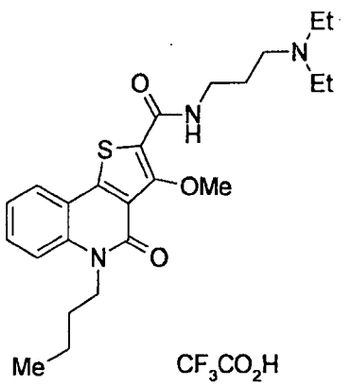
LC/MS 442 (M+H).

[1501]

Example 258

Production of 5-butyl-N-[3-(diethylamino)propyl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1502]



[1503]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and N,N-diethylpropane-1,3-diamine.

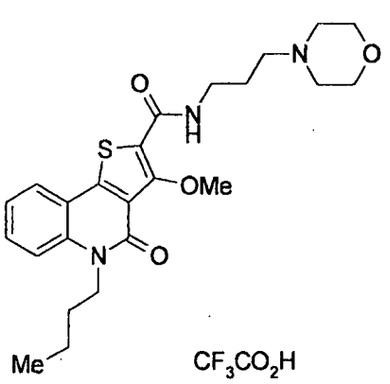
LC/MS 444 (M+H).

[1504]

Example 259

Production of 5-butyl-3-methoxy-N-(3-morpholin-4-ylpropyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1505]



[1506]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 3-morpholin-4-ylpropan-1-amine.

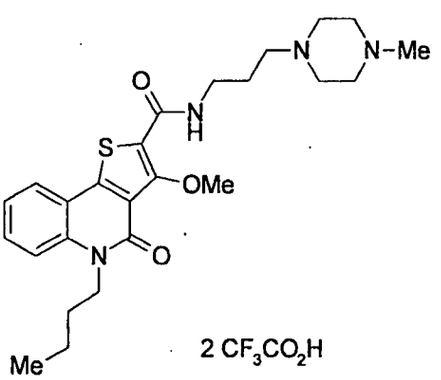
LC/MS 458 (M+H).

[1507]

Example 260

Production of 5-butyl-3-methoxy-N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1508]



[1509]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 3-(4-methylpiperazin-1-yl)propan-1-amine.

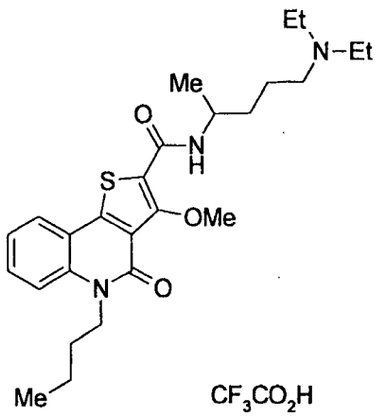
LC/MS 471 (M+H).

[1510]

Example 261

Production of 5-butyl-N-[4-(diethylamino)-1-methylbutyl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1511]



[1512]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and N^1,N^1-diethylpentane-1,4-diamine.

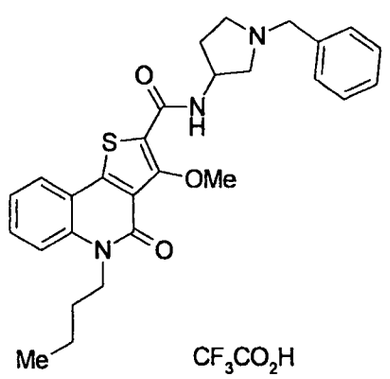
LC/MS 472 (M+H).

[1513]

Example 262

Production of N-(1-benzylpyrrolidin-3-yl)-5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1514]



[1515]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-benzylpyrrolidin-3-amine.

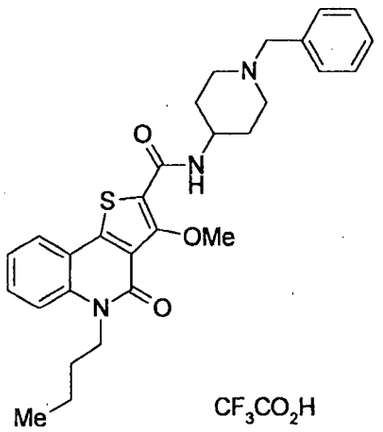
LC/MS 490 (M+H).

[1516]

Example 263

Production of N-(1-benzylpiperidin-4-yl)-5-butyl-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1517]



[1518]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-benzylpiperidin-4-amine.

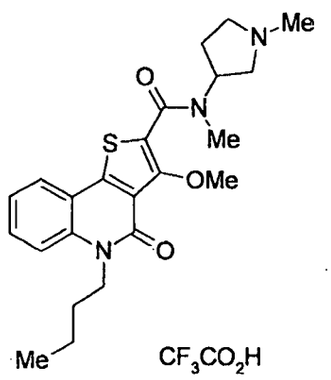
LC/MS 504 (M+H).

[1519]

Example 264

Production of 5-butyl-3-methoxy-N-methyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1520]



[1521]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and

N,1-dimethylpyrrolidin-3-amine.

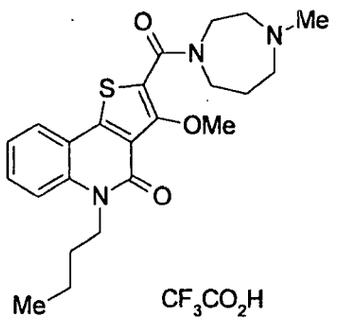
LC/MS 428 (M+H).

[1522]

Example 265

Production of 5-butyl-3-methoxy-2-[(4-methyl-1,4-diazepan-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1523]



[1524]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-methyl-1,4-diazepane.

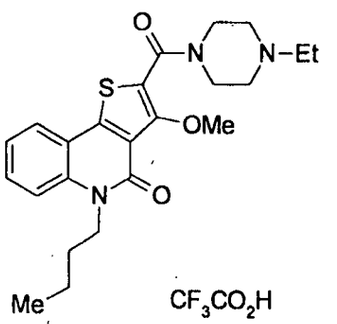
LC/MS 428 (M+H).

[1525]

Example 266

Production of 5-butyl-2-[(4-ethylpiperazin-1-yl)carbonyl]-3-methoxythieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1526]



[1527]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-ethylpiperazine.

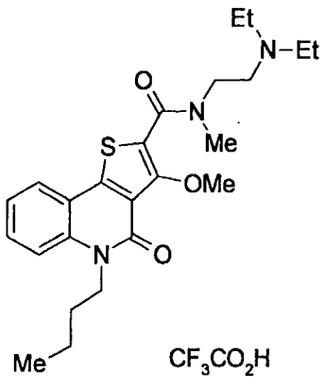
LC/MS 428 (M+H).

[1528]

Example 267

Production of 5-butyl-N-[2-(diethylamino)ethyl]-3-methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1529]



[1530]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and N,N-diethyl-N'-methylethane-1,2-diamine.

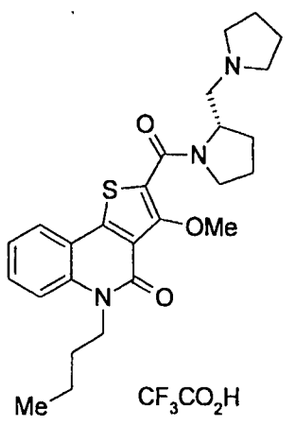
LC/MS 444 (M+H).

[1531]

Example 268

Production of 5-butyl-3-methoxy-2-{[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1532]



[1533]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-[(2S)-pyrrolidin-2-ylmethyl]pyrrolidine.

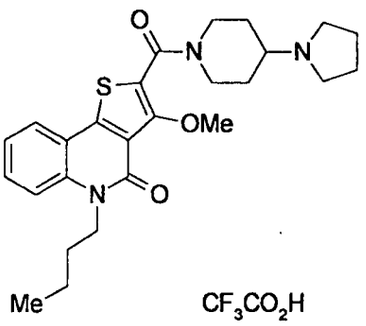
LC/MS 468 (M+H).

[1534]

Example 269

Production of 5-butyl-3-methoxy-2-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1535]



[1536]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 4-pyrrolidin-1-ylpiperidine.

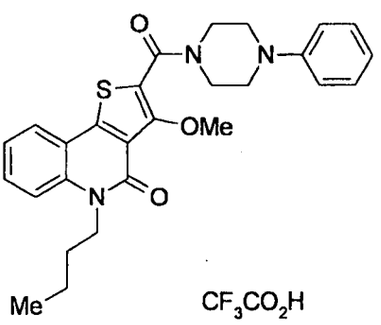
LC/MS 468 (M+H).

[1537]

Example 270

Production of 5-butyl-3-methoxy-2-[(4-phenylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1538]



[1539]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-phenylpiperazine.

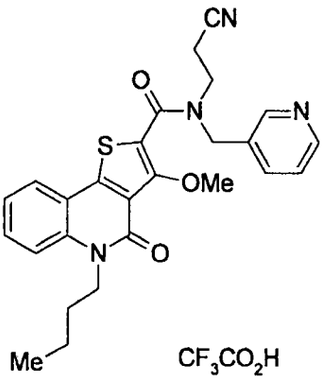
LC/MS 476 (M+H).

[1540]

Example 271

Production of 5-butyl-N-(2-cyanoethyl)-3-methoxy-4-oxo-N-(pyridin-3-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1541]



[1542]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 3-[(pyridin-3-ylmethyl)amino]propanenitrile.

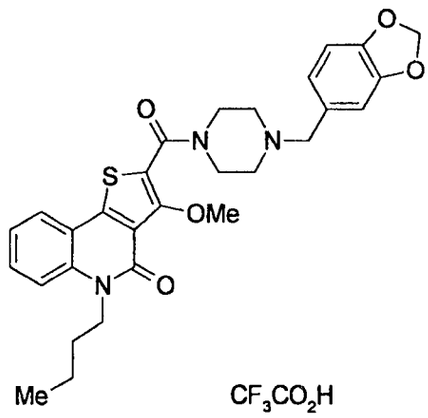
LC/MS 475 (M+H).

[1543]

Example 272

Production of 2-{[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]carbonyl}-5-butyl-3-methoxythieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1544]



[1545]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 103 and 1-(1,3-benzodioxol-5-ylmethyl)piperazine.

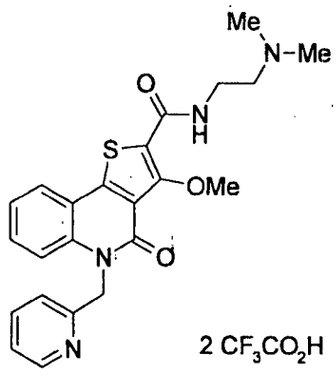
LC/MS 534 (M+H).

[1546]

Example 273

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1547]



[1548]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and N,N-dimethylethane-1,2-diamine.

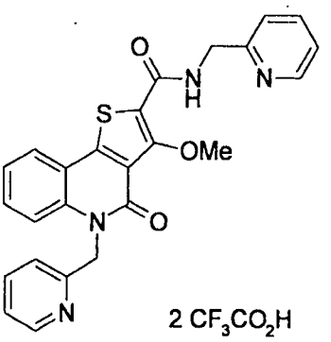
LC/MS 437 (M+H).

[1549]

Example 274

Production of 3-methoxy-4-oxo-N,5-bis(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1550]



[1551]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-pyridin-2-ylmethanamine.

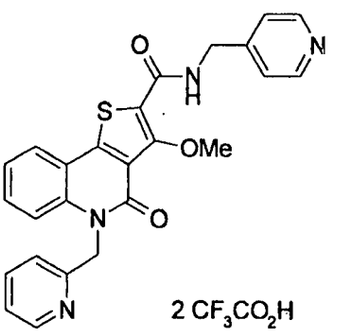
LC/MS 457 (M+H).

[1552]

Example 275

Production of 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-N-(pyridin-4-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1553]



[1554]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-pyridin-4-ylmethanamine.

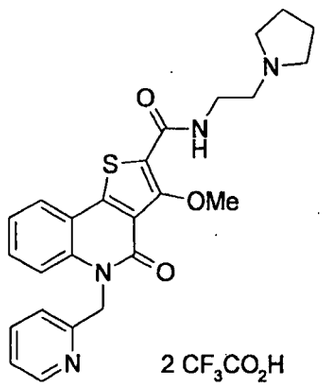
LC/MS 457 (M+H).

[1555]

Example 276

Production of 3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1556]



[1557]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 2-pyrrolidin-1-ylethanamine.

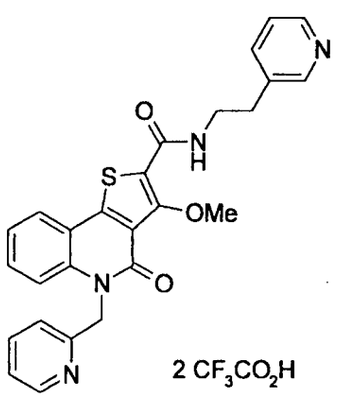
LC/MS 463 (M+H).

[1558]

Example 277

Production of 3-methoxy-4-oxo-N-(2-pyridin-3-ylethyl)-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1559]



[1560]

In the same manner as in Example 3, the title compound

was obtained from the compound of Reference Example 19 and 2-pyridin-3-ylethanamine.

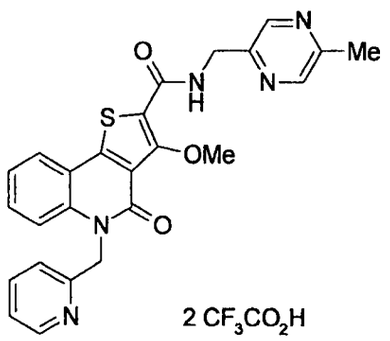
LC/MS 471 (M+H).

[1561]

Example 278

Production of 3-methoxy-N-[(5-methylpyrazin-2-yl)methyl]-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1562]



[1563]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-(5-methylpyrazin-2-yl)methanamine.

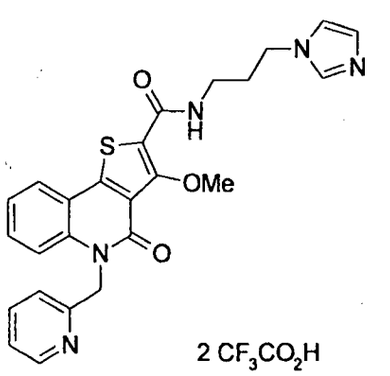
LC/MS 472 (M+H).

[1564]

Example 279

Production of N-[3-(1H-imidazol-1-yl)propyl]-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1565]



[1566]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 3-(1H-imidazol-1-yl)propan-1-amine.

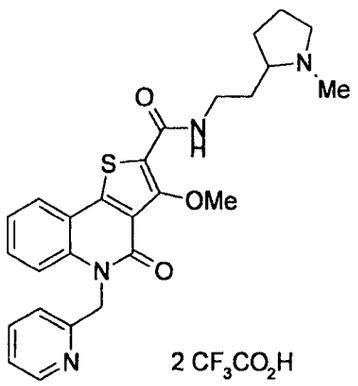
LC/MS 474 (M+H).

[1567]

Example 280

Production of 3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1568]



[1569]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 2-(1-methylpyrrolidin-2-yl)ethanamine.

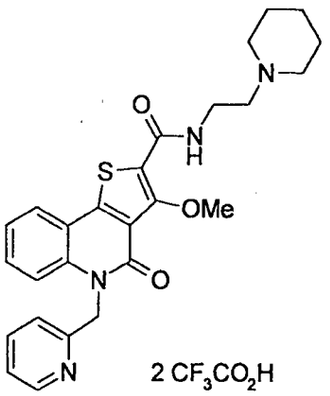
LC/MS 477 (M+H).

[1570]

Example 281

Production of 3-methoxy-4-oxo-N-(2-piperidin-1-ylethyl)-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1571]



[1572]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 2-piperidin-1-ylethanamine.

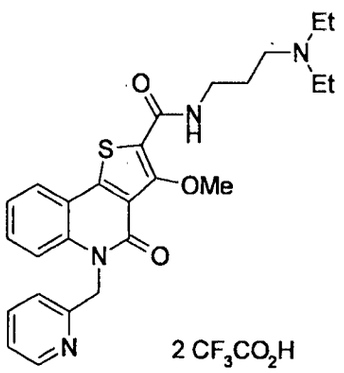
LC/MS 477 (M+H).

[1573]

Example 282

Production of N-[3-(diethylamino)propyl]-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1574]



[1575]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and N,N-diethylpropane-1,3-diamine.

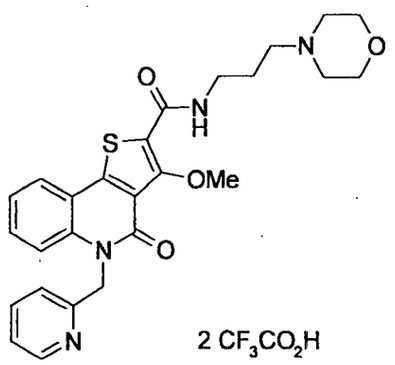
LC/MS 479 (M+H).

[1576]

Example 283

Production of 3-methoxy-N-(3-morpholin-4-ylpropyl)-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1577]



[1578]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 3-morpholin-4-ylpropan-1-amine.

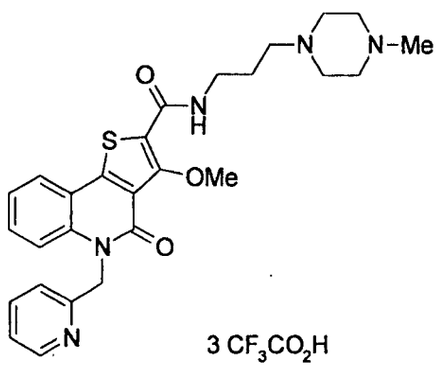
LC/MS 493 (M+H).

[1579]

Example 284

Production of 3-methoxy-N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide tritrifluoroacetate

[1580]



[1581]

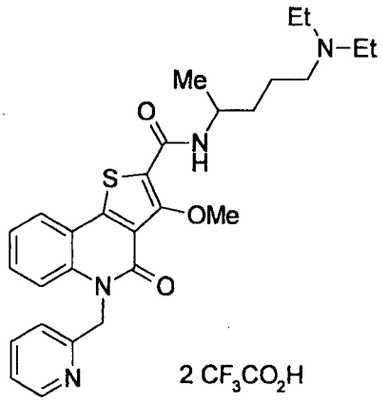
In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 3-(4-methylpiperazin-1-yl)propan-1-amine.

[1582]

Example 285

Production of N-[4-(diethylamino)-1-methylbutyl]-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1583]



[1584]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and N^1,N^1-diethylpentane-1,4-diamine.

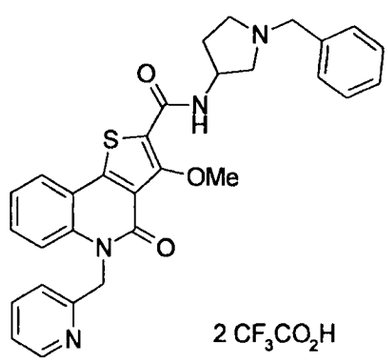
LC/MS 507 (M+H).

[1585]

Example 286

Production of N-(1-benzylpyrrolidin-3-yl)-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1586]



[1587]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-benzylpyrrolidin-3-amine.

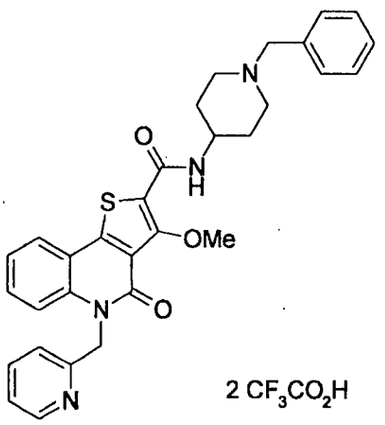
LC/MS 525 (M+H).

[1588]

Example 287

Production of N-(1-benzylpiperidin-4-yl)-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1589]



[1590]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-benzylpiperidin-4-amine.

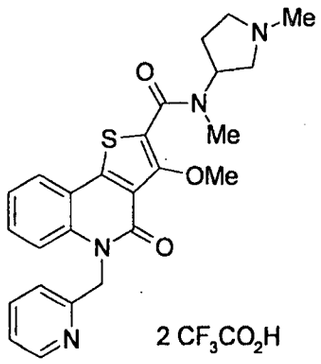
LC/MS 539 (M+H).

[1591]

Example 288

Production of 3-methoxy-N-methyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1592]



[1593]

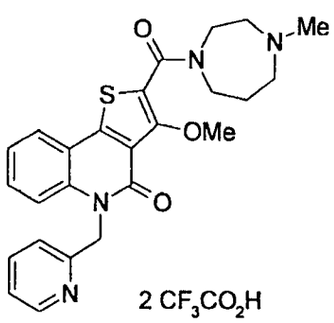
In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and N,1-dimethylpyrrolidin-3-amine.

[1594]

Example 289

Production of 3-methoxy-2-[(4-methyl-1,4-diazepan-1-yl)carbonyl]-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1595]



[1596]

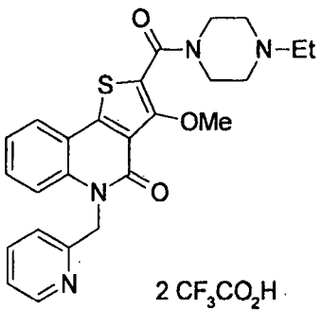
In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-methyl-1,4-diazepane.

[1597]

Example 290

Production of 2-[(4-ethylpiperazin-1-yl)carbonyl]-3-methoxy-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1598]



[1599]

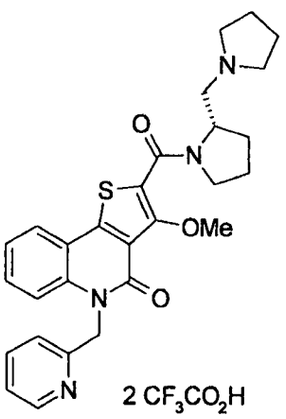
In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-ethylpiperazine.

[1600]

Example 291

Production of 3-methoxy-5-(pyridin-2-ylmethyl)-2-{[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]carbonyl}thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1601]



[1602]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-[(2S)-pyrrolidin-2-ylmethyl]pyrrolidine.

LC/MS 503 (M+H).

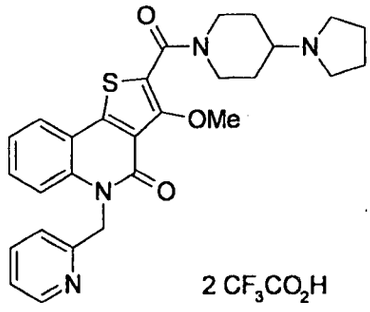
[1603]

Example 292

Production of 3-methoxy-5-(pyridin-2-ylmethyl)-2-[(4-pyrrolidin-1-ylpiperidin-1-yl)carbonyl]thieno[3,2-c]quinolin-

4(5H)-one ditrifluoroacetate

[1604]



[1605]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 4-pyrrolidin-1-ylpiperidine.

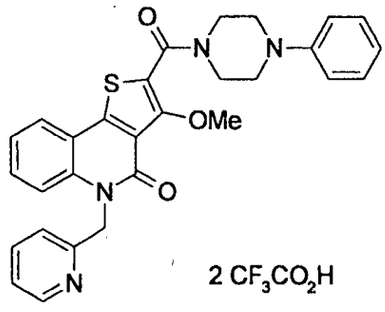
LC/MS 503 (M+H).

[1606]

Example 293

Production of 3-methoxy-2-[(4-phenylpiperazin-1-yl)carbonyl]-5-(pyridin-2-ylmethyl)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1607]



[1608]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 1-phenylpiperazine.

LC/MS 511 (M+H).

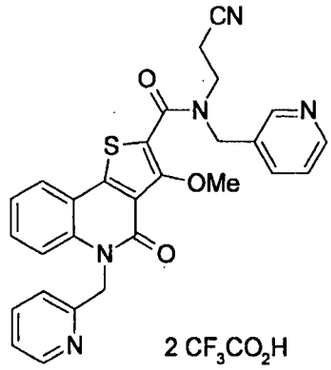
[1609]

Example 294

Production of N-(2-cyanoethyl)-3-methoxy-4-oxo-5-(pyridin-2-

ylmethyl)-N-(pyridin-3-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1610]



[1611]

In the same manner as in Example 3, the title compound was obtained from the compound of Reference Example 19 and 3-[(pyridin-3-ylmethyl)amino]propanenitrile.

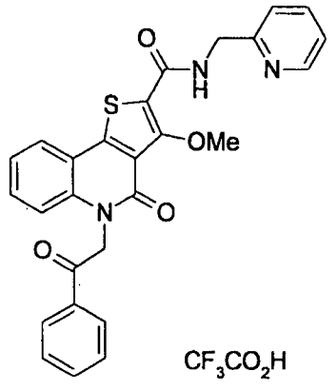
LC/MS 510 (M+H).

[1612]

Example 295

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1613]



[1614]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-pyridin-2-ylmethanamine.

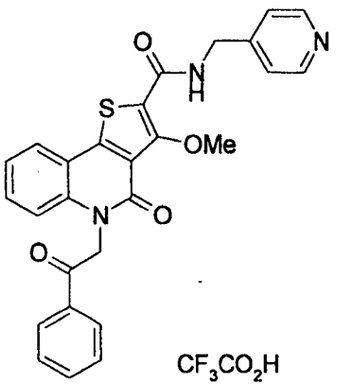
LC/MS 484 (M+H).

[1615]

Example 296

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyridin-4-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1616]



[1617]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-pyridin-4-ylmethanamine.

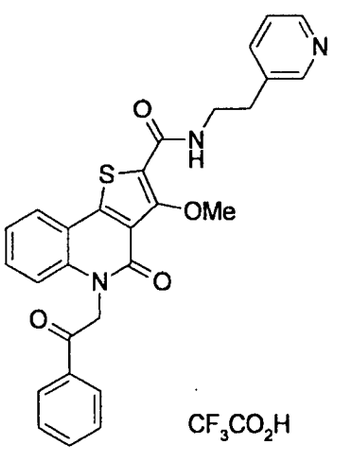
LC/MS 484 (M+H).

[1618]

Example 297

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2-pyridin-3-ylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1619]



[1620]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 2-pyridin-3-ylethanamine.

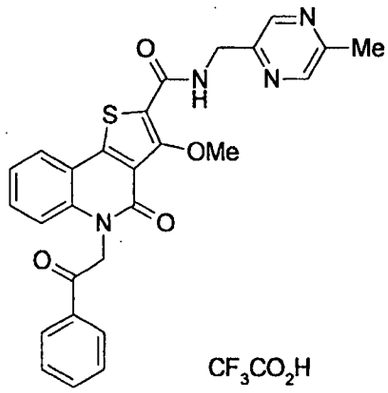
LC/MS 498 (M+H).

[1621]

Example 298

Production of 3-methoxy-N-[(5-methylpyrazin-2-yl)methyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1622]



[1623]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-(5-methylpyrazin-2-yl)methanamine.

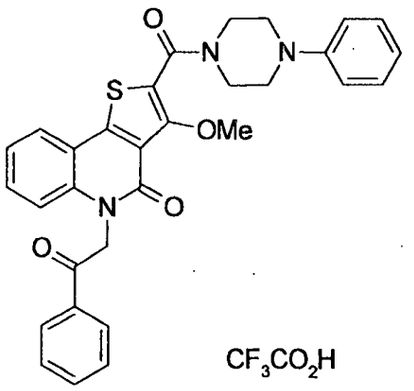
LC/MS 499 (M+H).

[1624]

Example 299

Production of 3-methoxy-5-(2-oxo-2-phenylethyl)-2-[(4-phenylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1625]



[1626]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 7 and 1-phenylpiperazine.

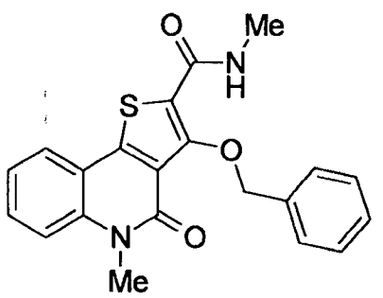
LC/MS 538 (M+H).

[1627]

Example 300

Production of 3-(benzyloxy)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1628]



[1629]

To a solution (0.15 M, 0.40 mL, 60 μmol) of the compound of Reference Example 91 in DMF were added a solution (0.66 M, 0.10 mL, 66 μmol) of methanamine (2.0 M THF solution) in DMF and a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was agitated at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, the organic layer was filtered through a Teflon (registered trade mark) filter to separate the aqueous layer, and the filtrate was concentrated under

reduced pressure. The residue was purified by preparative HPLC to give the title compound (12.4 mg, 55%).

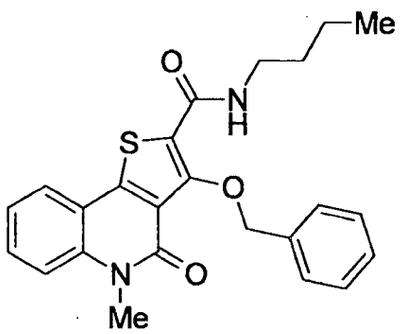
LC/MS 379 (M+H).

[1630]

Example 301

Production of 3-(benzyloxy)-N-butyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1631]



[1632]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and butan-1-amine.

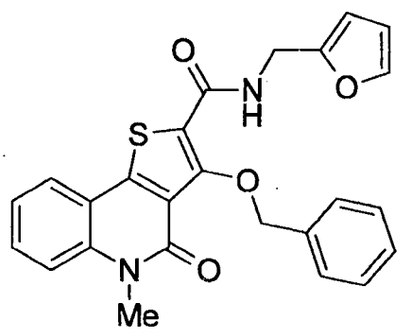
LC/MS 421 (M+H).

[1633]

Example 302

Production of 3-(benzyloxy)-N-(furan-2-ylmethyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1634]



[1635]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-

furan-2-ylmethanamine.

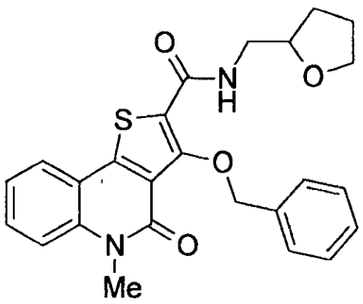
LC/MS 445 (M+H).

[1636]

Example 303

Production of 3-(benzyloxy)-5-methyl-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1637]



[1638]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-(tetrahydrofuran-2-yl)methanamine.

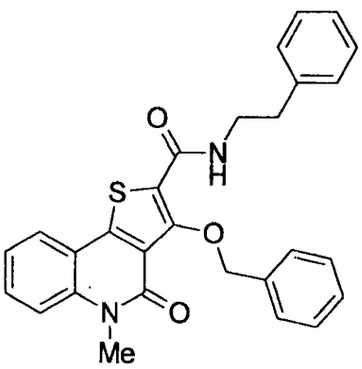
LC/MS 449 (M+H).

[1639]

Example 304

Production of 3-(benzyloxy)-5-methyl-4-oxo-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1640]



[1641]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 2-

phenylethanamine.

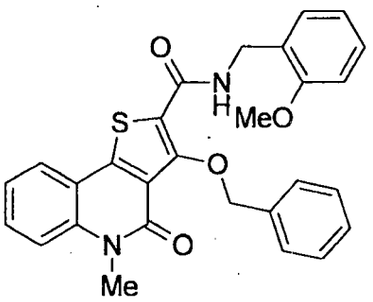
LC/MS 469 (M+H).

[1642]

Example 305

Production of 3-(benzyloxy)-N-(2-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1643]



[1644]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-(2-methoxyphenyl)methanamine.

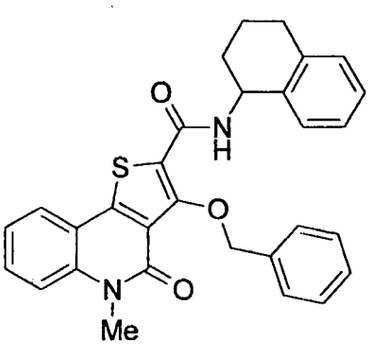
LC/MS 485 (M+H).

[1645]

Example 306

Production of 3-(benzyloxy)-5-methyl-4-oxo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1646]



[1647]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 91 and 1,2,3,4-tetrahydronaphthalen-1-amine.

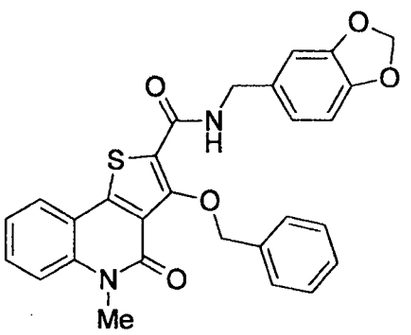
LC/MS 495 (M+H).

[1648]

Example 307

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-(benzyloxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1649]



[1650]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-(1,3-benzodioxol-5-yl)methanamine.

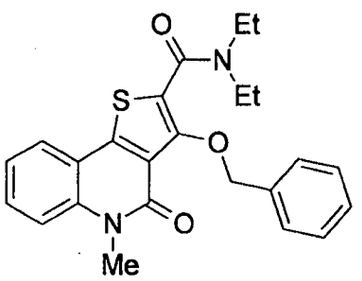
LC/MS 499 (M+H).

[1651]

Example 308

Production of 3-(benzyloxy)-N,N-diethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1652]



[1653]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N-ethylethanamine.

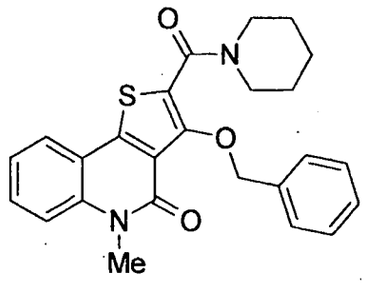
LC/MS 421 (M+H).

[1654]

Example 309

Production of 3-(benzyloxy)-5-methyl-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1655]



[1656]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and piperidine.

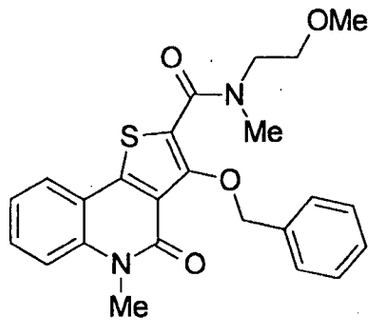
LC/MS 433 (M+H).

[1657]

Example 310

Production of 3-(benzyloxy)-N-(2-methoxyethyl)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1658]



[1659]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 2-methoxy-N-methylethanamine.

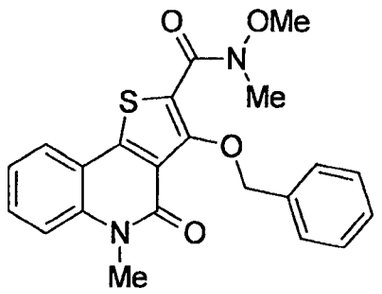
LC/MS 437 (M+H).

[1660]

Example 311

Production of 3-(benzyloxy)-N-methoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1661]



[1662]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 91 and N-methoxymethanamine hydrochloride.

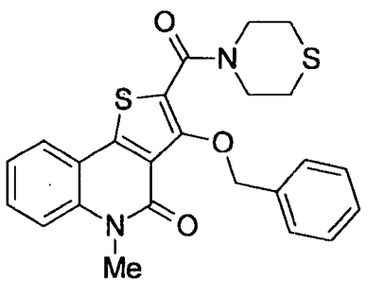
LC/MS 409 (M+H).

[1663]

Example 312

Production of 3-(benzyloxy)-5-methyl-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1664]



[1665]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and thiomorpholine.

LC/MS 451 (M+H).

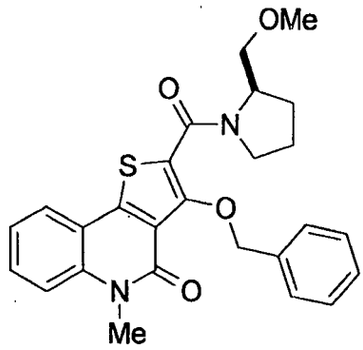
[1666]

Example 313

Production of 3-(benzyloxy)-2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylthieno[3,2-

c]quinolin-4(5H)-one

[1667]



[1668]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and (2R)-2-(methoxymethyl)pyrrolidine.

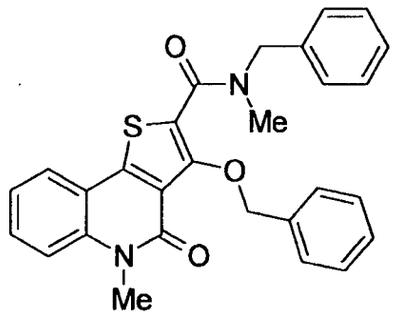
LC/MS 463 (M+H).

[1669]

Example 314

Production of N-benzyl-3-(benzyloxy)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1670]



[1671]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N-methyl-1-phenylmethanamine.

LC/MS 469 (M+H).

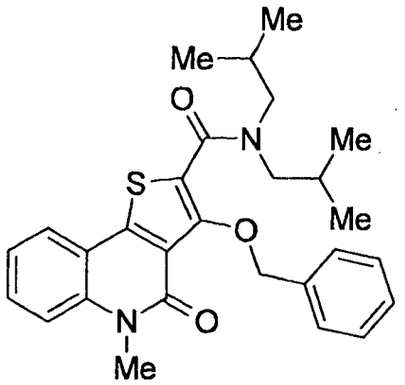
[1672]

Example 315

Production of 3-(benzyloxy)-5-methyl-N,N-bis(2-methylpropyl)-

4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1673]



[1674]

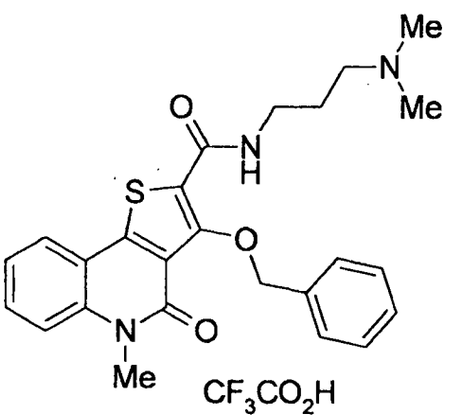
In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 91 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

LC/MS 477 (M+H).

Example 316

Production of 3-(benzyloxy)-N-[3-(dimethylamino)propyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1675]



[1676]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N,N-dimethylpropane-1,3-diamine.

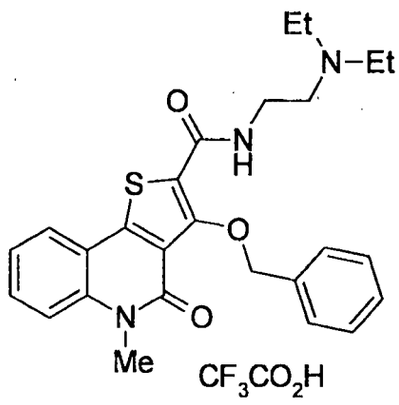
LC/MS 450 (M+H).

[1677]

Example 317

Production of 3-(benzyloxy)-N-[2-(diethylamino)ethyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1678]



[1679]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N,N-diethylethane-1,2-diamine.

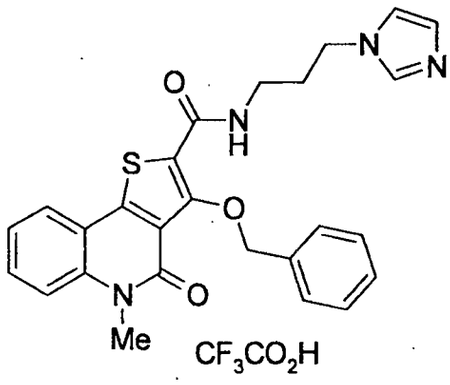
LC/MS 464 (M+H).

[1680]

Example 318

Production of 3-(benzyloxy)-N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1681]



[1682]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 91 and 3-(1H-imidazol-1-yl)propan-1-amine.

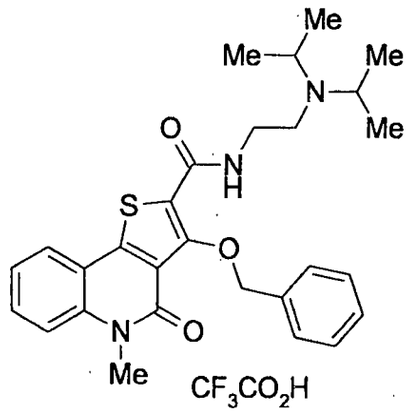
LC/MS 473 (M+H).

[1683]

Example 319

Production of 3-(benzyloxy)-N-{2-[bis(1-methylethyl)amino]ethyl}-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1684]



[1685]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

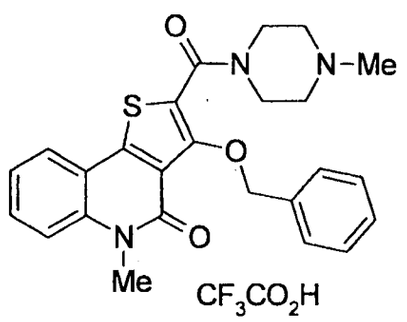
LC/MS 492 (M+H).

[1686]

Example 320

Production of 3-(benzyloxy)-5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1687]



[1688]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-methylpiperazine.

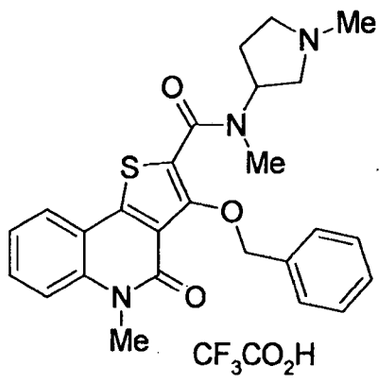
LC/MS 448 (M+H).

[1689]

Example 321

Production of 3-(benzyloxy)-N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1690]



[1691]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N,1-dimethylpyrrolidin-3-amine.

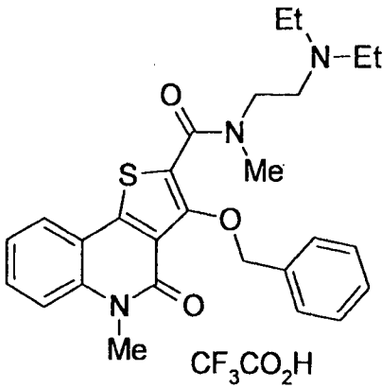
LC/MS 462 (M+H).

[1692]

Example 322

Production of 3-(benzyloxy)-N-[2-(diethylamino)ethyl]-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1693]



[1694]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and N,N-diethyl-N'-methylethane-1,2-diamine.

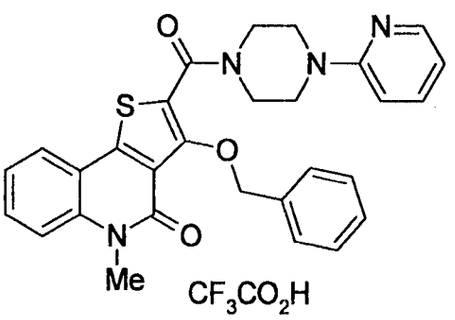
LC/MS 478 (M+H).

[1695]

Example 323

Production of 3-(benzyloxy)-5-methyl-2-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1696]



[1697]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 91 and 1-pyridin-2-ylpiperazine.

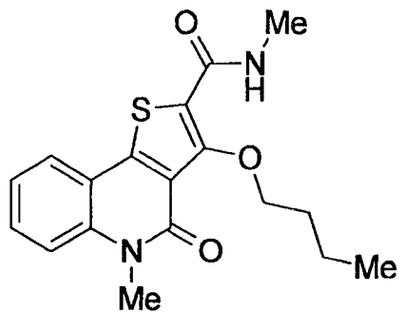
LC/MS 511 (M+H).

[1698]

Example 324

Production of 3-butoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1699]



[1700]

In the same manner as in Example 300, the title compound was obtained from the compound of Reference Example 92 and methanamine (2.0 M THF solution).

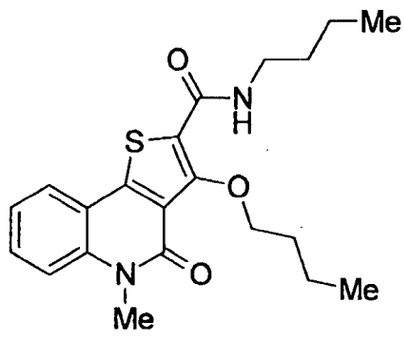
LC/MS 345 (M+H).

[1701]

Example 325

Production of 3-butoxy-N-butyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1702]



[1703]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and butan-1-amine.

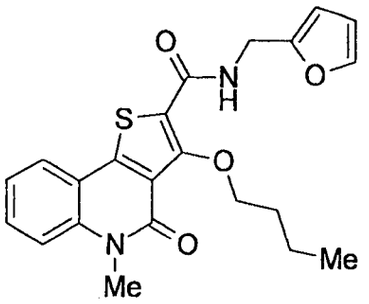
LC/MS 387 (M+H).

[1704]

Example 326

Production of 3-butoxy-N-(furan-2-ylmethyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1705]



[1706]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-furan-2-ylmethanamine.

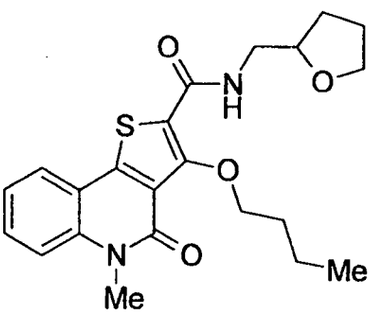
LC/MS 411 (M+H).

[1707]

Example 327

Production of 3-butoxy-5-methyl-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1708]



[1709]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-(tetrahydrofuran-2-yl)methanamine.

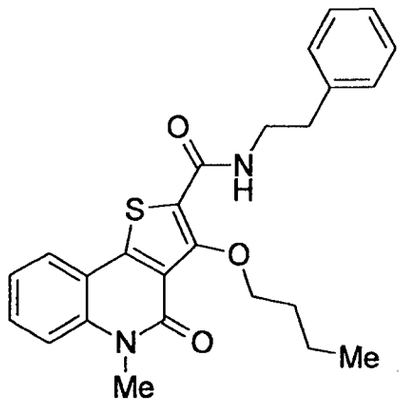
LC/MS 415 (M+H).

[1710]

Example 328

Production of 3-butoxy-5-methyl-4-oxo-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1711]



[1712]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 2-phenylethanamine.

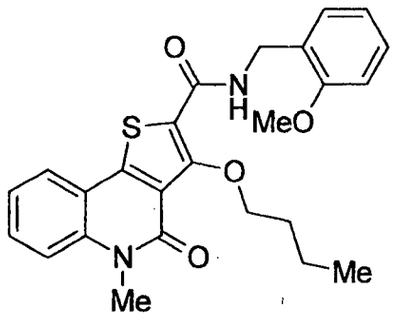
LC/MS 435 (M+H).

[1713]

Example 329

Production of 3-butoxy-N-(2-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1714]



[1715]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-(2-methoxyphenyl)methanamine.

LC/MS 451 (M+H).

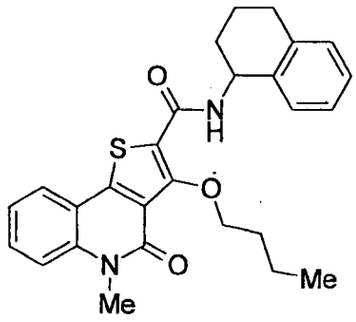
[1716]

Example 330

Production of 3-butoxy-5-methyl-4-oxo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-

2-carboxamide

[1717]



[1718]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1,2,3,4-tetrahydronaphthalen-1-amine.

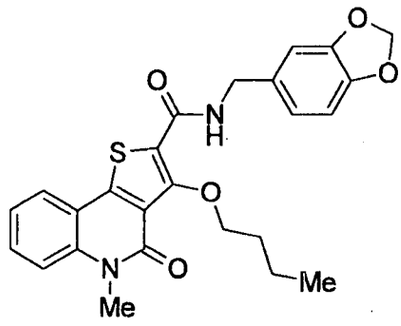
LC/MS 461 (M+H).

[1719]

Example 331

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-butoxy-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1720]



[1721]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-(1,3-benzodioxol-5-yl)methanamine.

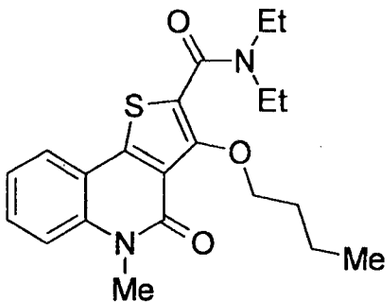
LC/MS 465 (M+H).

[1722]

Example 332

Production of 3-butoxy-N,N-diethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1723]



[1724]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N-ethylethanamine.

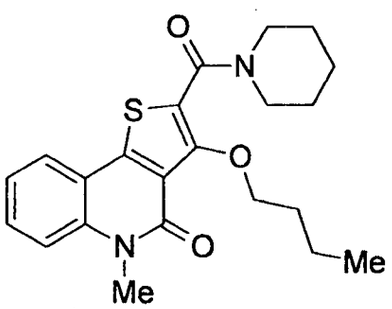
LC/MS 387 (M+H).

[1725]

Example 333

Production of 3-butoxy-5-methyl-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1726]



[1727]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and piperidine.

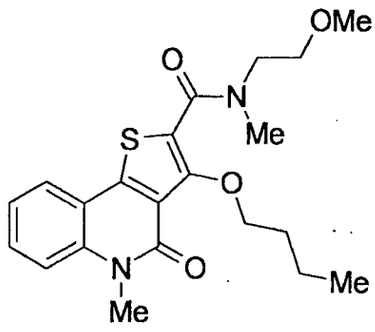
LC/MS 399 (M+H).

[1728]

Example 334

Production of 3-butoxy-N-(2-methoxyethyl)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1729]



[1730]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 2-methoxy-N-methylethanamine.

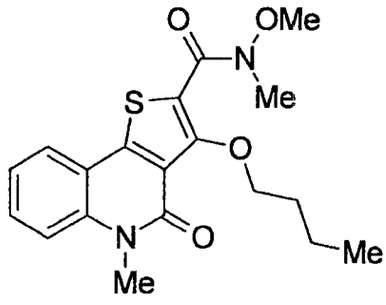
LC/MS 403 (M+H).

[1731]

Example 335

Production of 3-butoxy-N-methoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1732]



[1733]

To a solution (0.15 M, 0.40 mL, 60 μmol) of the compound of Reference Example 92 in DMF were added a mixture of a suspension (0.66 M, 0.111 mL, 73 μmol) of N-methoxymethanamine hydrochloride in DMF and triethylamine (10.9 μL, 78 μmol), and a solution (0.39 M, 0.20 mL, 78μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was shaken at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, the organic layer was filtered through a Teflon (registered trade mark) filter to separate

the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (16.6 mg, 74%).

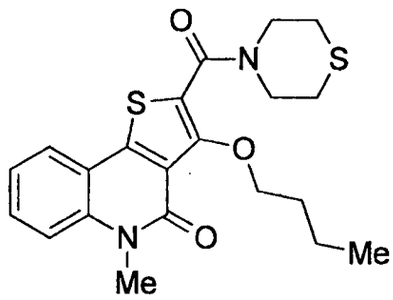
LC/MS 375 (M+H).

[1734]

Example 336

Production of 3-butoxy-5-methyl-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1735]



[1736]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and thiomorpholine.

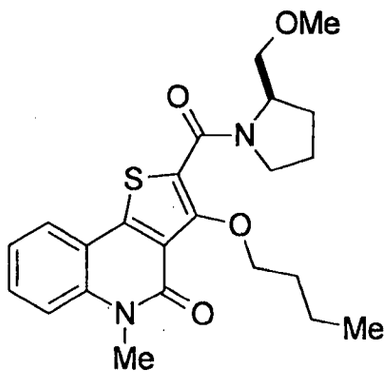
LC/MS 417 (M+H).

[1737]

Example 337

Production of 3-butoxy-2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylthieno[3,2-c]quinolin-4(5H)-one

[1738]



[1739]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and (2R)-2-(methoxymethyl)pyrrolidine.

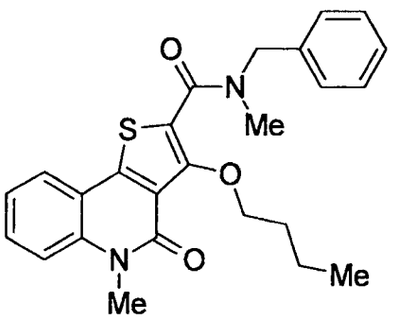
LC/MS 429 (M+H).

[1740]

Example 338

Production of N-benzyl-3-butoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1741]



[1742]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N-methyl-1-phenylmethanamine.

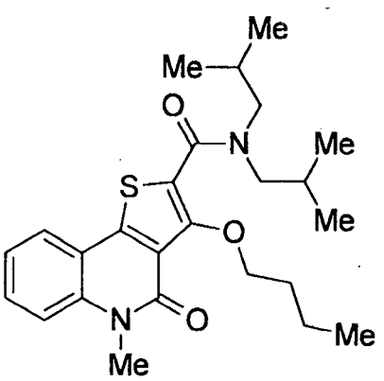
LC/MS 435 (M+H).

[1743]

Example 339

Production of 3-butoxy-5-methyl-N,N-bis(2-methylpropyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1744]



[1745]

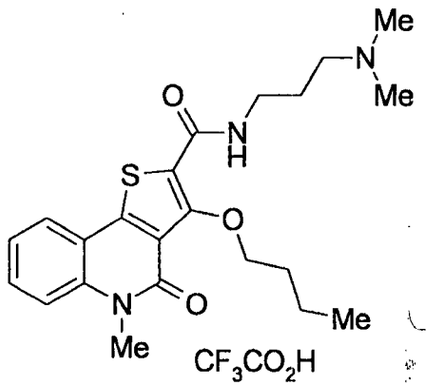
In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 92 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.
LC/MS 443 (M+H).

[1746]

Example 340

Production of 3-butoxy-N-[3-(dimethylamino)propyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1747]



[1748]

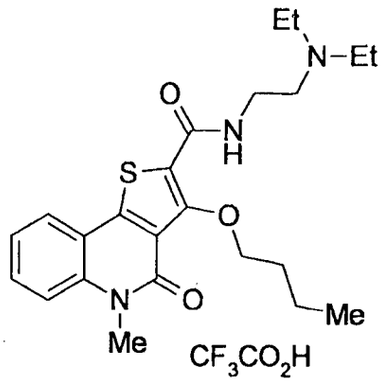
In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N,N-dimethylpropane-1,3-diamine.
LC/MS 416 (M+H).

[1749]

Example 341

Production of 3-butoxy-N-[2-(diethylamino)ethyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1750]



[1751]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N,N-diethylethane-1,2-diamine.

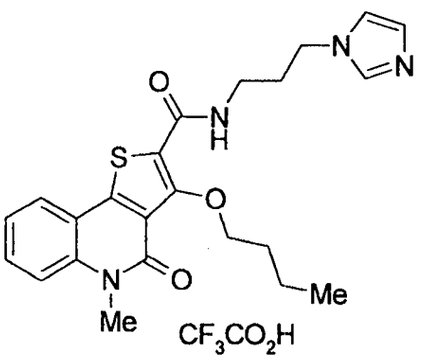
LC/MS 430 (M+H).

[1752]

Example 342

Production of 3-butoxy-N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1753]



[1754]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 3-(1H-imidazol-1-yl)propan-1-amine.

LC/MS 439 (M+H).

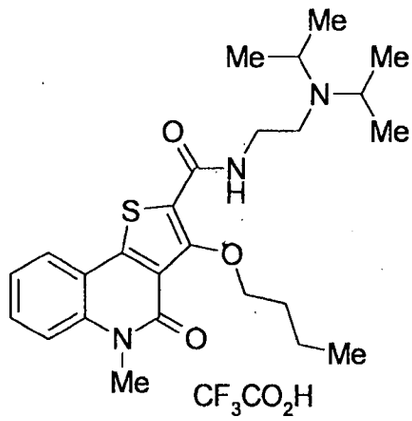
[1755]

Example 343

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-3-butoxy-5-

methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1756]



[1757]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

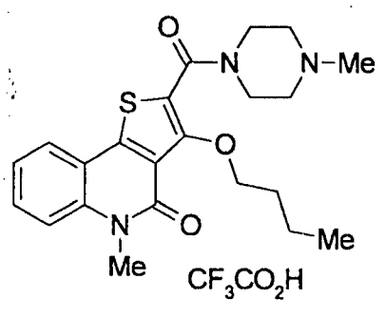
LC/MS 458 (M+H).

[1758]

Example 344

Production of 3-butoxy-5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1759]



[1760]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-methylpiperazine.

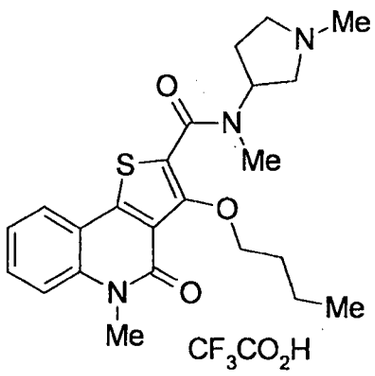
LC/MS 414 (M+H).

[1761]

Example 345

Production of 3-butoxy-N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1762]



[1763]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and N,1-dimethylpyrrolidin-3-amine.

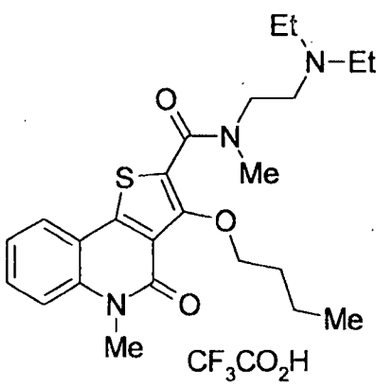
LC/MS 428 (M+H).

[1764]

Example 346

Production of 3-butoxy-N-[2-(diethylamino)ethyl]-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1765]



[1766]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and

N,N-diethyl-N'-methylethane-1,2-diamine.

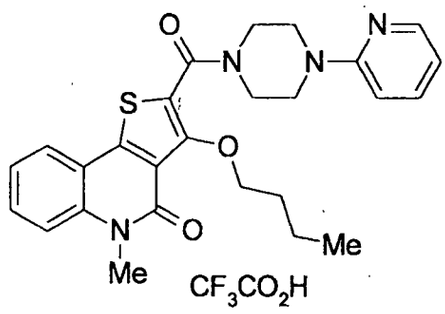
LC/MS 444 (M+H).

[1767]

Example 347

Production of 3-butoxy-5-methyl-2-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1768]



[1769]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 92 and 1-pyridin-2-ylpiperazine.

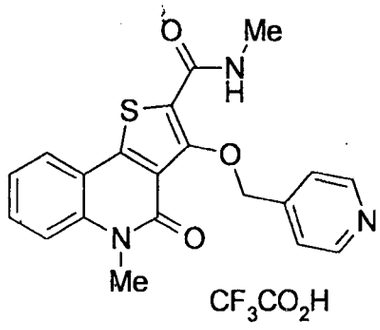
LC/MS 477 (M+H).

[1770]

Example 348

Production of N,5-dimethyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1771]



[1772]

To a solution (0.10 M, 0.40 mL, 40 μmol) of the compound of Reference Example 93 in DMF were added a solution (0.66 M, 0.10 mL, 66 μmol) of methanamine (2.0 M THF solution) in DMF

and a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was shaken at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, the organic layer was filtered through a Teflon (registered trade mark) filter to separate the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (13.2 mg, 67%).

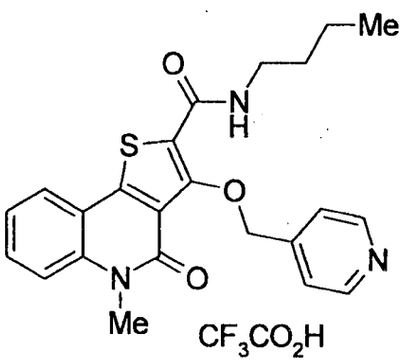
LC/MS 380 (M+H).

[1773]

Example 349

Production of N-butyl-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1774]



[1775]

To a solution (0.10 M, 0.40 mL, 40 μmol) of the compound of Reference Example 93 in DMF were added a solution (0.66 M, 0.10 mL, 66 μmol) of butan-1-amine in DMF and a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was shaken at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, the organic layer was filtered through a Teflon (registered trade mark) filter to separate the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue

was purified by preparative HPLC to give the title compound (13.5 mg, 63%).

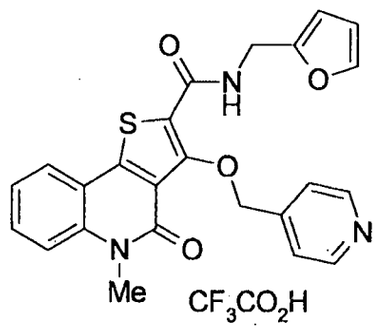
LC/MS 422 (M+H).

[1776]

Example 350

Production of N-(furan-2-ylmethyl)-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1777]



[1778]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-furan-2-ylmethanamine.

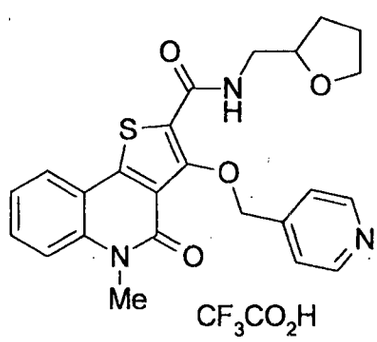
LC/MS 446 (M+H).

[1779]

Example 351

Production of 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1780]



[1781]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-(tetrahydrofuran-2-yl)methanamine.

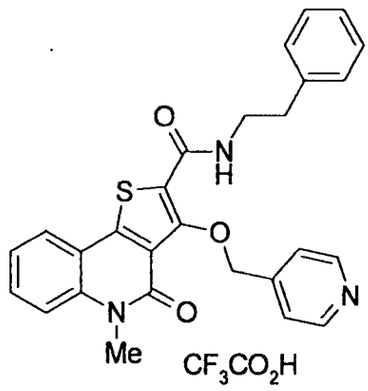
LC/MS 450 (M+H).

[1782]

Example 352

Production of 5-methyl-4-oxo-N-(2-phenylethyl)-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1783]



[1784]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 2-phenylethanamine.

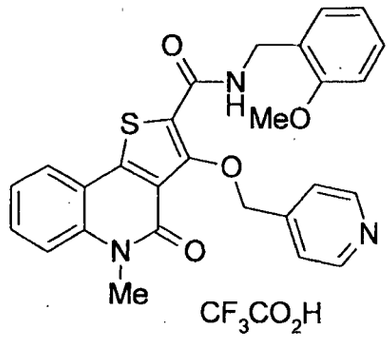
LC/MS 470 (M+H).

[1785]

Example 353

Production of N-(2-methoxybenzyl)-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1786]



[1787]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-(2-methoxyphenyl)methanamine.

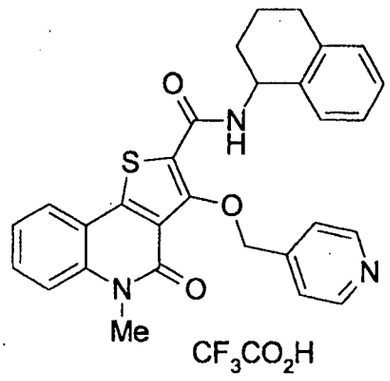
LC/MS 486 (M+H).

[1788]

Example 354

Production of 5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1789]



[1790]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1,2,3,4-tetrahydronaphthalen-1-amine.

LC/MS 496 (M+H).

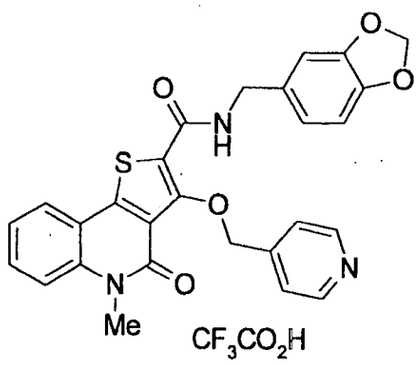
[1791]

Example 355

Production of N-(1,3-benzodioxol-5-ylmethyl)-5-methyl-4-oxo-3-

(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1792]



[1793]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-(1,3-benzodioxol-5-yl)methanamine.

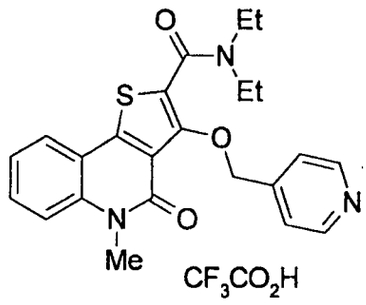
LC/MS 500 (M+H).

[1794]

Example 356

Production of N,N-diethyl-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1795]



[1796]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N-ethylethanamine.

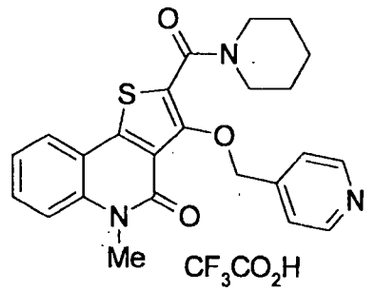
LC/MS 422 (M+H).

[1797]

Example 357

Production of 5-methyl-2-(piperidin-1-ylcarbonyl)-3-(pyridin-4-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1798]



[1799]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and piperidine.

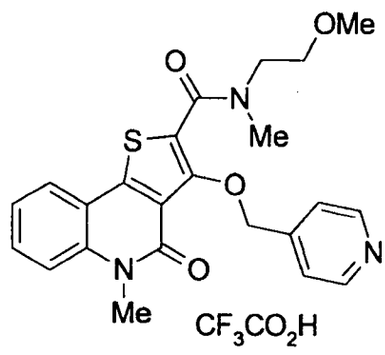
LC/MS 434 (M+H).

[1800]

Example 358

Production of N-(2-methoxyethyl)-N,5-dimethyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1801]



[1802]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 2-methoxy-N-methylethanamine.

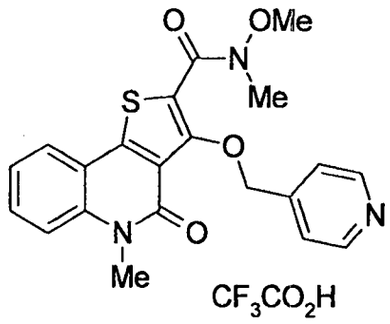
LC/MS 438 (M+H).

[1803]

Example 359

Production of N-methoxy-N,5-dimethyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1804]



[1805]

To a solution (0.10 M, 0.40 mL, 40 μmol) of the compound of Reference Example 93 in DMF were added a mixture of a suspension (0.66 M, 0.111 mL, 73 μmol) of N-methoxymethanamine hydrochloride in DMF and triethylamine (10.9 μL, 78 μmol), and a solution (0.39 M, 0.20 mL, 78 μmol) of HOBt and WSCD in 1:1 mixture in DMF. The obtained mixture was shaken at room temperature for 14 hr. Dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (1 mL) were added to the reaction mixture, the organic layer was filtered through a Teflon (registered trade mark) filter to separate the aqueous layer, and the filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (12.3 mg, 59%).

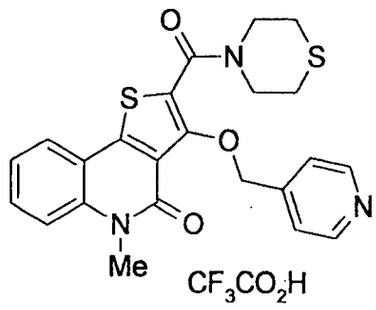
LC/MS 410 (M+H).

[1806]

Example 360

Production of 5-methyl-3-(pyridin-4-ylmethoxy)-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1807]



[1808]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and thiomorpholine.

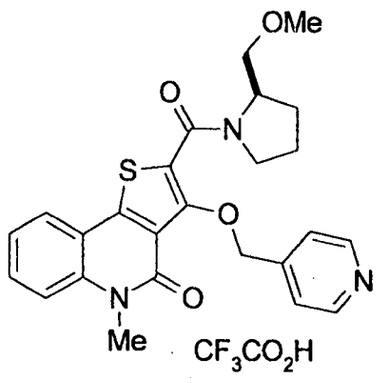
LC/MS 452 (M+H).

[1809]

Example 361

Production of 2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methyl-3-(pyridin-4-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1810]



[1811]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and (2R)-2-(methoxymethyl)pyrrolidine.

LC/MS 464 (M+H).

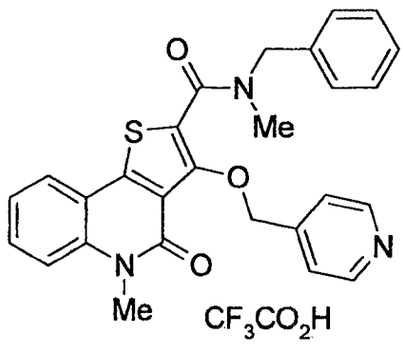
[1812]

Example 362

Production of N-benzyl-N,5-dimethyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

trifluoroacetate

[1813]



[1814]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N-methyl-1-phenylmethanamine.

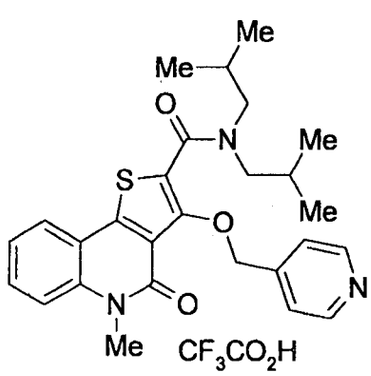
LC/MS 470 (M+H).

[1815]

Example 363

Production of 5-methyl-N,N-bis(2-methylpropyl)-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1816]



[1817]

In the same manner as in Example 359, the title compound was obtained from the compound of Reference Example 93 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

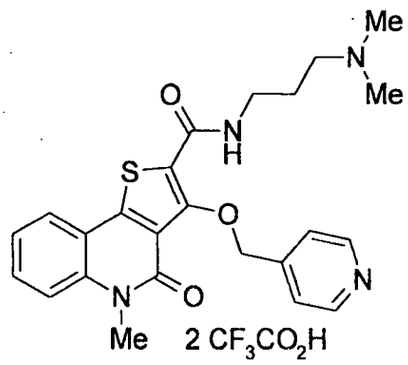
LC/MS 478 (M+H).

[1818]

Example 364

Production of N-[3-(dimethylamino)propyl]-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1819]



[1820]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N,N-dimethylpropane-1,3-diamine.

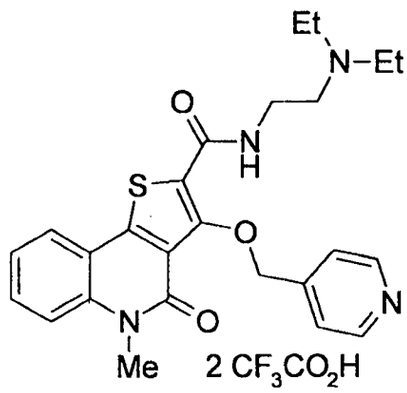
LC/MS 451 (M+H).

[1821]

Example 365

Production of N-[2-(diethylamino)ethyl]-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1822]



[1823]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and

N,N-diethylethane-1,2-diamine.

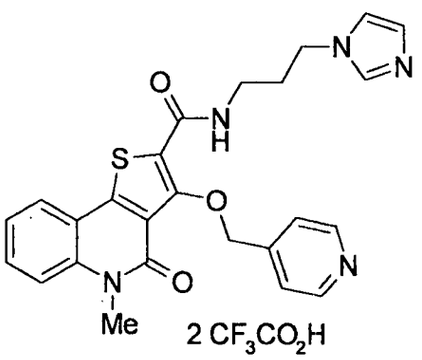
LC/MS 465 (M+H).

[1824]

Example 366

Production of N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1825]



[1826]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 3-(1H-imidazol-1-yl)propan-1-amine.

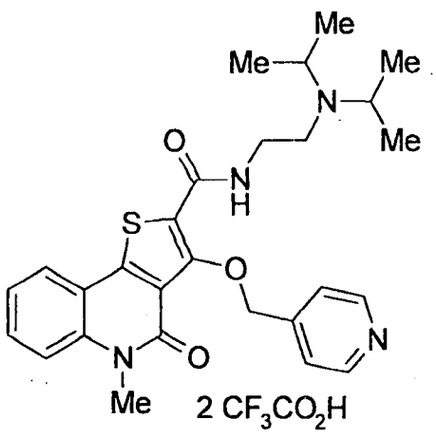
LC/MS 474 (M+H).

[1827]

Example 367

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-5-methyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1828]



[1829]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

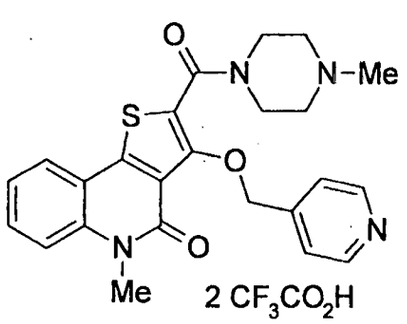
LC/MS 493 (M+H).

[1830]

Example 368

Production of 5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]-3-(pyridin-4-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1831]



[1832]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-methylpiperazine.

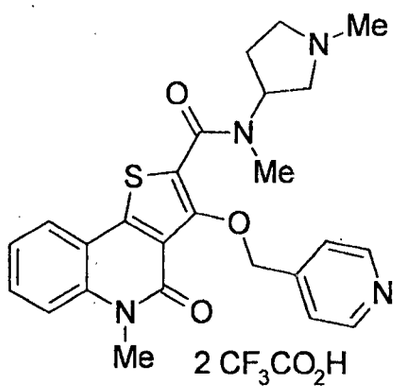
[1833]

Example 369

Production of N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-

carboxamide ditrifluoroacetate

[1834]



[1835]

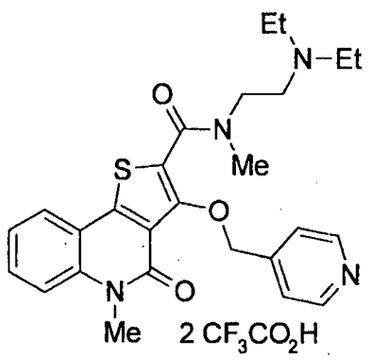
In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N,1-dimethylpyrrolidin-3-amine.

[1836]

Example 370

Production of N-[2-(diethylamino)ethyl]-N,5-dimethyl-4-oxo-3-(pyridin-4-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1837]



[1838]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and N,N-diethyl-N'-methylethane-1,2-diamine.

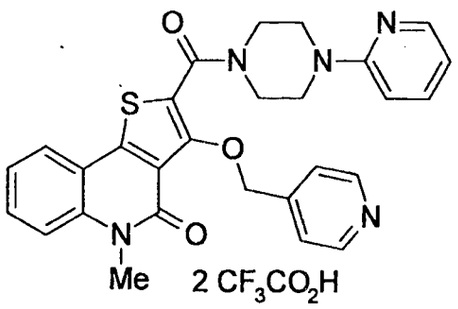
[1839]

Example 371

Production of 5-methyl-3-(pyridin-4-ylmethoxy)-2-[(4-pyridin-

2-ylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one 2 trifluoroacetate

[1840]



[1841]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 93 and 1-pyridin-2-ylpiperazine.

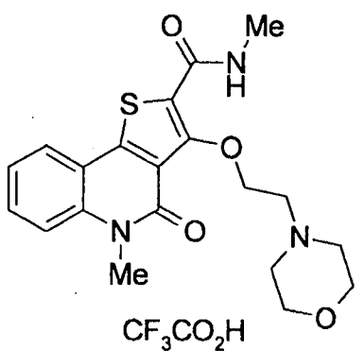
LC/MS 512 (M+H).

[1842]

Example 372

Production of N,5-dimethyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1843]



[1844]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and methanamine (2.0 M THF solution).

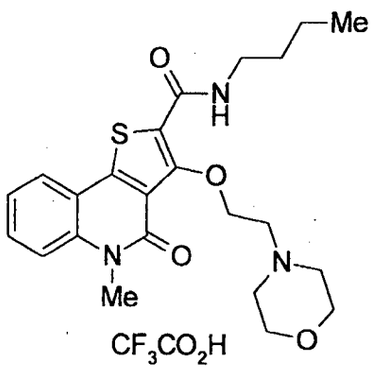
LC/MS 402 (M+H).

[1845]

Example 373

Production of N-butyl-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1846]



[1847]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and butan-1-amine.

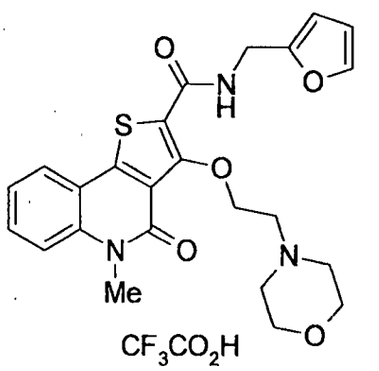
LC/MS 444 (M+H).

[1848]

Example 374

Production of N-(furan-2-ylmethyl)-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1849]



[1850]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-

furan-2-ylmethanamine.

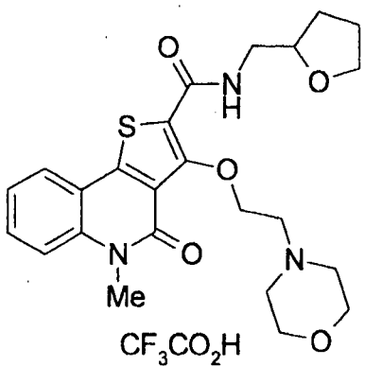
LC/MS 468 (M+H).

[1851]

Example 375

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1852]



[1853]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-(tetrahydrofuran-2-yl)methanamine.

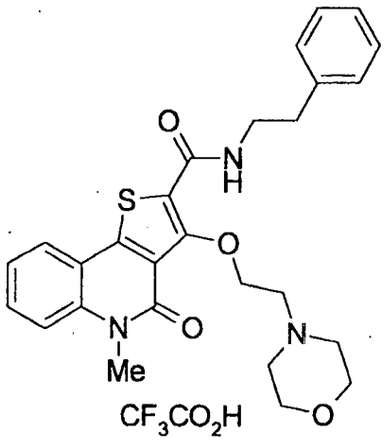
LC/MS 472 (M+H).

[1854]

Example 376

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1855]



[1856]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 2-phenylethanamine.

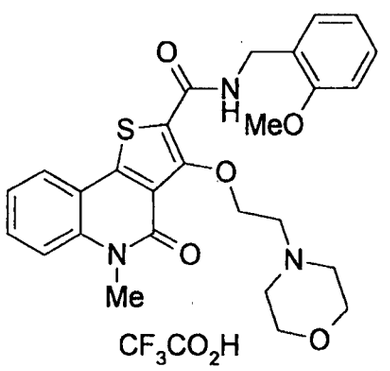
LC/MS 492 (M+H).

[1857]

Example 377

Production of N-(2-methoxybenzyl)-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1858]



[1859]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-(2-methoxyphenyl)methanamine.

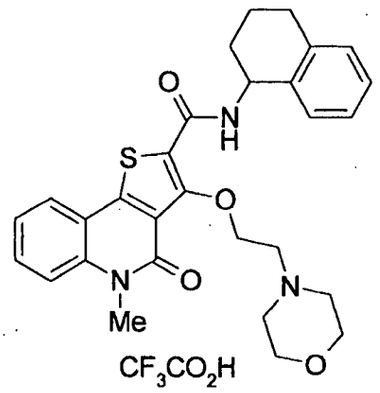
LC/MS 508 (M+H).

[1860]

Example 378

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1861]



[1862]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1,2,3,4-tetrahydronaphthalen-1-amine.

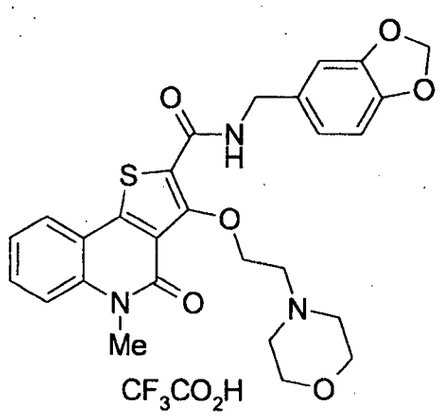
LC/MS 518 (M+H).

[1863]

Example 379

Production of N-(1,3-benzodioxol-5-ylmethyl)-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1864]



[1865]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-(1,3-benzodioxol-5-yl)methanamine.

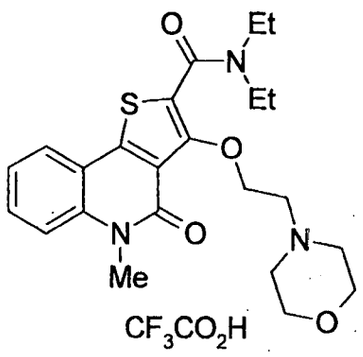
LC/MS 522 (M+H).

[1866]

Example 380

Production of N,N-diethyl-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1867]



[1868]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N-ethylethanamine.

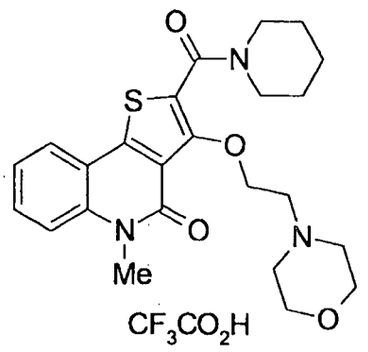
LC/MS 444 (M+H).

[1869]

Example 381

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1870]



[1871]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and piperidine.

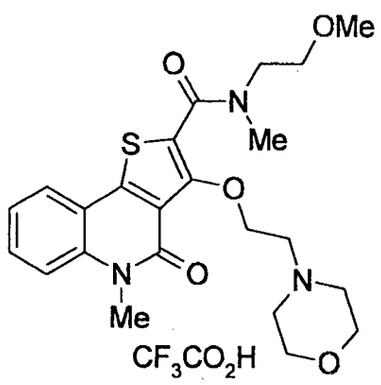
LC/MS 456 (M+H).

[1872]

Example 382

Production of N-(2-methoxyethyl)-N,5-dimethyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1873]



[1874]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 2-methoxy-N-methylethanamine.

LC/MS 460 (M+H).

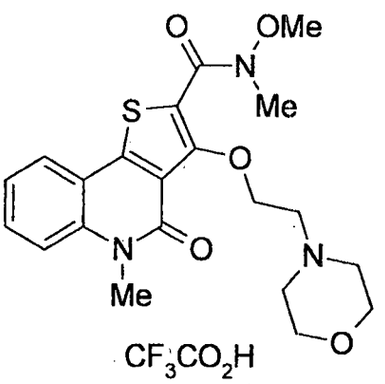
[1875]

Example 383

Production of N-methoxy-N,5-dimethyl-3-(2-morpholin-4-

ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1876]



[1877]

In the same manner as in Example 359, the title compound was obtained from the compound of Reference Example 94 and N-methoxymethanamine hydrochloride.

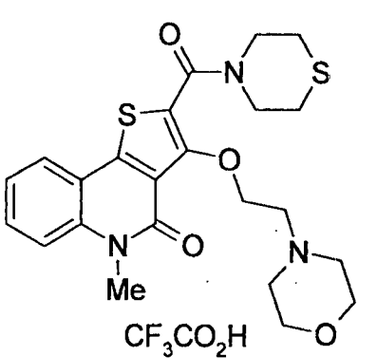
LC/MS 432 (M+H).

[1878]

Example 384

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1879]



[1880]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and thiomorpholine.

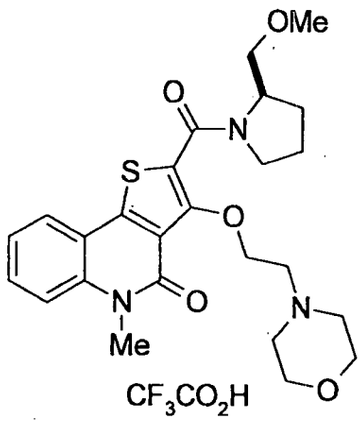
LC/MS 474 (M+H).

[1881]

Example 385

Production of 2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methyl-3-(2-morpholin-4-ylethoxy)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1882]



[1883]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and (2R)-2-(methoxymethyl)pyrrolidine.

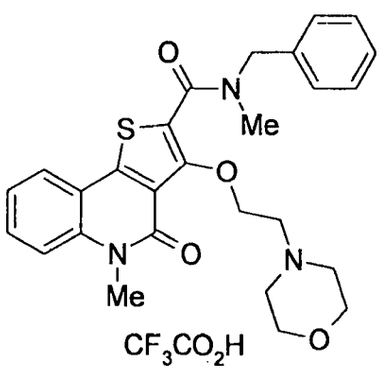
LC/MS 486 (M+H).

[1884]

Example 386

Production of N-benzyl-N,5-dimethyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1885]



[1886]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N-methyl-1-phenylmethanamine.

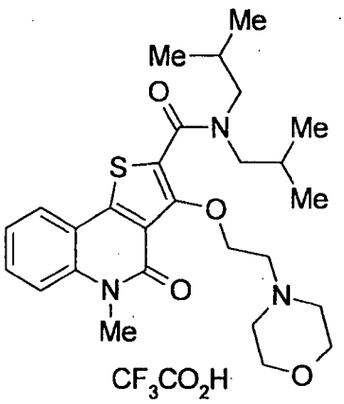
LC/MS 492 (M+H).

[1887]

Example 387

Production of 5-methyl-N,N-bis(2-methylpropyl)-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1888]



[1889]

In the same manner as in Example 359, the title compound was obtained from the compound of Reference Example 94 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

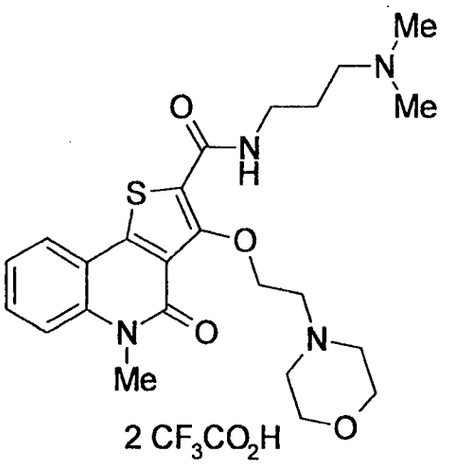
LC/MS 500 (M+H).

[1890]

Example 388

Production of N-[3-(dimethylamino)propyl]-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1891]



[1892]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N,N-dimethylpropane-1,3-diamine.

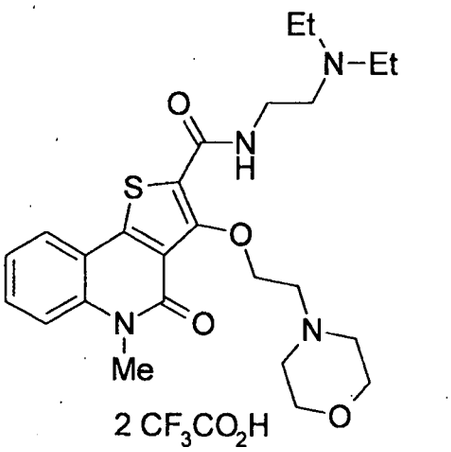
LC/MS 473 (M+H).

[1893]

Example 389

Production of N-[2-(diethylamino)ethyl]-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1894]



[1895]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N,N-diethylethane-1,2-diamine.

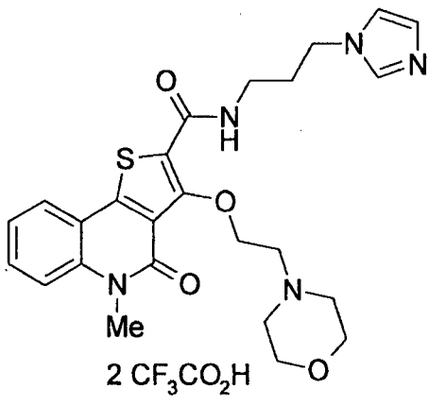
LC/MS 487 (M+H).

[1896]

Example 390

Production of N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1897]



[1898]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 3-(1H-imidazol-1-yl)propan-1-amine.

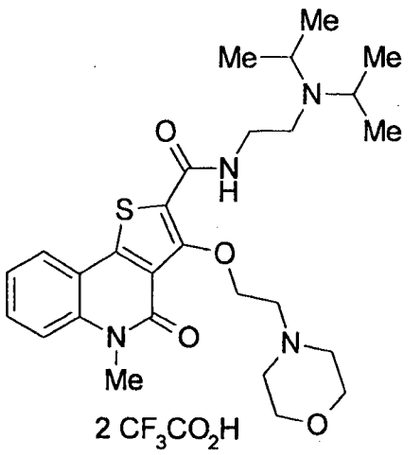
LC/MS 496 (M+H).

[1899]

Example 391

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-5-methyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1900]



[1901]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

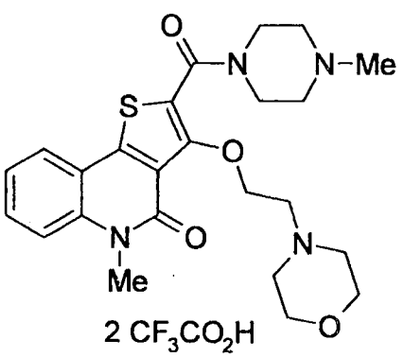
LC/MS 515 (M+H).

[1902]

Example 392

Production of 5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]-3-(2-morpholin-4-ylethoxy)thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1903]



[1904]

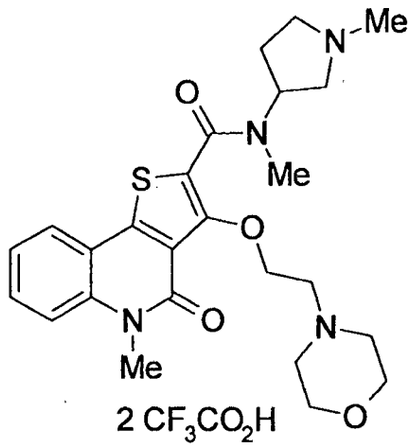
In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-methylpiperazine.

[1905]

Example 393

Production of N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1906]



[1907]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N,1-dimethylpyrrolidin-3-amine.

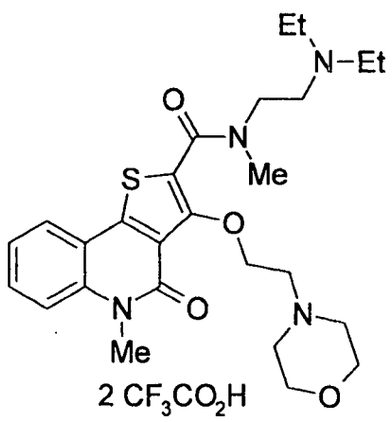
LC/MS 485 (M+H).

[1908]

Example 394

Production of N-[2-(diethylamino)ethyl]-N,5-dimethyl-3-(2-morpholin-4-ylethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide ditrifluoroacetate

[1909]



[1910]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and N,N-diethyl-N'-methylethane-1,2-diamine.

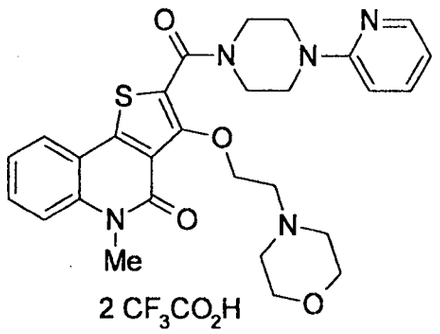
LC/MS 501 (M+H).

[1911]

Example 395

Production of 5-methyl-3-(2-morpholin-4-ylethoxy)-2-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one ditrifluoroacetate

[1912]



[1913]

In the same manner as in Example 349, the title compound was obtained from the compound of Reference Example 94 and 1-pyridin-2-ylpiperazine.

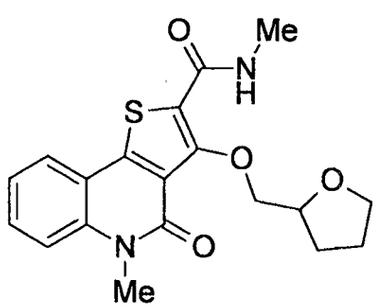
LC/MS 534 (M+H).

[1914]

Example 396

Production of N,5-dimethyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1915]



[1916]

In the same manner as in Example 300, the title compound was obtained from the compound of Reference Example 95 and methanamine (2.0 M THF solution).

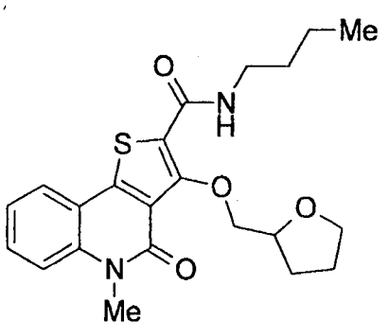
LC/MS 373 (M+H).

[1917]

Example 397

Production of N-butyl-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1918]



[1919]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and butan-1-amine.

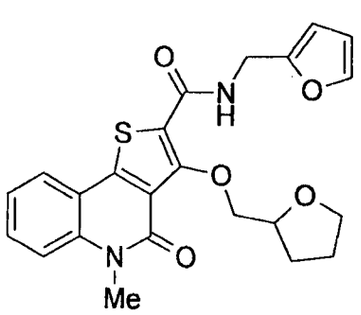
LC/MS 415 (M+H).

[1920]

Example 398

Production of N-(furan-2-ylmethyl)-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1921]



[1922]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-furan-2-ylmethanamine.

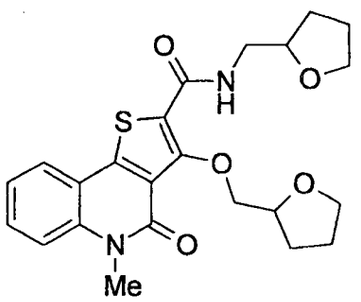
LC/MS 439 (M+H).

[1923]

Example 399

Production of 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1924]



[1925]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-(tetrahydrofuran-2-yl)methanamine.

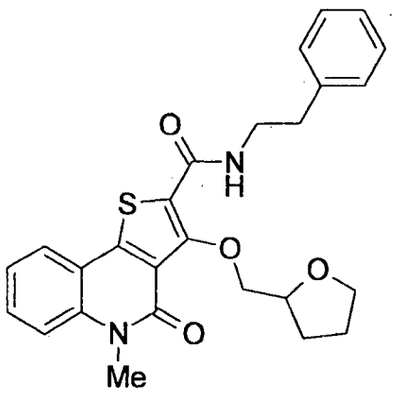
LC/MS 443 (M+H).

[1926]

Example 400

Production of 5-methyl-4-oxo-N-(2-phenylethyl)-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1927]



[1928]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 2-phenylethanamine.

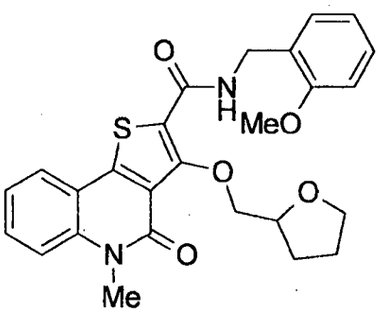
LC/MS 463 (M+H).

[1929]

Example 401

Production of N-(2-methoxybenzyl)-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1930]



[1931]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-(2-methoxyphenyl)methanamine.

LC/MS 479 (M+H).

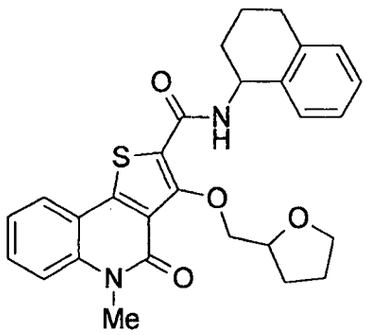
[1932]

Example 402

Production of 5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-

N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1933]



[1934]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1,2,3,4-tetrahydronaphthalen-1-amine.

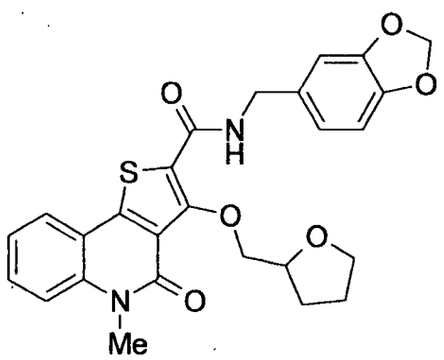
LC/MS 489 (M+H).

[1935]

Example 403

Production of N-(1,3-benzodioxol-5-ylmethyl)-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1936]



[1937]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-(1,3-benzodioxol-5-yl)methanamine.

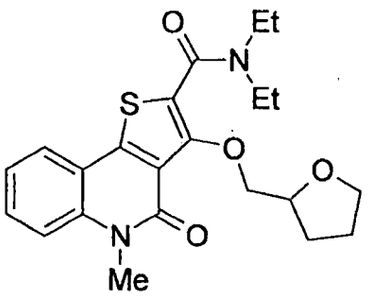
LC/MS 493 (M+H).

[1938]

Example 404

Production of N,N-diethyl-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1939]



[1940]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N-ethylethanamine.

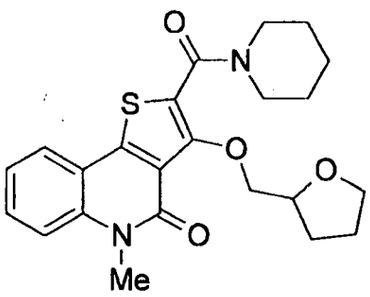
LC/MS 415 (M+H).

[1941]

Example 405

Production of 5-methyl-2-(piperidin-1-ylcarbonyl)-3-(tetrahydrofuran-2-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one

[1942]



[1943]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and piperidine.

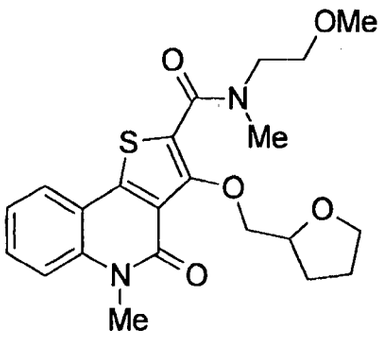
LC/MS 427 (M+H).

[1944]

Example 406

Production of N-(2-methoxyethyl)-N,5-dimethyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1945]



[1946]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 2-methoxy-N-methylethanamine.

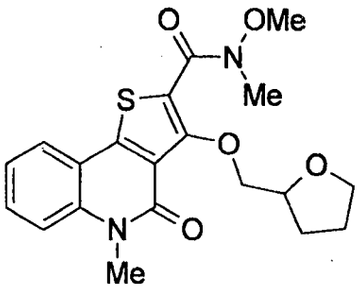
LC/MS 461 (M+H).

[1947]

Example 407

Production of N-methoxy-N,5-dimethyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1948]



[1949]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 95 and N-methoxymethanamine hydrochloride.

LC/MS 403 (M+H).

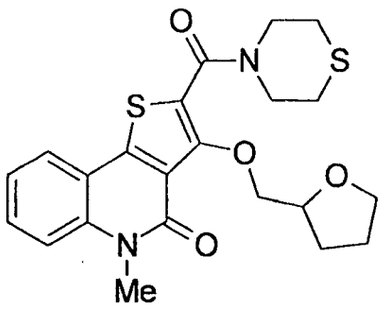
[1950]

Example 408

Production of 5-methyl-3-(tetrahydrofuran-2-ylmethoxy)-2-

(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[1951]



[1952]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and thiomorpholine.

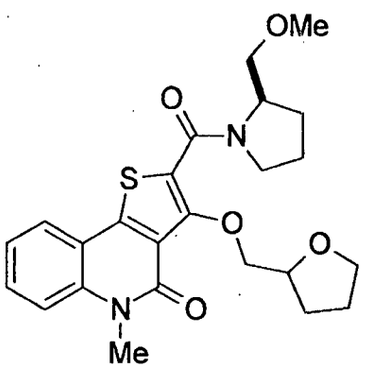
LC/MS 445 (M+H).

[1953]

Example 409

Production of 2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methyl-3-(tetrahydrofuran-2-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one

[1954]



[1955]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and (2R)-2-(methoxymethyl)pyrrolidine.

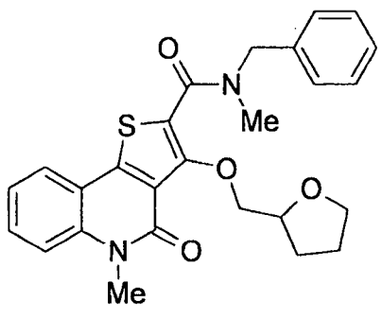
LC/MS 457 (M+H).

[1956]

Example 410

Production of N-benzyl-N,5-dimethyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1957]



[1958]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N-methyl-1-phenylmethanamine.

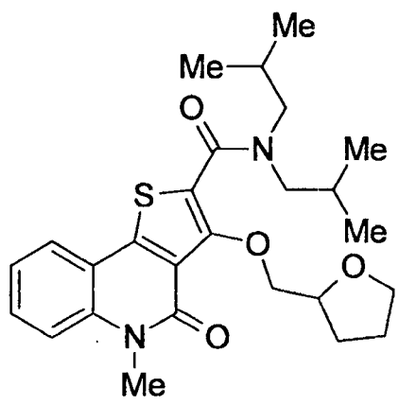
LC/MS 463 (M+H).

[1959]

Example 411

Production of 5-methyl-N,N-bis(2-methylpropyl)-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1960]



[1961]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 95 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

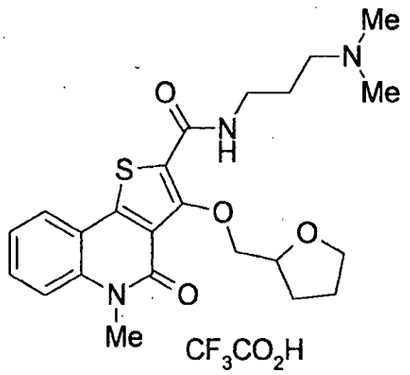
LC/MS 471 (M+H).

[1962]

Example 412

Production of N-[3-(dimethylamino)propyl]-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1963]



[1964]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N,N-dimethylpropane-1,3-diamine.

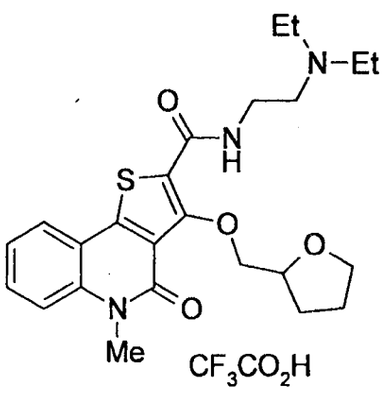
LC/MS 444 (M+H).

[1965]

Example 413

Production of N-[2-(diethylamino)ethyl]-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1966]



[1967]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 95 and N,N-diethylethane-1,2-diamine.

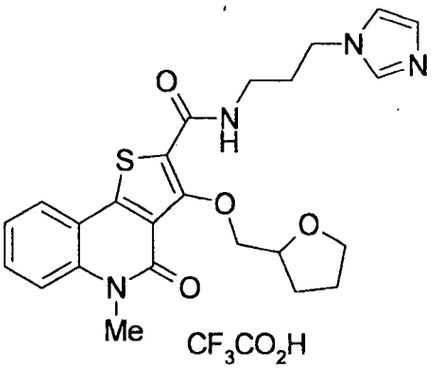
LC/MS 458 (M+H).

[1968]

Example 414

Production of N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1969]



[1970]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 3-(1H-imidazol-1-yl)propan-1-amine.

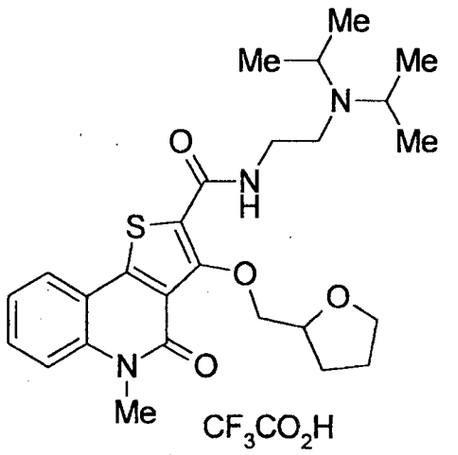
LC/MS 467 (M+H).

[1971]

Example 415

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-5-methyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1972]



[1973]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

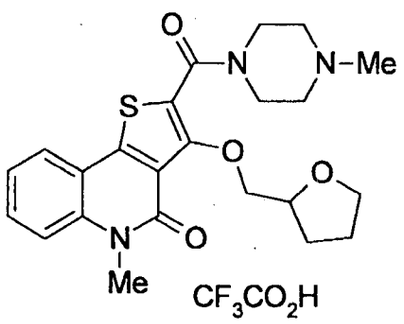
LC/MS 486 (M+H).

[1974]

Example 416

Production of 5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]-3-(tetrahydrofuran-2-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1975]



[1976]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-methylpiperazine.

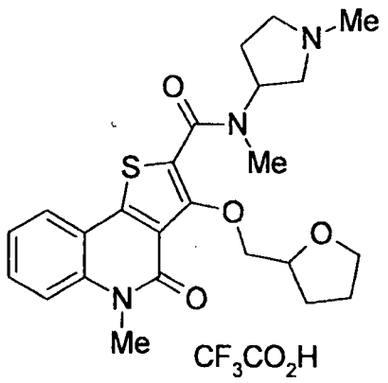
LC/MS 442 (M+H).

[1977]

Example 417

Production of N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1978]



[1979]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N,1-dimethylpyrrolidin-3-amine.

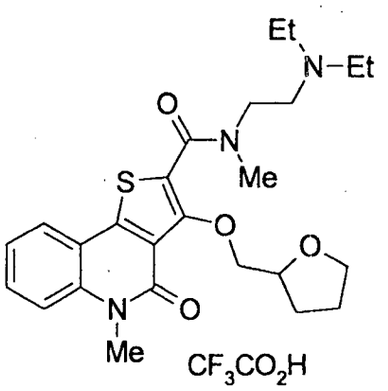
LC/MS 456 (M+H).

[1980]

Example 418

Production of N-[2-(diethylamino)ethyl]-N,5-dimethyl-4-oxo-3-(tetrahydrofuran-2-ylmethoxy)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[1981]



[1982]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and N,N-diethyl-N'-methylethane-1,2-diamine.

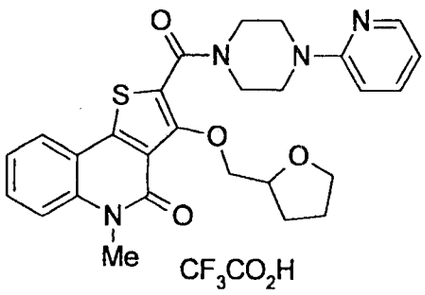
LC/MS 472 (M+H).

[1983]

Example 419

Production of 5-methyl-2-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-3-(tetrahydrofuran-2-ylmethoxy)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[1984]



[1985]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 95 and 1-pyridin-2-ylpiperazine.

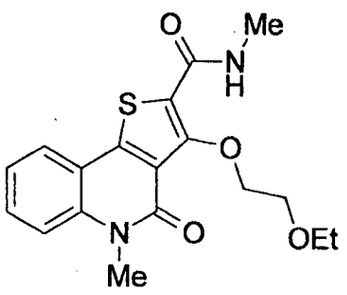
LC/MS 505 (M+H).

[1986]

Example 420

Production of 3-(2-ethoxyethoxy)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1987]



[1988]

In the same manner as in Example 300, the title compound was obtained from the compound of Reference Example 96 and methanamine (2.0 M THF solution).

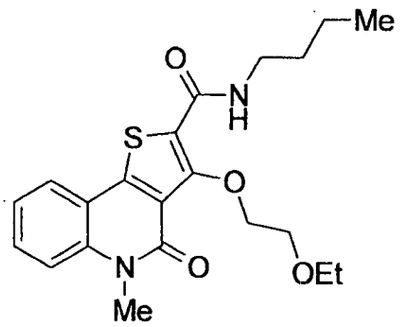
LC/MS 361 (M+H).

[1989]

Example 421

Production of N-butyl-3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1990]



[1991]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and butan-1-amine.

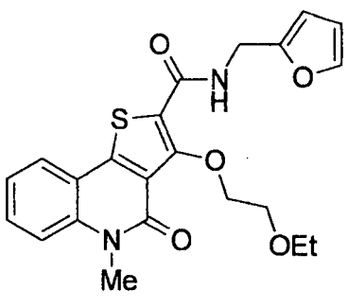
LC/MS 403 (M+H).

[1992]

Example 422

Production of 3-(2-ethoxyethoxy)-N-(furan-2-ylmethyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1993]



[1994]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-furan-2-ylmethanamine.

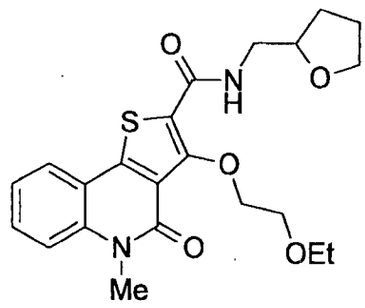
LC/MS 427 (M+H).

[1995]

Example 423

Production of 3-(2-ethoxyethoxy)-5-methyl-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1996]



[1997]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-(tetrahydrofuran-2-yl)methanamine.

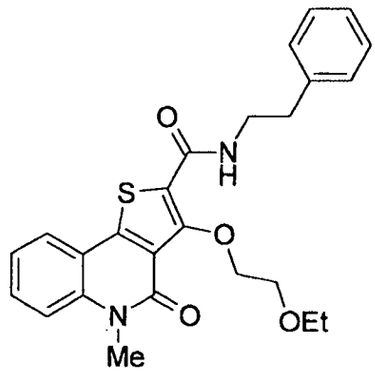
LC/MS 431 (M+H).

[1998]

Example 424

Production of 3-(2-ethoxyethoxy)-5-methyl-4-oxo-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[1999]



[2000]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 2-phenylethanamine.

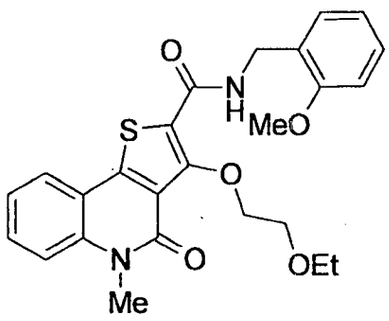
LC/MS 451 (M+H).

[2001]

Example 425

Production of 3-(2-ethoxyethoxy)-N-(2-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2002]



[2003]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-(2-methoxyphenyl)methanamine.

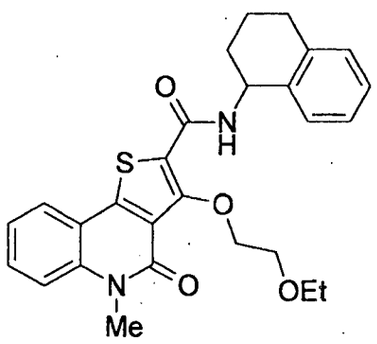
LC/MS 467 (M+H).

[2004]

Example 426

Production of 3-(2-ethoxyethoxy)-5-methyl-4-oxo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2005]



[2006]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1,2,3,4-tetrahydronaphthalen-1-amine.

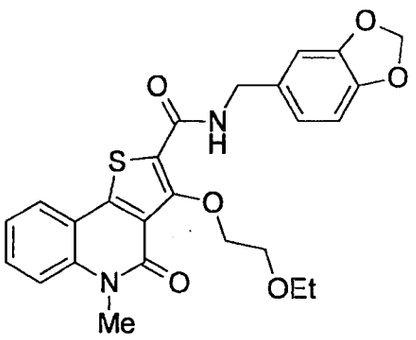
LC/MS 477 (M+H).

[2007]

Example 427

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2008]



[2009]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-(1,3-benzodioxol-5-yl)methanamine.

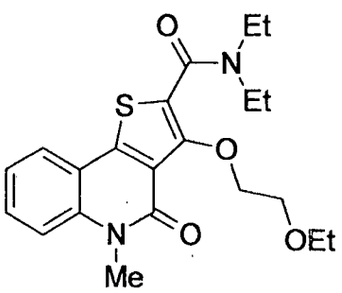
LC/MS 481 (M+H).

[2010]

Example 428

Production of 3-(2-ethoxyethoxy)-N,N-diethyl-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2011]



[2012]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N-ethylethanamine.

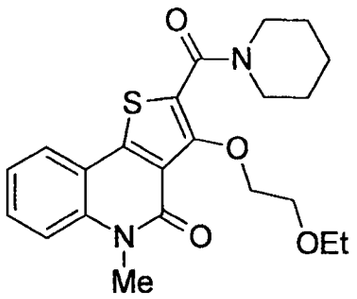
LC/MS 403 (M+H).

[2013]

Example 429

Production of 3-(2-ethoxyethoxy)-5-methyl-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2014]



[2015]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and piperidine.

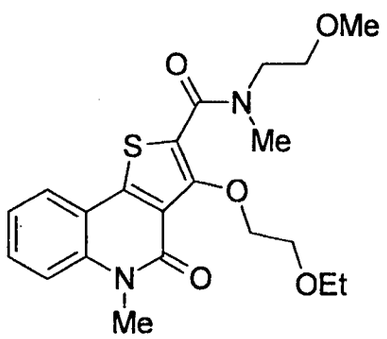
LC/MS 415 (M+H).

[2016]

Example 430

Production of 3-(2-ethoxyethoxy)-N-(2-methoxyethyl)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2017]



[2018]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 2-methoxy-N-methylethanamine.

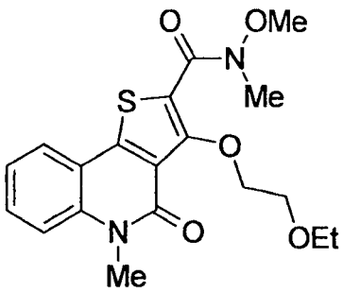
LC/MS 419 (M+H).

[2019]

Example 431

Production of 3-(2-ethoxyethoxy)-N-methoxy-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2020]



[2021]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 96 and N-methoxymethanamine hydrochloride.

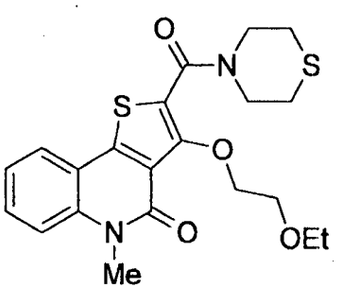
LC/MS 391 (M+H).

[2022]

Example 432

Production of 3-(2-ethoxyethoxy)-5-methyl-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2023]



[2024]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and thiomorpholine.

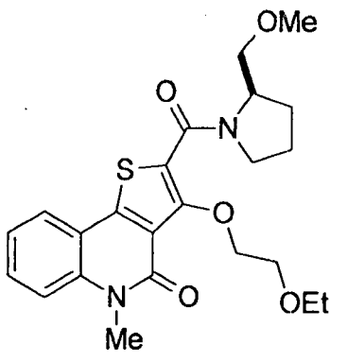
LC/MS 433 (M+H).

[2025]

Example 433

Production of 3-(2-ethoxyethoxy)-2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-methylthieno[3,2-c]quinolin-4(5H)-one

[2026]



[2027]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and (2R)-2-(methoxymethyl)pyrrolidine.

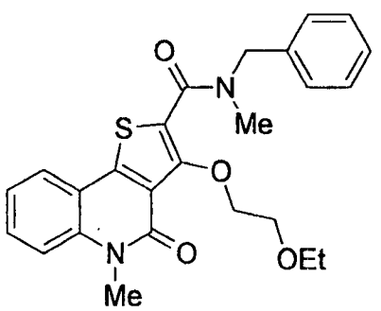
LC/MS 445 (M+H).

[2028]

Example 434

Production of N-benzyl-3-(2-ethoxyethoxy)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2029]



[2030]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N-methyl-1-phenylmethanamine.

LC/MS 451 (M+H).

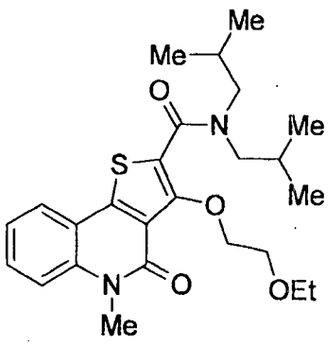
[2031]

Example 435

Production of 3-(2-ethoxyethoxy)-5-methyl-N,N-bis(2-methylpropyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-

carboxamide

[2032]



[2033]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 96 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

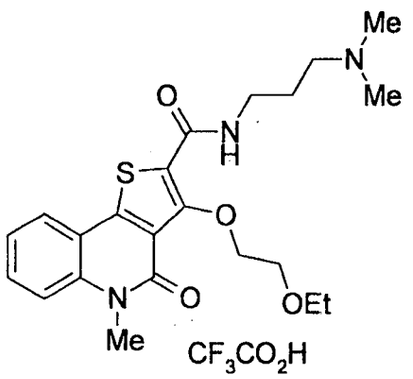
LC/MS 459 (M+H).

[2034]

Example 436

Production of N-[3-(dimethylamino)propyl]-3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2035]



[2036]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N,N-dimethylpropane-1,3-diamine.

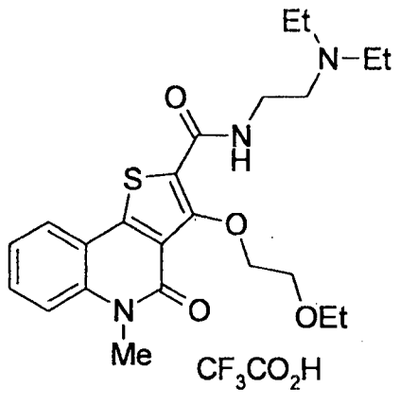
LC/MS 432 (M+H).

[2037]

Example 437

Production of N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2038]



[2039]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N,N-diethylethane-1,2-diamine.

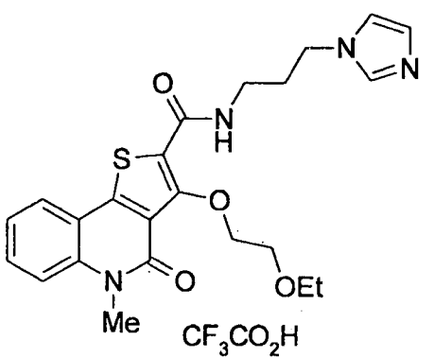
LC/MS 446 (M+H).

[2040]

Example 438

Production of 3-(2-ethoxyethoxy)-N-[3-(1H-imidazol-1-yl)propyl]-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2041]



[2042]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 3-

(1H-imidazol-1-yl)propan-1-amine.

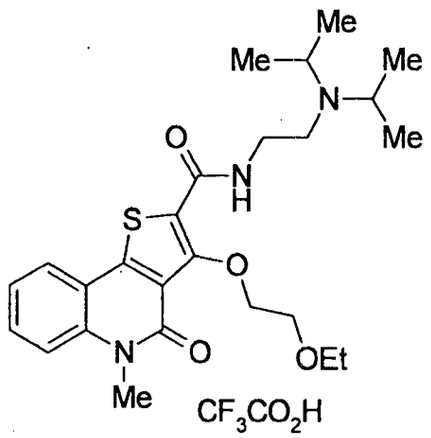
LC/MS 455 (M+H).

[2043]

Example 439

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-3-(2-ethoxyethoxy)-5-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2044]



[2045]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

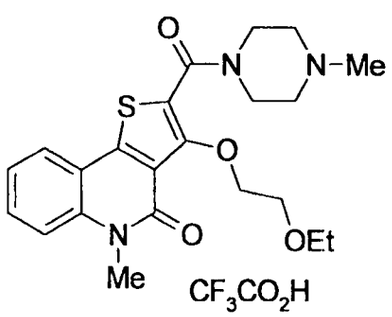
LC/MS 474 (M+H).

[2046]

Example 440

Production of 3-(2-ethoxyethoxy)-5-methyl-2-[(4-methylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2047]



[2048]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-methylpiperazine.

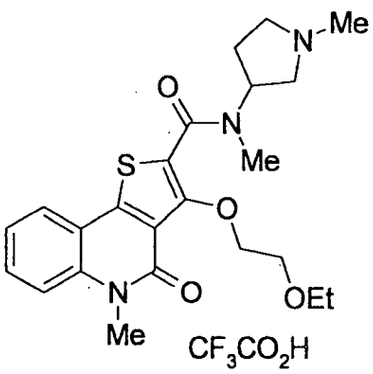
LC/MS 430 (M+H).

[2049]

Example 441

Production of 3-(2-ethoxyethoxy)-N,5-dimethyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2050]



[2051]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N,1-dimethylpyrrolidin-3-amine.

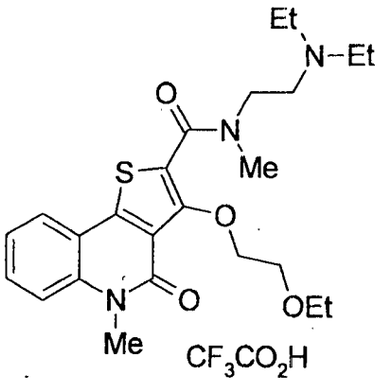
LC/MS 444 (M+H).

[2052]

Example 442

Production of N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-N,5-dimethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2053]



[2054]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and N,N-diethyl-N'-methylethane-1,2-diamine.

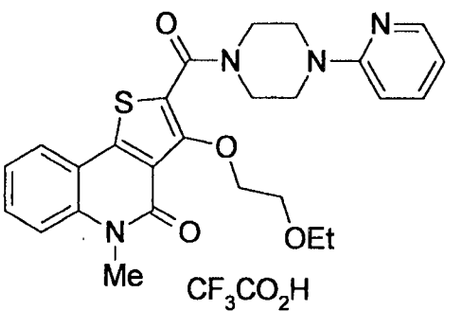
LC/MS 460 (M+H).

[2055]

Example 443

Production of 3-(2-ethoxyethoxy)-5-methyl-2-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2056]



[2057]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 96 and 1-pyridin-2-ylpiperazine.

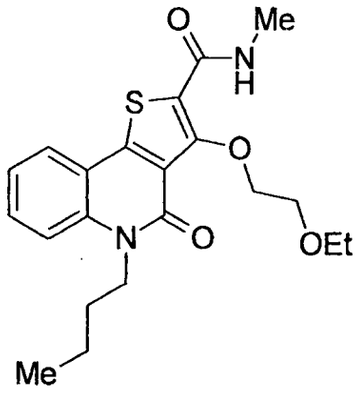
LC/MS 493 (M+H).

[2058]

Example 444

Production of 5-butyl-3-(2-ethoxyethoxy)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2059]



[2060]

In the same manner as in Example 300, the title compound was obtained from the compound of Reference Example 104 and methanamine (2.0 M THF solution).

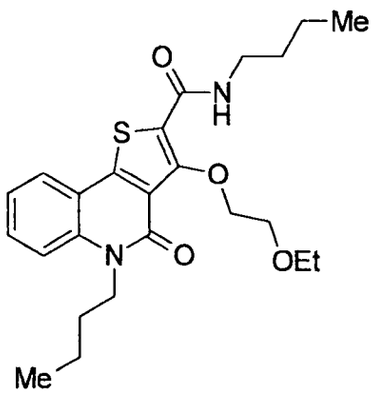
LC/MS 403 (M+H).

[2061]

Example 445

Production of N,5-dibutyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2062]



[2063]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and butan-1-amine.

LC/MS 445 (M+H).

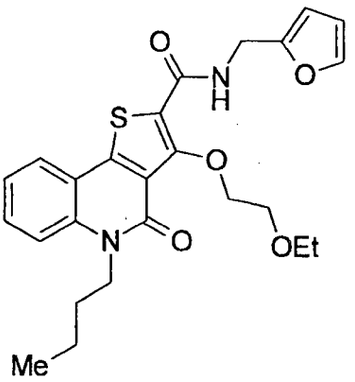
[2064]

Example 446

Production of 5-butyl-3-(2-ethoxyethoxy)-N-(furan-2-ylmethyl)-

4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2065]



[2066]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-furan-2-ylmethanamine.

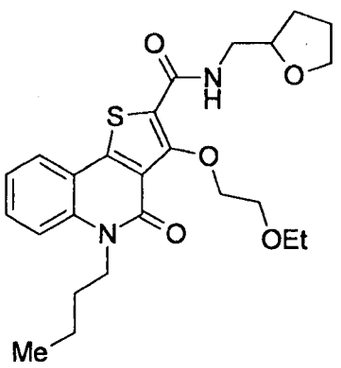
LC/MS 469 (M+H).

[2067]

Example 447

Production of 5-butyl-3-(2-ethoxyethoxy)-4-oxo-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2068]



[2069]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-(tetrahydrofuran-2-yl)methanamine.

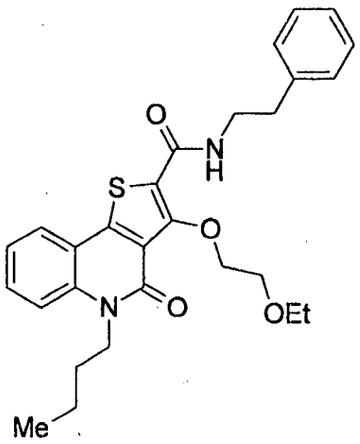
LC/MS 473 (M+H).

[2070]

Example 448

Production of 5-butyl-3-(2-ethoxyethoxy)-4-oxo-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2071]



[2072]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 2-phenylethanamine.

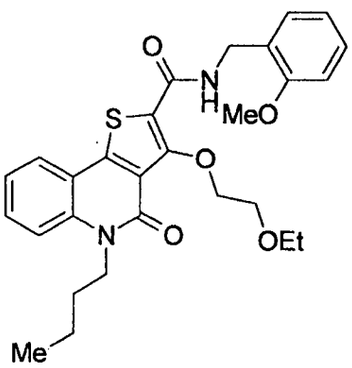
LC/MS 493 (M+H).

[2073]

Example 449

Production of 5-butyl-3-(2-ethoxyethoxy)-N-(2-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2074]



[2075]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-

(2-methoxyphenyl)methanamine.

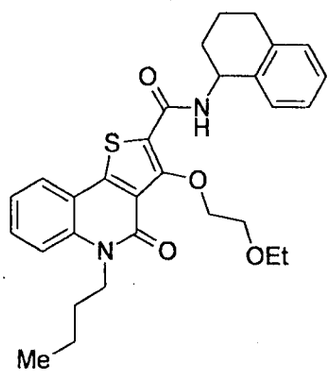
LC/MS 509 (M+H).

[2076]

Example 450

Production of 5-butyl-3-(2-ethoxyethoxy)-4-oxo-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2077]



[2078]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1,2,3,4-tetrahydronaphthalen-1-amine.

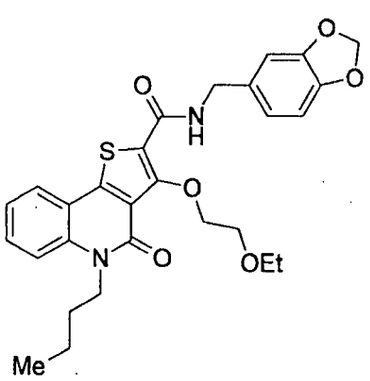
LC/MS 519 (M+H).

[2079]

Example 451

Production of N-(1,3-benzodioxol-5-ylmethyl)-5-butyl-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2080]



[2081]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-(1,3-benzodioxol-5-yl)methanamine.

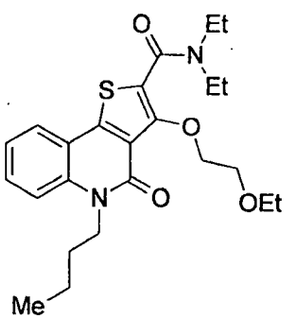
LC/MS 523 (M+H).

[2082]

Example 452

Production of 5-butyl-3-(2-ethoxyethoxy)-N,N-diethyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2083]



[2084]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N-ethylethanamine.

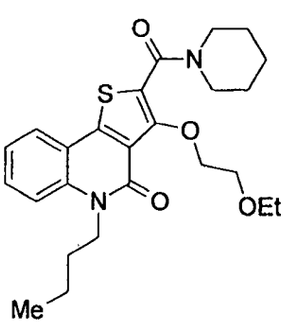
LC/MS 445 (M+H).

[2085]

Example 453

Production of 5-butyl-3-(2-ethoxyethoxy)-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2086]



[2087]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and piperidine.

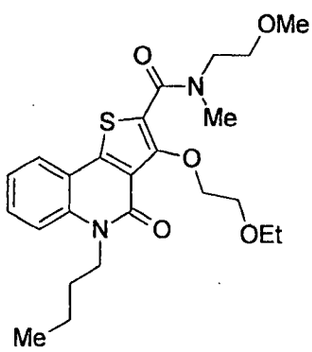
LC/MS 457 (M+H).

[2088]

Example 454

Production of 5-butyl-3-(2-ethoxyethoxy)-N-(2-methoxyethyl)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2089]



[2090]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 2-methoxy-N-methylethanamine.

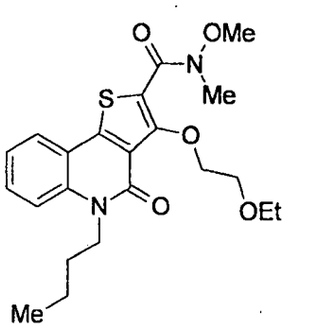
LC/MS 461 (M+H).

[2091]

Example 455

Production of 5-butyl-3-(2-ethoxyethoxy)-N-methoxy-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2092]



[2093]

In the same manner as in Example 335, the title compound

was obtained from the compound of Reference Example 104 and N-methoxymethanamine hydrochloride.

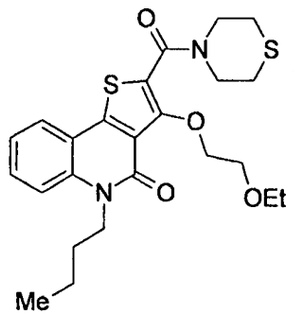
LC/MS 433 (M+H).

[2094]

Example 456

Production of 5-butyl-3-(2-ethoxyethoxy)-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2095]



[2096]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and thiomorpholine.

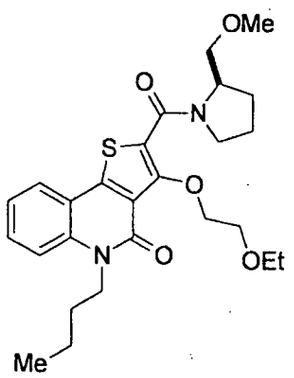
LC/MS 475 (M+H).

[2097]

Example 457

Production of 5-butyl-3-(2-ethoxyethoxy)-2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}thieno[3,2-c]quinolin-4(5H)-one

[2098]



[2099]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and (2R)-2-(methoxymethyl)pyrrolidine.

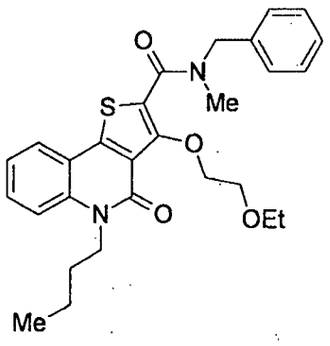
LC/MS 487 (M+H).

[2100]

Example 458

Production of N-benzyl-5-butyl-3-(2-ethoxyethoxy)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2101]



[2102]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N-methyl-1-phenylmethanamine.

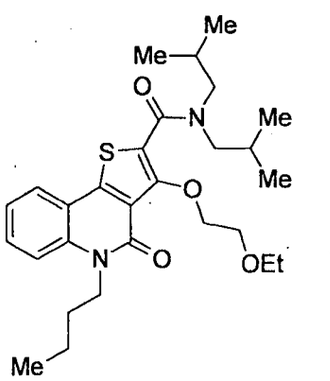
LC/MS 493 (M+H).

[2103]

Example 459

Production of 5-butyl-3-(2-ethoxyethoxy)-N,N-bis(2-methylpropyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2104]



[2105]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 104 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

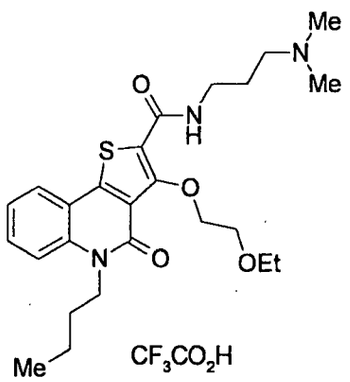
LC/MS 501 (M+H).

[2106]

Example 460

Production of 5-butyl-N-[3-(dimethylamino)propyl]-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2107]



[2108]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N,N-dimethylpropane-1,3-diamine.

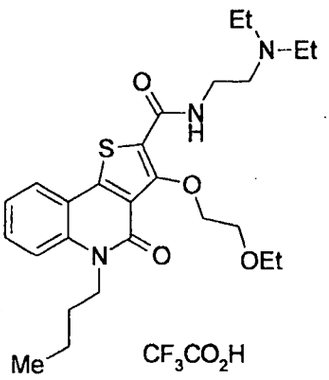
LC/MS 474 (M+H).

[2109]

Example 461

Production of 5-butyl-N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2110]



[2111]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N,N-diethylethane-1,2-diamine.

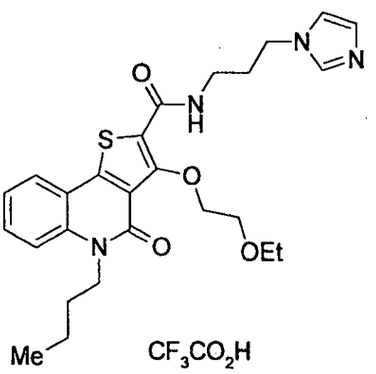
LC/MS 488 (M+H).

[2112]

Example 462

Production of 5-butyl-3-(2-ethoxyethoxy)-N-[3-(1H-imidazol-1-yl)propyl]-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2113]



[2114]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 3-(1H-imidazol-1-yl)propan-1-amine.

LC/MS 497 (M+H).

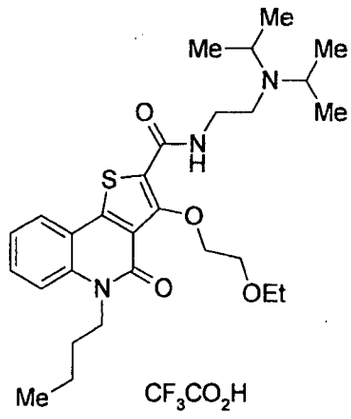
[2115]

Example 463

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-5-butyl-3-

(2-ethoxyethoxy)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2116]



[2117]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

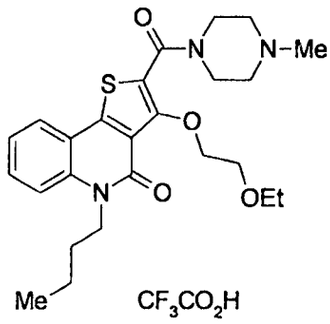
LC/MS 516 (M+H).

[2118]

Example 464

Production of 5-butyl-3-(2-ethoxyethoxy)-2-[(4-methylpiperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2119]



[2120]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-methylpiperazine.

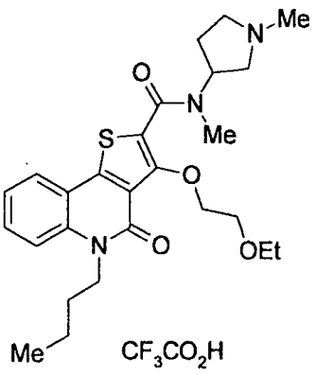
LC/MS 472 (M+H).

[2121]

Example 465

Production of 5-butyl-3-(2-ethoxyethoxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2122]



[2123]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and N,1-dimethylpyrrolidin-3-amine.

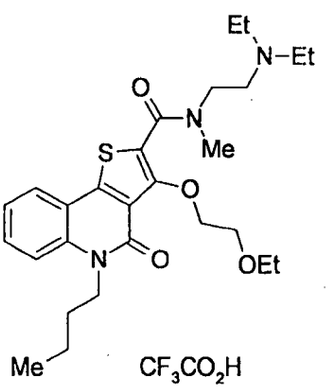
LC/MS 486 (M+H).

[2124]

Example 466

Production of 5-butyl-N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-N-methyl-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2125]



[2126]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 104 and N,N-diethyl-N'-methylethane-1,2-diamine.

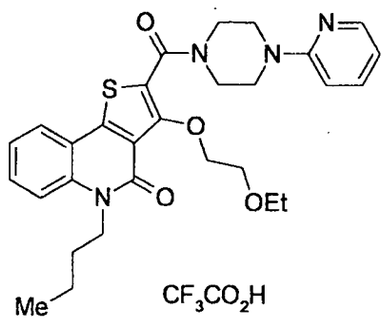
LC/MS 502 (M+H).

[2127]

Example 467

Production of 5-butyl-3-(2-ethoxyethoxy)-2-[(4-(pyridin-2-yl)piperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2128]



[2129]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 104 and 1-(pyridin-2-yl)piperazine.

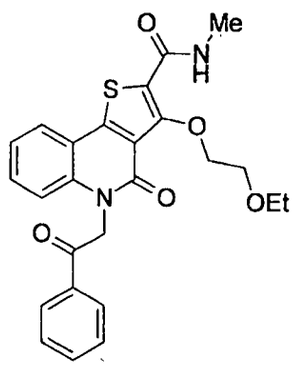
LC/MS 535 (M+H).

[2130]

Example 468

Production of 3-(2-ethoxyethoxy)-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2131]



[2132]

In the same manner as in Example 300, the title compound was obtained from the compound of Reference Example 21 and methanamine (2.0 M THF solution).

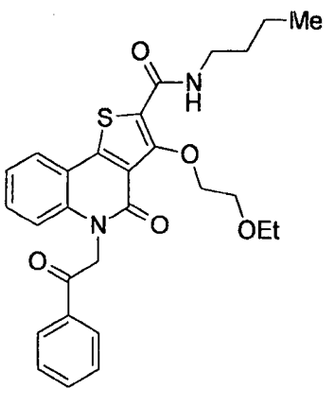
LC/MS 465 (M+H).

[2133]

Example 469

Production of N-butyl-3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2134]



[2135]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and butan-1-amine.

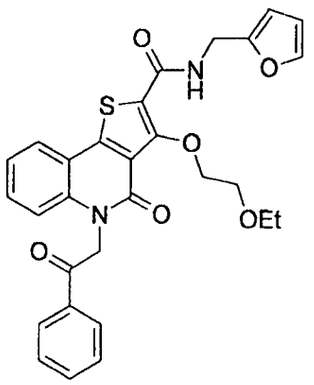
LC/MS 507 (M+H).

[2136]

Example 470

Production of 3-(2-ethoxyethoxy)-N-(furan-2-ylmethyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2137]



[2138]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-furan-2-ylmethanamine.

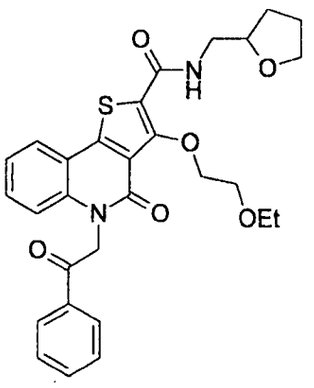
LC/MS 531 (M+H).

[2139]

Example 471

Production of 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2140]



[2141]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-(tetrahydrofuran-2-yl)methanamine.

LC/MS 535 (M+H).

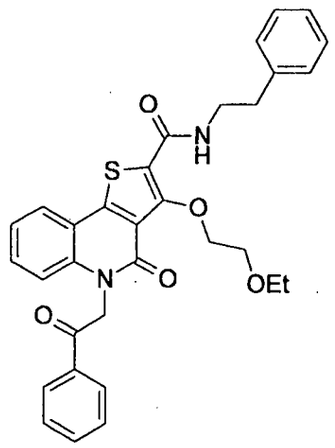
[2142]

Example 472

Production of 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-

phenylethyl)-N-(2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2143]



[2144]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 2-phenylethanamine.

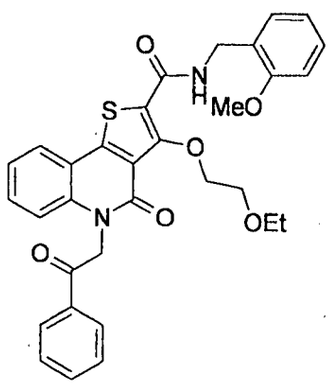
LC/MS 555 (M+H).

[2145]

Example 473

Production of 3-(2-ethoxyethoxy)-N-(2-methoxybenzyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2146]



[2147]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-

(2-methoxyphenyl)methanamine.

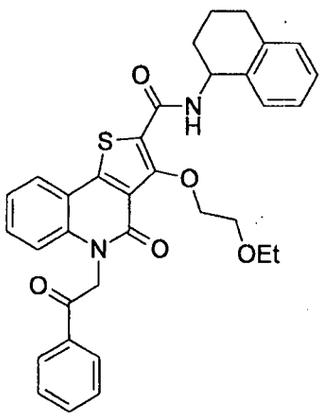
LC/MS 571 (M+H).

[2148]

Example 474

Production of 3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2149]



[2150]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1,2,3,4-tetrahydronaphthalen-1-amine.

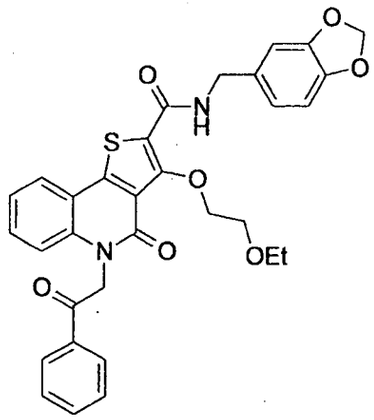
LC/MS 581 (M+H).

[2151]

Example 475

Production of N-(1,3-benzodioxol-5-ylmethyl)-3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2152]



[2153]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-(1,3-benzodioxol-5-yl)methanamine.

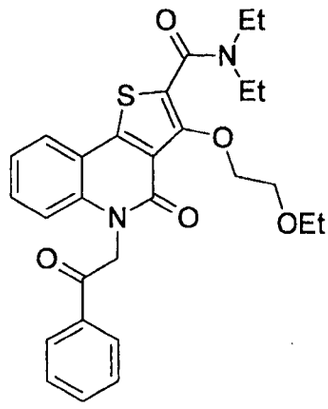
LC/MS 585 (M+H).

[2154]

Example 476

Production of 3-(2-ethoxyethoxy)-N,N-diethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2155]



[2156]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N-ethylethanamine.

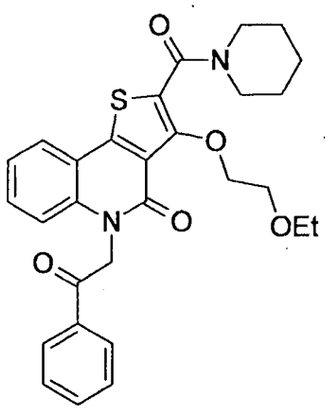
LC/MS 507 (M+H).

[2157]

Example 477

Production of 3-(2-ethoxyethoxy)-5-(2-oxo-2-phenylethyl)-2-(piperidin-1-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2158]



[2159]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and piperidine.

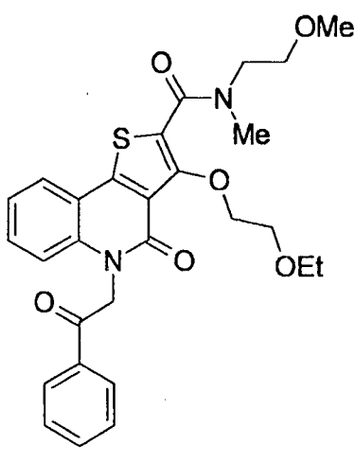
LC/MS 519 (M+H).

[2160]

Example 478

Production of 3-(2-ethoxyethoxy)-N-(2-methoxyethyl)-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2161]



[2162]

In the same manner as in Example 5, the title compound

was obtained from the compound of Reference Example 21 and 2-methoxy-N-methylethanamine.

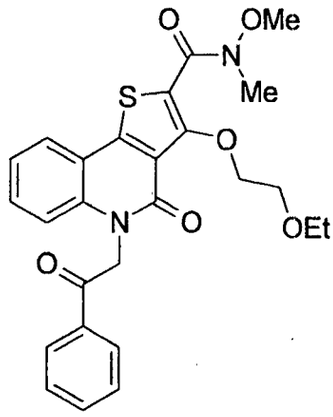
LC/MS 523 (M+H).

[2163]

Example 479

Production of 3-(2-ethoxyethoxy)-N-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2164]



[2165]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 21 and N-methoxymethanamine hydrochloride.

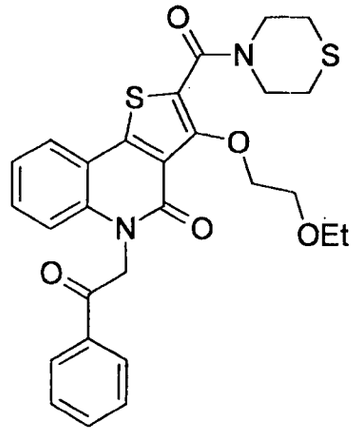
LC/MS 495 (M+H).

[2166]

Example 480

Production of 3-(2-ethoxyethoxy)-5-(2-oxo-2-phenylethyl)-2-(thiomorpholin-4-ylcarbonyl)thieno[3,2-c]quinolin-4(5H)-one

[2167]



[2168]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and thiomorpholine.

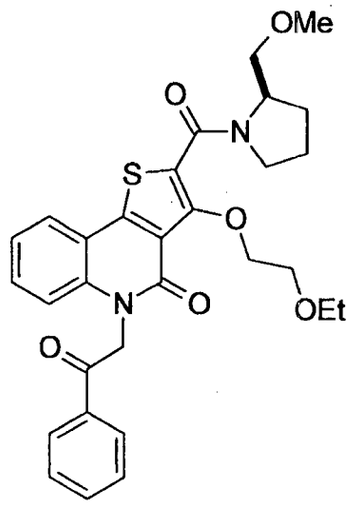
LC/MS 537 (M+H).

[2169]

Example 481

Production of 3-(2-ethoxyethoxy)-2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl}-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one

[2170]



[2171]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and (2R)-2-(methoxymethyl)pyrrolidine.

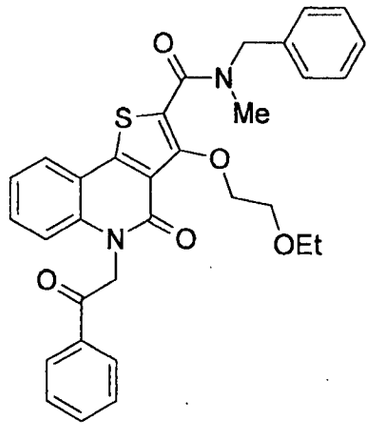
LC/MS 549 (M+H).

[2172]

Example 482

Production of N-benzyl-3-(2-ethoxyethoxy)-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2173]



[2174]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N-methyl-1-phenylmethanamine.

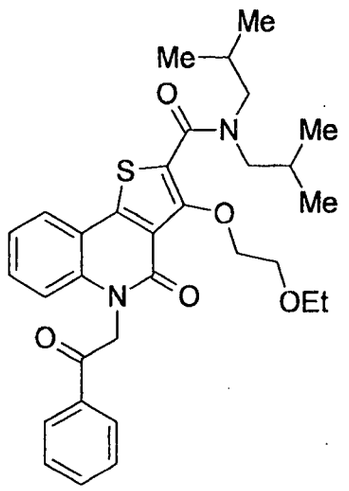
LC/MS 555 (M+H).

[2175]

Example 483

Production of 3-(2-ethoxyethoxy)-N,N-bis(2-methylpropyl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2176]



[2177]

In the same manner as in Example 335, the title compound was obtained from the compound of Reference Example 21 and 2-methyl-N-(2-methylpropyl)propan-1-amine hydrochloride.

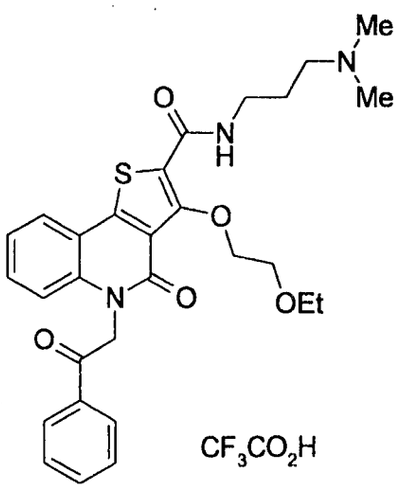
LC/MS 563 (M+H).

[2178]

Example 484

Production of N-[3-(dimethylamino)propyl]-3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2179]



[2180]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N,N-dimethylpropane-1,3-diamine.

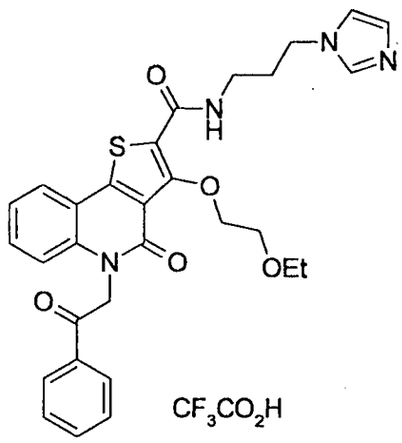
LC/MS 536 (M+H).

[2181]

Example 485

Production of 3-(2-ethoxyethoxy)-N-[3-(1H-imidazol-1-yl)propyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2182]



[2183]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 3-(1H-imidazol-1-yl)propan-1-amine.

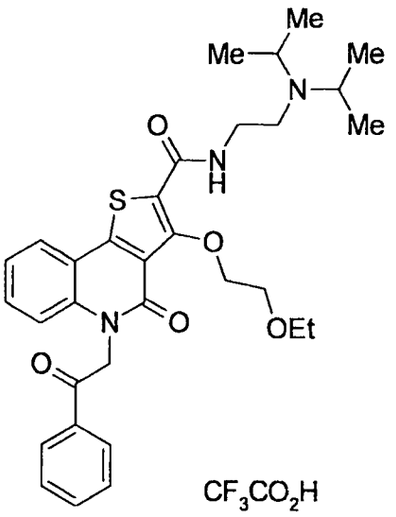
LC/MS 559 (M+H).

[2184]

Example 486

Production of N-{2-[bis(1-methylethyl)amino]ethyl}-3-(2-ethoxyethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2185]



[2186]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N,N-bis(1-methylethyl)ethane-1,2-diamine.

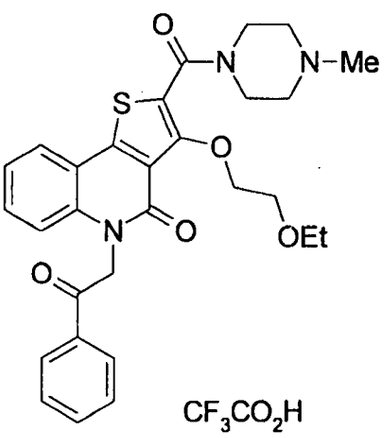
LC/MS 578 (M+H).

[2187]

Example 487

Production of 3-(2-ethoxyethoxy)-2-[(4-methylpiperazin-1-yl)carbonyl]-5-(2-oxo-2-phenylethyl)thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2188]



[2189]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-methylpiperazine.

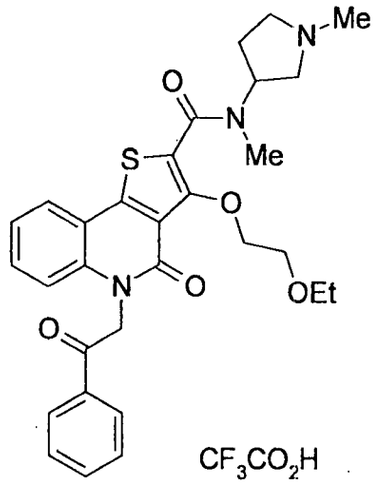
LC/MS 534 (M+H).

[2190]

Example 488

Production of 3-(2-ethoxyethoxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2191]



[2192]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N,1-dimethylpyrrolidin-3-amine.

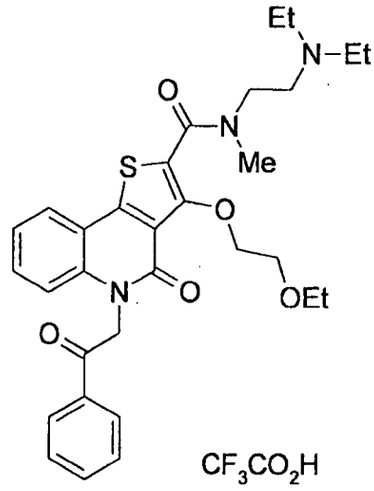
LC/MS 548 (M+H).

[2193]

Example 489

Production of N-[2-(diethylamino)ethyl]-3-(2-ethoxyethoxy)-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2194]



[2195]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and N,N-diethyl-N'-methylethane-1,2-diamine.

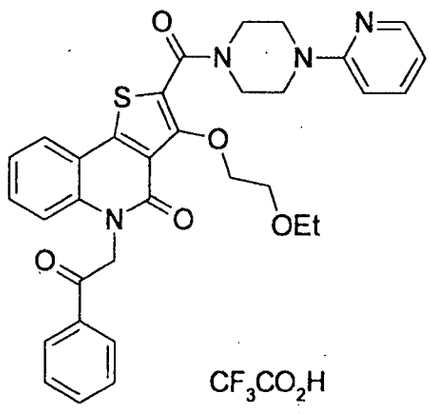
LC/MS 564 (M+H).

[2196]

Example 490

Production of 3-(2-ethoxyethoxy)-5-(2-oxo-2-phenylethyl)-2-[(4-(pyridin-2-yl)piperazin-1-yl)carbonyl]thieno[3,2-c]quinolin-4(5H)-one trifluoroacetate

[2197]



[2198]

In the same manner as in Example 5, the title compound was obtained from the compound of Reference Example 21 and 1-(pyridin-2-yl)piperazine.

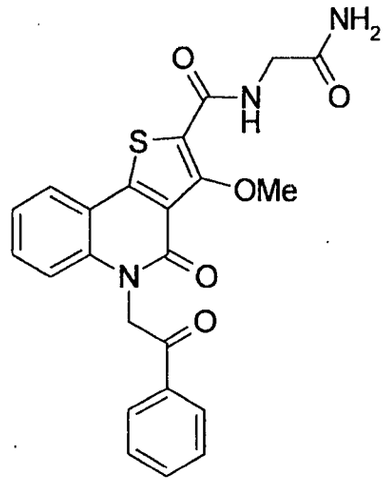
LC/MS 597 (M+H).

[2199]

Example 491

Production of N-(2-amino-2-oxoethyl)-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2200]



[2201]

To a solution of the compound of Reference Example 7 (175 mg, 0.44 mmol), glycine amide (56 mg, 0.51 mmol), HOBt (89 mg, 0.66 mmol) and WSCD (126 mg, 0.66 mmol) in DMF (5.0 mL) was added triethylamine (0.16 ml, 1.2 mmol), and the mixture was stirred at room temperature for 25 hr. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The obtained solid was washed with water, ethanol and diethyl ether, and recrystallized from DMF to give the title compound (124 mg, 54%) as white crystals.

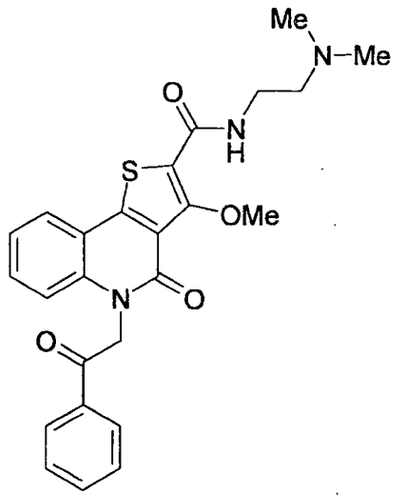
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.95 (2H, d, J = 5.3 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.19 (1H, s), 7.30-7.40 (1H, m), 7.45-7.69 (5H, m), 7.73-7.82 (1H, m), 8.06 (1H, dd, J = 7.9, 1.3 Hz), 8.13-8.22 (2H, m), 8.28 (1H, t, J = 5.3 Hz).

[2202]

Example 492

Production of N-[2-(dimethylamino)ethyl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2203]



[2204]

In the same manner as in Example 25, the title compound (124 mg, 81%) was obtained as a white powder from the compound of Reference Example 7 (130 mg, 0.33 mmol) and N,N-dimethylethylenediamine (44 mg, 0.49 mmol).

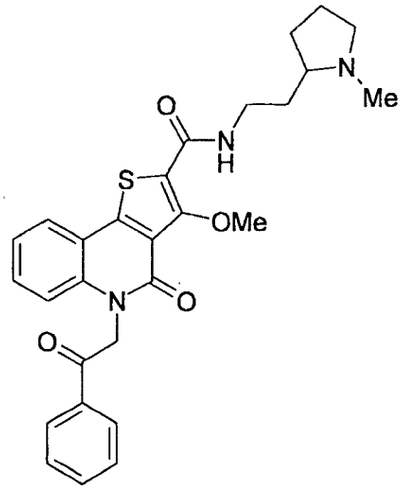
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.23 (6H, s), 2.45 (2H, d, J = 6.2 Hz), 3.42 (2H, q, J = 5.9 Hz), 4.02 (3H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.48 (1H, d, J = 8.7 Hz), 7.57 (1H, dd, J = 7.2, 1.5 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.05 (1H, dd, J = 8.1, 1.5 Hz), 8.13-8.19 (3H, m).

[2205]

Example 493

Production of 3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2206]



[2207]

In the same manner as in Example 25, the title compound (86 mg, 52%) was obtained as a white powder from the compound of Reference Example 7 (130 mg, 0.33 mmol) and 2-(2-aminoethyl)-1-methylpyrrolidine (63 mg, 0.49 mmol).

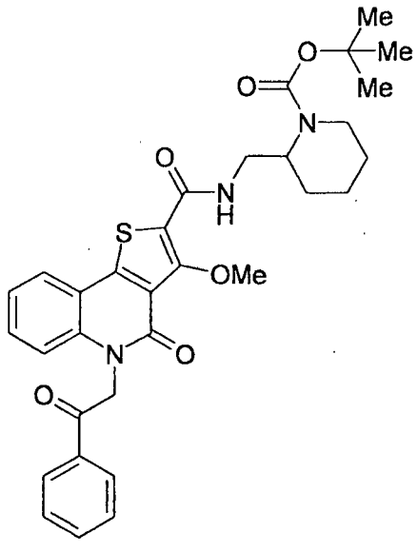
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.45-1.70 (4H, m), 1.78-2.15 (4H, m), 2.23 (3H, s), 2.90-2.97 (1H, m), 3.35-3.50 (2H, m), 4.01 (3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.1 Hz), 7.56 (1H, dd, J = 7.2, 1.5 Hz), 7.60-7.67 (2H, m), 7.77 (1H, t, J = 7.5 Hz), 8.04 (1H, dd, J = 7.8, 1.5 Hz), 8.16-8.22 (3H, m).

[2208]

Example 494

Production of tert-butyl 2-[({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]piperidine-1-carboxylate

[2209]



[2210]

In the same manner as in Example 25, the title compound (190 mg, 85%) was obtained as a white powder from the compound of Reference Example 7 (150 mg, 0.38 mmol) and 2-aminomethyl-N-Boc-piperidine (122 mg, 0.57 mmol).

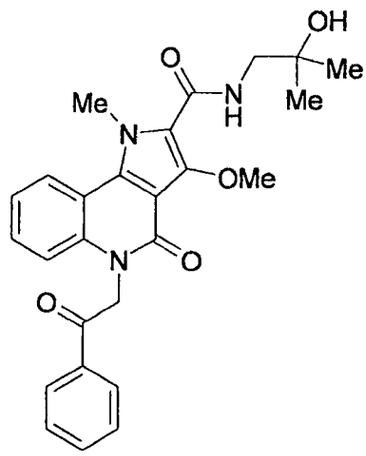
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.39 (9H, s), 1.40-1.60 (1H, m), 1.60-1.80 (5H, m), 2.94 (1H, t, J = 12.6 Hz), 3.51-3.57 (1H, m), 3.70-3.90 (1H, br), 4.03 (1H, d, J = 14.4 Hz), 4.15 (3H, s), 4.45-4.60 (1H, m), 5.86 (2H, s), 7.01 (1H, d, J = 8.4 Hz), 7.26-7.28 (1H, m), 7.47 (1H, td, J = 8.1, 1.5 Hz), 7.59 (2H, t, J = 7.4 Hz), 7.65-7.70 (2H, m), 7.90 (1H, dd, J = 7.8, 1.2 Hz), 8.10-8.13 (2H, m).

[2211]

Example 495

Production of N-(2-hydroxy-2-methylpropyl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2212]



[2213]

In the same manner as in Example 25, the title compound (215 mg, 91%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-amino-2-methylpropan-2-ol (59.3 mg, 0.666 mmol).

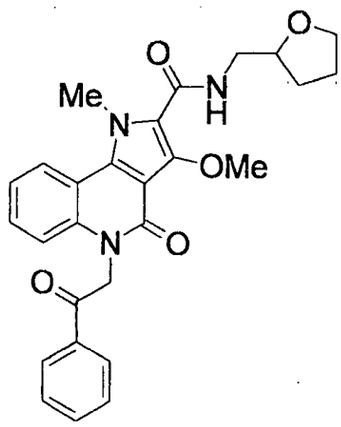
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (6H, s), 3.29 (2H, d, J = 5.7 Hz), 4.02 (3H, s), 4.38 (3H, s), 4.69 (1H, s), 5.98 (2H, s), 7.29-7.40 (2H, m), 7.46-7.51 (1H, m), 7.64 (2H, t, J = 7.4 Hz), 7.73-7.79 (1H, m), 8.03 (1H, t, J = 5.7 Hz), 8.16-8.19 (2H, m), 8.39 (1H, dd, J = 8.3, 1.1 Hz).

[2214]

Example 496

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2215]



[2216]

In the same manner as in Example 25, the title compound (199 mg, 82%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-(tetrahydrofuran-2-yl)methanamine (68.7 μL, 0.666 mmol).

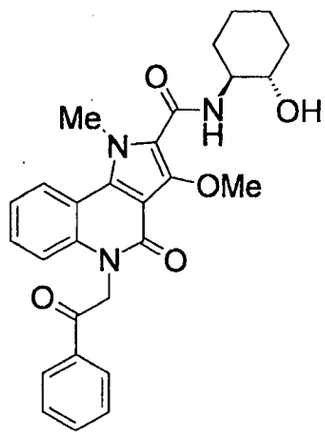
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.56-1.67 (1H, m), 1.76-1.99 (3H, m), 3.36-3.48 (2H, m), 3.63-3.71 (1H, m), 3.79-3.86 (1H, m), 3.96-4.04 (4H, m), 4.36 (3H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.03 (1H, t, J = 5.7 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[2217]

Example 497

Production of N-[trans-2-hydroxycyclohexyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2218]



[2219]

In the same manner as in Example 25, the title compound (168 mg, 67%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and trans-2-aminocyclohexanol hydrochloride (101 mg, 0.666 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.36 (4H, m), 1.55-1.70 (2H, m), 1.80-1.95 (1H, m), 1.95-2.10 (1H, m), 3.30-3.45 (1H, m), 3.55-3.70 (1H, m), 3.98 (3H, s), 4.36 (3H, s), 4.78 (1H, d, J = 5.4 Hz), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m),

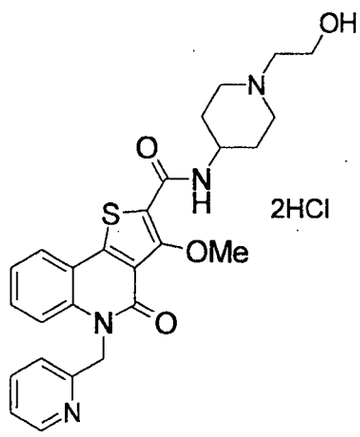
7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.87 (1H, d, J = 7.5 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[2220]

Example 498

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide dihydrochloride

[2221]



[2222]

A mixture of the compound of Example 667 (60 mg, 0.15 mmol), 2-(chloromethyl)pyridine hydrochloride (37 mg, 0.22 mmol), potassium carbonate (52 mg, 0.37 mmol) and DMF (2 mL) was stirred at room temperature for 3 hr and at 40°C for 1 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate, ethyl acetate/methanol=50/1 to 50/2) to give a white solid. To a solution of the white solid in ethyl acetate (2 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL), and precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (4.2 mg, 5%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.91-2.27 (4H, m), 3.05-3.30 (4H,

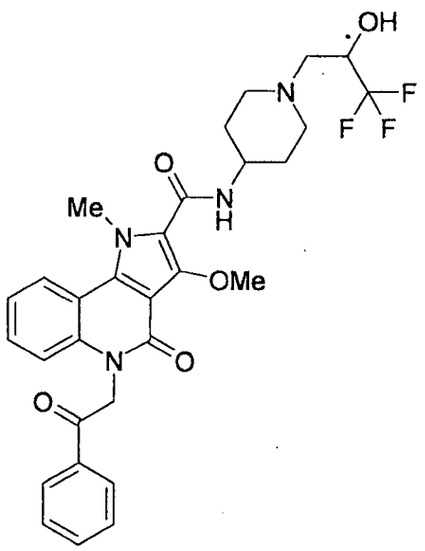
m), 3.60-3.80 (4H, m), 4.07-4.10 (4H, m), 5.69 (2H, s), 7.28-7.34 (3H, m), 7.41-7.58 (2H, m), 7.77 (1H, t, J = 8.6 Hz), 7.88 (1H, d, J = 7.5 Hz), 8.02 (1H, d, J = 8.1 Hz), 8.50 (1H, d, J = 2.7 Hz), 9.40-9.55 (2H, br), 9.60-9.70 (1H, br).

[2223]

Example 499

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-[1-(3,3,3-trifluoro-2-hydroxypropyl)piperidin-4-yl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2224]



[2225]

In the same manner as in Example 79, the title compound (150 mg, 64%) was obtained as a white powder from the compound of Example 77 (200 mg, 0.400 mmol), 3-bromo-1,1,1-trifluoropropan-2-ol (62.2 μL, 0.600 mmol) and potassium carbonate (249 mg, 1.80 mmol).

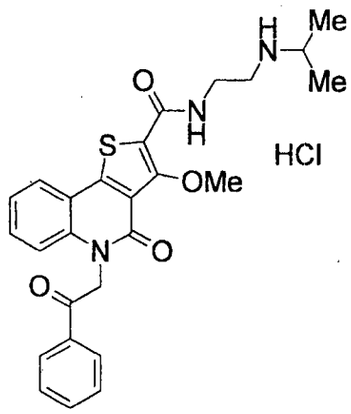
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.70 (2H, m), 1.80-1.95 (2H, m), 2.15-2.35 (2H, m), 2.45-2.60 (2H, m), 2.75-2.90 (2H, m), 3.75-3.90 (1H, m), 3.98 (3H, s), 4.05-4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.09-6.16 (1H, m), 7.28-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.7 Hz), 7.73-7.79 (1H, m), 7.90 (1H, d, J = 8.1 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.3, 1.4 Hz).

[2226]

Example 500

Production of 3-methoxy-N-{2-[(1-methylethyl)amino]ethyl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[2227]



[2228]

To a solution of the compound of Example 97 (150 mg, 0.30 mmol) in ethyl acetate (10 mL) was added 4N hydrogen chloride ethyl acetate solution (0.1 mL), and the resulting precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (107 mg, 69%) as a white powder.

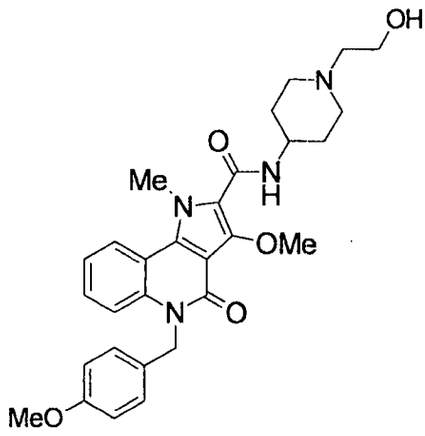
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (6H, d, J = 6.6 Hz), 3.13 (2H, br s), 3.30-3.45 (1H, m), 3.68 (2H, q, J = 5.9 Hz), 4.07 (3H, s), 6.00 (2H, s), 7.36 (1H, t, J = 7.5 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.57-7.67 (3H, m), 7.78 (1H, t, J = 7.4 Hz), 8.06 (1H, dd, J = 7.8, 1.2 Hz), 8.18 (2H, d, J = 8.4 Hz), 8.29 (1H, t, J = 5.9 Hz), 8.77 (2H, br s).

[2229]

Example 501

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2230]



[2231]

In the same manner as in Example 79, the title compound (1.91 g, 75%) was obtained as white crystals from the compound of Example 681 (2.50 g, 4.89 mmol).

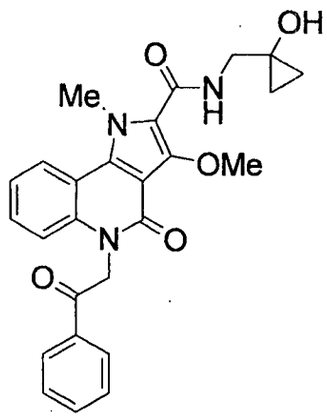
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58 (2H, q, J = 9.9 Hz), 1.85 (2H, d, J = 9.6 Hz), 2.18 (2H, t, J = 9.9 Hz), 2.40 (2H, t, J = 6.3 Hz), 2.78 (2H, d, J = 11.4 Hz), 3.50 (2H, q, J = 6.0 Hz), 3.69 (3H, s), 3.70-3.85 (1H, br), 4.04 (3H, s), 4.29 (3H, s), 4.35-4.40 (1H, m), 5.40-5.65 (2H, br), 6.86 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.24-7.30 (1H, m), 7.42-7.49 (2H, m), 7.91 (1H, d, J = 7.8 Hz), 8.33 (1H, d, J = 8.1 Hz).

[2232]

Example 502

Production of N-[(1-hydroxycyclopropyl)methyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2233]



[2234]

In the same manner as in Example 25, the title compound (219 mg, 93%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-(aminomethyl)cyclopropanol (58.0 mg, 0.666 mmol).

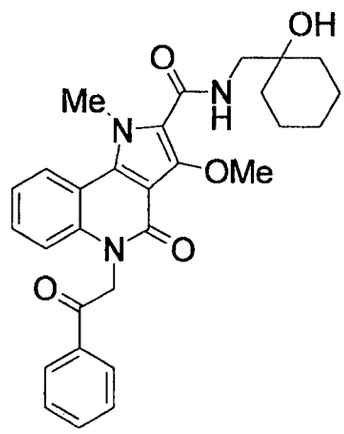
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.55-0.65 (4H, m), 3.46 (2H, d, J = 5.8 Hz), 4.01 (3H, s), 4.37 (3H, s), 5.50 (1H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.10 (1H, t, J = 5.8 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.1, 1.2 Hz).

[2235]

Example 503

Production of N-[(1-hydroxycyclohexyl)methyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2236]



[2237]

In the same manner as in Example 25, the title compound (235 mg, 92%) was obtained as a white powder from the compound of Reference Example 28 (200 mg, 0.512 mmol) and 1-(aminomethyl)cyclohexanol (110 mg, 0.666 mmol).

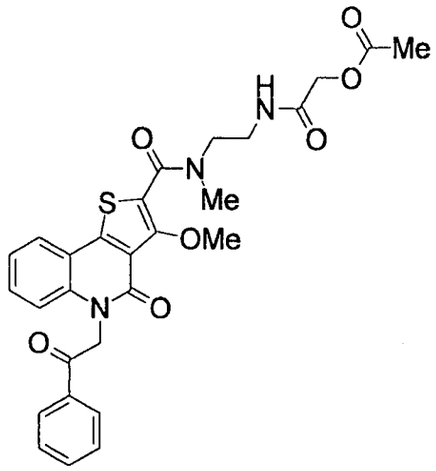
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.70 (10H, m), 3.25-3.40 (2H, m), 4.01 (3H, s), 4.38 (3H, s), 4.50 (1H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.7 Hz), 7.73-7.79 (1H, m), 8.02 (1H, t, J = 5.6 Hz), 8.16-8.19 (2H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

[2238]

Example 504

Production of 2-({2-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]ethyl}amino)-2-oxoethyl acetate

[2239]



[2240]

To a solution of the compound of Example 103 (150 mg, 0.31 mmol) and triethylamine (69 mg, 0.68 mmol) in THF (10 mL) was added acetoxyacetyl chloride (46 mg, 0.34 mmol) under ice-cooling. After stirring at room temperature for 1 hr, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate to ethyl acetate/methanol=50/1) to give a white solid. Recrystallization of the white solid from ethyl acetate-hexane gave the title compound (140 mg, 82%) as white crystals.

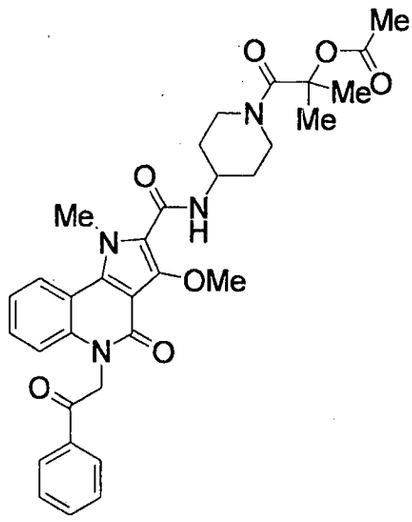
^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.28 (3H, s), 3.19 (3H, s), 3.62 (2H, br s), 3.77 (2H, br s), 4.02 (3H, s), 4.60 (2H, s), 5.87 (2H, s), 7.04 (1H, d, J = 8.4 Hz), 7.20-7.28 (1H, m), 7.45-7.50 (2H, m), 7.56 (2H, t, J = 7.5 Hz), 7.67 (1H, dd, J = 7.5, 1.5 Hz), 7.84 (1H, dd, J = 8.1, 1.2 Hz), 8.10-8.13 (2H, m).

[2241]

Example 505

Production of 2-[4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-1,1-dimethyl-2-oxoethyl acetate

[2242]



[2243]

In the same manner as in Example 504, the title compound was obtained as a colorless oil from the compound of Example 77 (200 mg, 0.423 mmol) and 2-chloro-1,1-dimethyl-2-oxoethyl acetate (63.0 μL, 0.440 mmol).

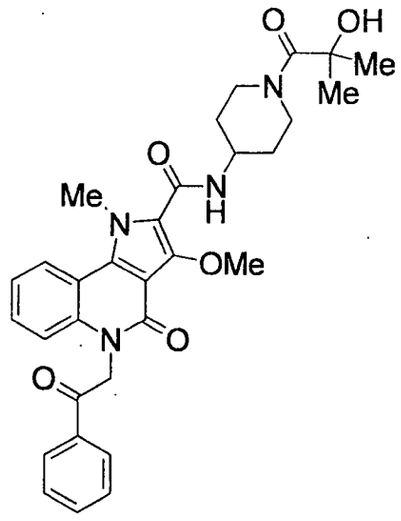
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.36-1.50 (10H, m), 1.80-1.95 (2H, m), 2.07 (3H, s), 2.75-3.40 (2H, m), 3.96 (3H, s), 4.00-4.25 (1H, m), 4.29 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2244]

Example 506

Production of N-[1-(2-hydroxy-2-methylpropanoyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2245]



[2246]

In the same manner as in Example 508, the title compound (123 mg, 55%) was obtained as a white powder from the compound of Example 505, 8N aqueous sodium hydroxide solution (1.5 mL) and ethanol (12 mL).

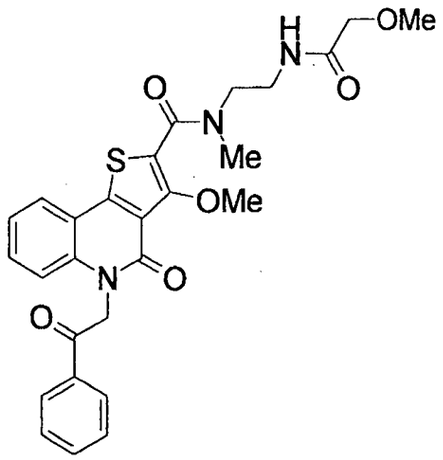
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.33 (6 H, s), 1.40-1.60 (2 H, m), 1.80-1.95 (2 H, m), 2.75-3.45 (2 H, m), 3.97 (3 H, s), 4.00-4.20 (1 H, m), 4.31 (3H, s), 4.20-4.80 (2H, m), 5.39 (1 H, s), 5.97 (2 H, s), 7.29-7.39 (2 H, m), 7.45-7.50 (1 H, m), 7.63 (2 H, t, J = 7.5 Hz), 7.73-7.79 (1 H, m), 7.93 (1 H, d, J = 8.1 Hz), 8.15-8.18 (2 H, m), 8.37 (1 H, d, J = 8.3, 1.4 Hz).

[2247]

Example 507

Production of 3-methoxy-N-{2-[(methoxyacetyl)amino]ethyl}-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2248]



[2249]

To a solution of the compound of Example 103 (100 mg, 0.21 mmol) and triethylamine (46 mg, 0.45 mmol) in THF (10 mL) was added methoxyacetyl chloride (25 mg, 0.23 mmol) under ice-cooling. After stirring at room temperature for 2 hr, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate to ethyl acetate/methanol=50/1) to give a white solid. Recrystallization of the white solid from ethyl acetate-hexane gave the title compound (61 mg, 56%) as a white powder.

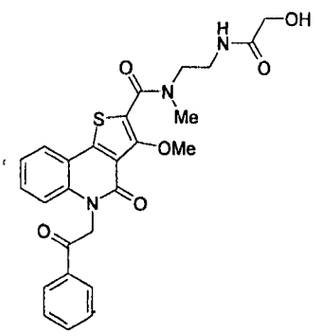
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.06 (3H, s), 3.30-3.50 (5H, m), 3.50-3.65 (2H, br), 3.70-3.95 (5H, m), 5.98 (2H, s), 7.34 (1H, t, J = 7.4 Hz), 7.46-7.96 (7H, m), 8.18 (2H, d, J = 7.5 Hz).

[2250]

Example 508

Production of N-{2-[(hydroxyacetyl)amino]ethyl}-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2251]



[2252]

A mixed solution of the compound of Example 504 (120 mg, 0.22 mmol) and 4N aqueous sodium hydroxide solution (2 mL) in THF (4 mL)-methanol (4 mL) was stirred at room temperature for 2 hr, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. Recrystallization of the crude solid from ethyl acetate-hexane gave the title compound (65 mg, 58%) as white crystals.

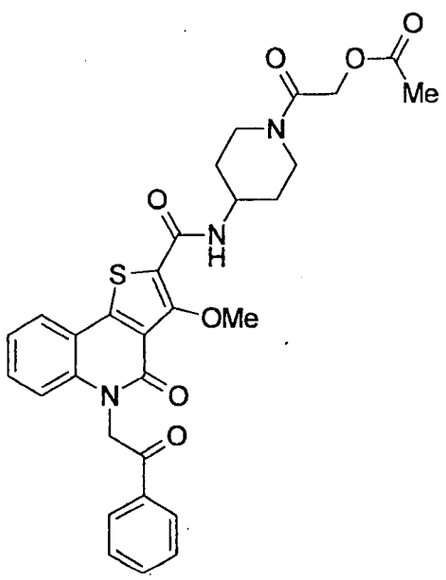
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.06 (3H, s), 3.20-3.40 (2H, m), 3.45-3.60 (2H, br), 3.70-3.86 (5H, m), 5.40-5.55 (1H, br), 5.98 (2H, s), 7.34 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 8.4 Hz), 7.55 (1H, t, J = 7.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 7.87-7.96 (2H, m), 8.16-8.19 (2H, m).

[2253]

Example 509

Production of 2-[4-({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2254]



[2255]

In the same manner as in Example 123, the title compound (429 mg, 56%) was obtained as a white solid from the compound of Example 105 (620 mg, 1.20 mmol).

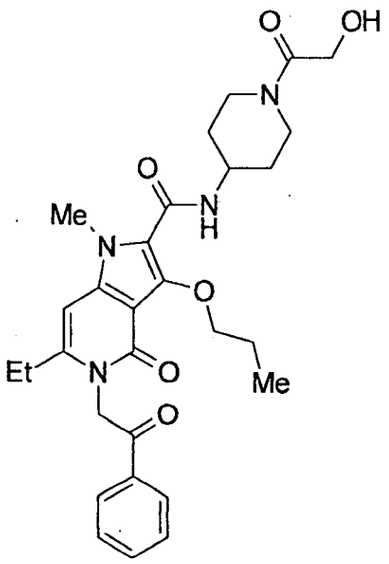
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.44-1.64 (2H, m), 2.01-2.28 (5H, m), 2.88-3.05 (1H, m), 3.17-3.34 (1H, m), 3.59-3.75 (1H, m), 4.15 (3H, s), 4.19-4.35 (1H, m), 4.41-4.54 (1H, m), 4.65-4.84 (2H, m), 5.87 (2H, s), 7.03 (1H, d, J = 8.5 Hz), 7.28-7.35 (1H, m), 7.43-7.52 (1H, m), 7.52-7.63 (3H, m), 7.65-7.74 (1H, m), 7.91 (1H, dd, J = 7.9, 1.3 Hz), 8.06-8.18 (2H, m).

[2256]

Example 510

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-propoxy-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2257]



[2258]

In the same manner as in Example 140, the title compound (199 mg, 74%) was obtained as a white powder from the compound of Reference Example 173 (198 mg, 0.50 mmol).

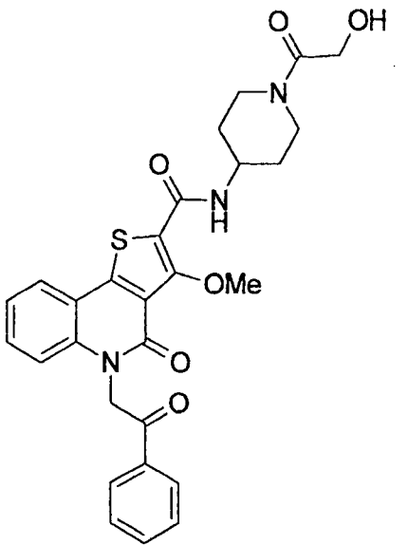
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.92 (3H, t, J = 7.4 Hz), 1.18 (3H, t, J = 7.3 Hz), 1.26-1.55 (2H, m), 1.59-1.75 (2H, m), 1.83-1.97 (2H, m), 2.57 (2H, q, J = 7.4 Hz), 2.77-2.91 (1H, m), 3.01-3.18 (1H, m), 3.60-3.75 (1H, m), 3.89 (3H, s), 3.97-4.14 (3H, m), 4.20-4.34 (3H, m), 4.51 (1H, t, J = 5.4 Hz), 5.59 (2H, s), 6.48 (1H, s), 7.56-7.68 (3H, m), 7.69-7.78 (1H, m), 8.07-8.15 (2H, m).

[2259]

Example 511

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2260]



[2261]

To a mixed solution of the compound of Example 509 (200 mg, 0.35 mmol) in THF (3.2 mL)-ethanol (11 mL) was added 8N aqueous sodium hydroxide solution (1.6 mL, 13 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was neutralized with 2N hydrochloric acid, and extracted with ethyl acetate-THF mixed solvent. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and subjected to aminosilica gel filtration. The filtrate was concentrated under reduced pressure, the residue was recrystallized from THF-ethyl acetate to give the title compound (93 mg, 50%) as a white solid.

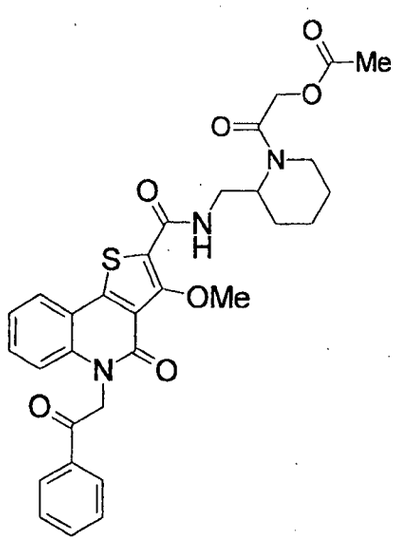
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.43-1.64 (2H, m), 2.07-2.24 (2H, m), 2.98-3.24 (2H, m), 3.44-3.58 (1H, m), 3.62 (1H, t, J = 4.3 Hz), 4.15 (3H, s), 4.19 (2H, d, J = 4.3 Hz), 4.22-4.35 (1H, m), 4.44-4.57 (1H, m), 5.86 (2H, s), 7.03 (1H, d, J = 8.5 Hz), 7.28-7.34 (1H, m), 7.44-7.63 (4H, m), 7.64-7.73 (1H, m), 7.91 (1H, dd, J = 7.8, 1.4 Hz), 8.06-8.16 (2H, m).

[2262]

Example 512

Production of 2-{2-[({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]piperidin-1-yl}-2-oxoethyl acetate

[2263]



[2264]

In the same manner as in Example 123, the title compound was obtained as a colorless oil from the compound of Example 84 (500 mg, 0.95 mmol) and acetoxyacetyl chloride (142 mg, 1.04 mmol).

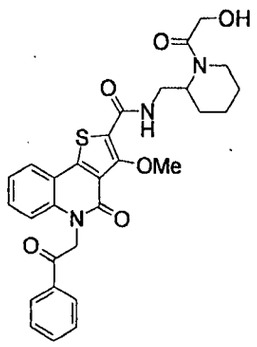
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.80 (6H, m), 2.00 (3H, s), 2.81 (0.5H, t, J = 13.1 Hz), 3.20-3.90 (3H, m), 3.99-4.04 (3.5H, m), 4.24 (0.5H, d, J = 10.5 Hz), 4.65 (0.5H, d, J = 14.7 Hz), 4.80-4.82 (2H, m), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.2 Hz), 7.89 (0.5H, br t), 8.04 (1H, d, J = 8.1 Hz), 8.17-8.19 (2H, m), 8.26 (0.5H, br s).

[2265]

Example 513

Production of N-{[1-(hydroxyacetyl)piperidin-2-yl]methyl}-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2266]



[2267]

In the same manner as in Example 508, the title compound (109 mg, 58%) was obtained as a white powder from the compound of Example 512 (200 mg, 0.34 mmol).

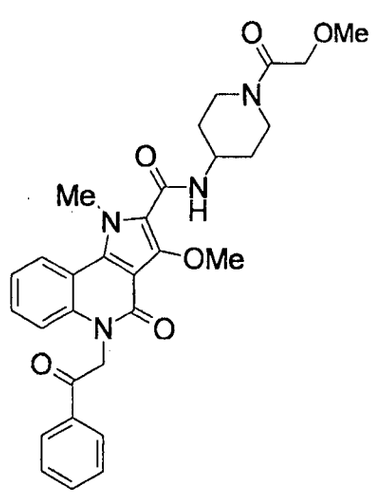
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.10-1.80 (6H, m), 2.86 (0.5H, t, J = 12.9 Hz), 3.26 (0.5H, t, J = 15.0 Hz), 3.35-3.48 (1.5H, m), 3.70-3.90 (0.5H, m), 3.90-4.05 (4H, m), 4.05-4.15 (1.5H, m), 4.25-4.40 (1.5H, m), 4.75-4.90 (0.5H, m), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 7.85-7.95 (0.5H, br), 8.04 (1H, dd, J = 7.8, 1.2 Hz), 8.16-8.19 (2.5H, m).

[2268]

Example 514

Production of 3-methoxy-N-[1-(methoxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2269]



[2270]

In the same manner as in Example 507, the title compound was obtained (159 mg, 73%) as a white powder from the compound of Example 77 (200 mg, 0.423 mmol) and methoxyacetyl chloride (40.3 μL, 0.440 mmol).

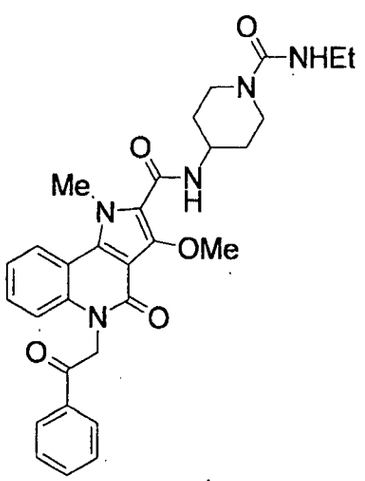
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.35-1.65 (2 H, m), 1.80-2.00 (2 H, m), 2.80-2.95 (1 H, m), 3.05-3.25 (1 H, m), 3.30 (3 H, s), 3.65-3.85 (1 H, m), 3.97 (3 H, s), 4.00-4.25 (4 H, m), 4.31 (3 H, s), 5.97 (2 H, s), 7.29-7.39 (2 H, m), 7.45-7.50 (1 H, m), 7.63 (2 H, t, J = 7.7 Hz), 7.73-7.79 (1 H, m), 7.95 (1 H, d, J = 8.1 Hz), 8.15-8.18 (2 H, m), 8.37 (1 H, dd, J = 8.3, 1.1 Hz).

[2271]

Example 515

Production of N-[1-(ethylcarbamoyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2272]



[2273]

To a mixture of the compound of Example 77 (200 mg, 0.423 mmol) and THF (10 mL) was added ethyl isocyanate (101 μL, 1.27 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). Recrystallization of the obtained solid from ethyl

acetate-THF gave the title compound (172 mg, 75%) as a white powder.

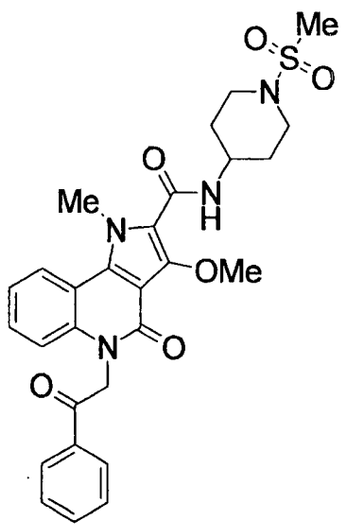
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.01 (3H, t, J = 7.1 Hz), 1.35-1.50 (2H, m), 1.75-1.90 (2H, m), 2.80-3.10 (4H, m), 3.80-3.95 (2H, m), 3.96 (3H, s), 3.95-4.10 (1H, m), 4.30 (3H, s), 5.97 (2H, s), 6.48 (1H, t, J = 5.4 Hz), 7.28-7.39 (2H, m), 7.44-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.93 (1H, d, J = 8.1 Hz), 8.15-8.18 (2H, m), 8.36 (1H, dd, J = 8.3, 1.1 Hz).

[2274]

Example 516

Production of 3-methoxy-1-methyl-N-[1-(methylsulfonyl)piperidin-4-yl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2275]



[2276]

To a mixture of the compound of Example 77 (200 mg, 0.423 mmol), triethylamine (423 μL, 3.18 mmol) and THF (10 mL) was added methanesulfonyl chloride (98.3 μL, 1.27 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate).

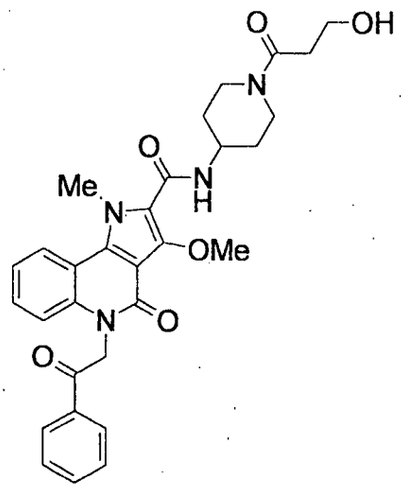
Recrystallization of the obtained solid from ethyl acetate gave the title compound (141 mg, 61%) as a white powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.60-1.75 (2H, m), 1.90-2.05 (2H, m), 2.85-3.05 (5H, m), 3.45-3.60 (2H, m), 3.90-4.05 (1H, m), 3.98 (3H, s), 4.30 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 8.00 (1H, d, J = 7.8 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2277]

Example 517

Production of N-[1-(3-hydroxypropanoyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2278]



[2279]

To a mixture of the compound of Example 77 (200 mg, 0.423 mmol), triethylamine (423 μL, 3.18 mmol) and THF (10 mL) was added β-propiolactone (39.9 μL, 0.635 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). Recrystallization of the obtained solid from ethyl acetate gave the title compound (70.0 mg, 30%) as a white powder.

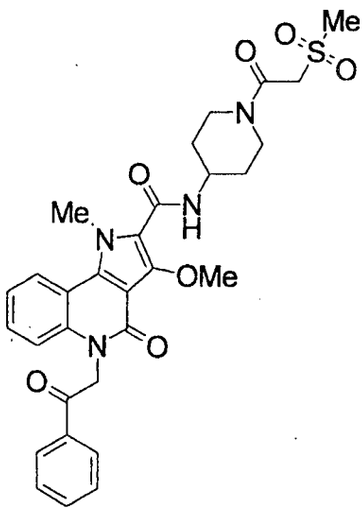
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.30-1.60 (2 H, m), 1.80-2.00 (2 H, m), 2.45-2.55 (2 H, m), 2.80-2.90 (1 H, m), 3.15-3.25 (1 H, m), 3.61-3.70 (2 H, m), 3.80-3.95 (1 H, m), 3.97 (3 H, s), 4.00-4.15 (1 H, m), 4.15-4.35 (1 H, m), 4.31 (3H, s), 4.51 (1 H, t, J=5.4 Hz), 5.97 (2 H, s), 7.29-7.39 (2 H, m), 7.45-7.50 (1 H, m), 7.63 (2 H, t, J =7.5 Hz), 7.73-7.79 (1 H, m), 7.94 (1 H, d, J = 7.8 Hz), 8.15-8.22 (2 H, m), 8.37 (1 H, dd, J = 8.4, 1.2 Hz).

[2280]

Example 518

Production of 3-methoxy-1-methyl-N-{1-[(methylsulfonyl)acetyl]piperidin-4-yl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2281]



[2282]

To a solution of the compound of Example 77 (200 mg, 0.423 mmol), (methylsulfonyl)acetic acid (76.0 mg, 0.550 mmol) and HOBt (85.8 mg, 0.635 mmol) in DMF (4 mL) was added WSCD (122 mg, 0.635 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over

magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). Recrystallization of the obtained solid from ethyl acetate gave the title compound (60.3 mg, 24%) as white crystals.

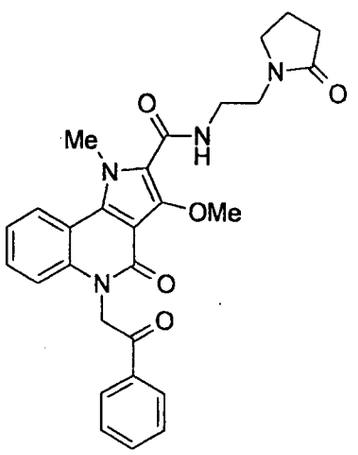
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.35-1.70 (2H, m), 1.85-2.00 (2H, m), 2.90-3.05 (1H, m), 3.10 (3H, s), 3.20-3.35 (1H, m), 3.90-4.20 (5H, m), 4.20-4.35 (1H, m), 4.30 (3H, s), 4.50 (2H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.45-7.50 (1H, m), 7.63 (2H, t, J = 7.7 Hz), 7.73-7.79 (1H, m), 7.98 (1H, d, J = 7.8 Hz), 8.16-8.18 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2283]

Example 519

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2284]



[2285]

In the same manner as in Example 25, the title compound (153 mg, 60%) was obtained as a pale-yellow solid from the compound of Reference Example 28 (200 mg, 0.51 mmol), 1-(2-aminoethyl)pyrrolidin-2-one (72 mg, 0.56 mmol), HOBt (89 mg, 0.66 mmol), WSCD (127 mg, 0.66 mmol) and DMF (6.0 mL).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.97-2.14 (2H, m), 2.40 (2H, t, J = 8.1 Hz), 3.44-3.59 (4H, m), 3.60-3.70 (2H, m), 4.18 (3H, s),

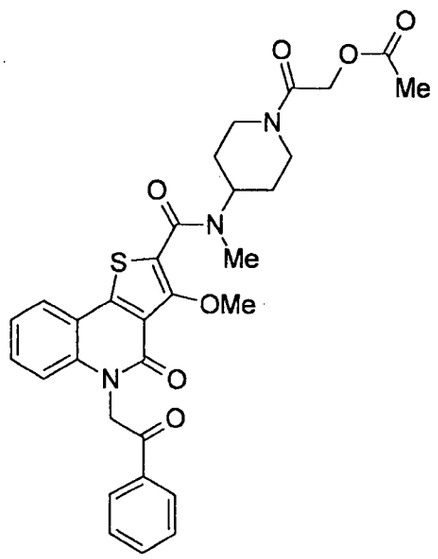
4.47 (3H, s), 5.88 (2H, s), 7.00-7.09 (1H, m), 7.21-7.33 (1H, m), 7.35-7.45 (1H, m), 7.49-7.59 (2H, m), 7.62-7.71 (1H, m), 7.81 (1H, t, J = 5.4 Hz), 8.07-8.16 (2H, m), 8.25 (1H, dd, J = 8.3, 1.3 Hz).

[2286]

Example 520

Production of 2-{4-[{[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]piperidin-1-yl}-2-oxoethyl acetate

[2287]



[2288]

In the same manner as in Example 73, N-methyl-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride was obtained from the compound of Reference Example 7 (500 mg, 1.3 mmol) and tert-butyl 4-(methylamino)piperidine-1-carboxylate (327 mg, 1.5 mmol), and followed by the same manners as in Example 500 and 130 the title compound (182 mg, 24%) was obtained as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.59-1.91 (4H, m), 2.08 (3H, s), 2.57-2.77 (1H, m), 2.91 (3H, s), 2.99-3.17 (1H, m), 3.32 (1H, m), 3.69-3.90 (4H, m), 4.29-4.50 (1H, m), 4.78 (2H, s), 5.98 (2H, s), 7.30-7.38 (1H, m), 7.43-7.70 (4H, m), 7.73-7.82 (1H,

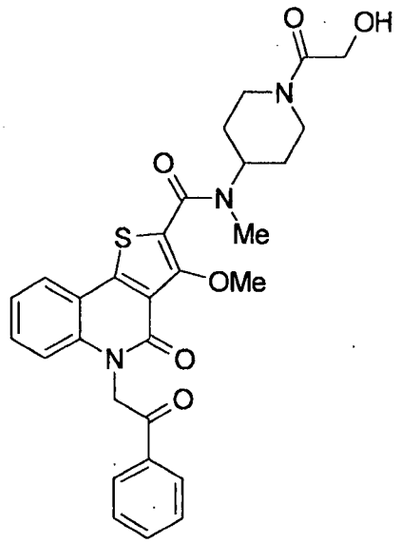
m), 7.97 (1H, dd, J = 7.9, 1.3 Hz), 8.11-8.22 (2H, m).

[2289]

Example 521

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-N-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2290]



[2291]

In the same manner as in Example 511, the title compound (115 mg, 66%) was obtained as a white solid from the compound of Reference Example 520 (187 mg, 0.32 mmol), 8N aqueous sodium hydroxide solution (1.6 mL), THF (3.2 mL) and ethanol (11 mL).

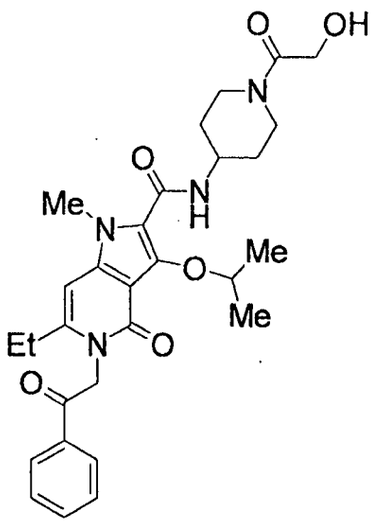
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.64-1.98 (4H, m), 2.67-2.89 (1H, m), 3.00 (3H, s), 3.05-3.19 (1H, m), 3.52-3.66 (2H, m), 4.01 (3H, s), 4.10-4.26 (3H, m), 4.66-4.85 (1H, m), 5.87 (2H, s), 7.04 (1H, d, J = 8.5 Hz), 7.23-7.32 (1H, m), 7.42-7.51 (1H, m), 7.52-7.62 (2H, m), 7.63-7.75 (1H, m), 7.84 (1H, dd, J = 7.9, 1.3 Hz), 7.99-8.20 (2H, m).

[2292]

Example 522

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-3-(1-methylethoxy)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2293]



[2294]

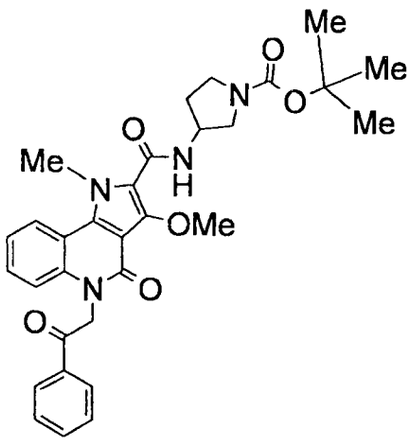
In the same manner as in Example 140, the title compound (237 mg, 88%) was obtained as a colorless powder from the compound of Reference Example 174 (188 mg, 0.50 mmol).
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.12-1.26 (9H, m), 1.26-1.57 (2H, m), 1.84-1.97 (2H, m), 2.57 (2H, q, J = 7.4 Hz), 2.76-2.94 (1H, m), 3.02-3.20 (1H, m), 3.59-3.76 (1H, m), 3.91 (3H, s), 3.96-4.19 (3H, m), 4.21-4.34 (1H, m), 4.50 (1H, t, J = 5.5 Hz), 4.94-5.09 (1H, m), 5.59 (2H, s), 6.48 (1H, s), 7.56-7.69 (3H, m), 7.69-7.78 (1H, m), 8.06-8.16 (2H, m).

[2295]

Example 523

Production of tert-butyl 3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)pyrrolidine-1-carboxylate

[2296]



[2297]

In the same manner as in Example 25, the title compound was obtained as a white powder from the compound of Reference Example 28 (400 mg, 1.02 mmol) and tert-butyl 3-aminopyrrolidine-1-carboxylate (248 mg, 1.33 mmol).

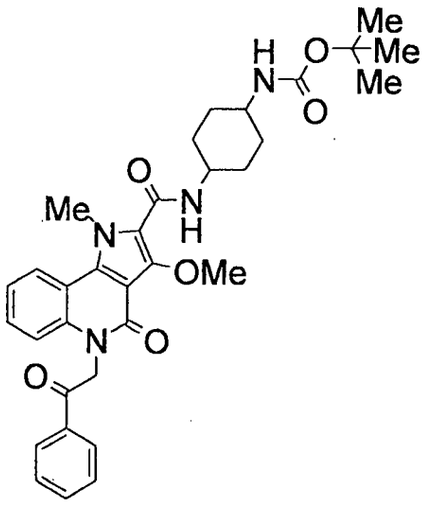
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.41 (9 H, s), 1.87-2.02 (1 H, m), 2.05-2.19 (1 H, m, J = 14.7 Hz), 3.19-3.46 (3 H, m), 3.48-3.61 (1 H, m), 3.95 (3 H, s), 4.30 (3 H, s), 4.40-4.52 (1 H, m), 5.97 (2 H, s), 7.27-7.41 (2 H, m), 7.44-7.53 (1 H, m), 7.63 (2 H, t, J =7.6 Hz), 7.72-7.80 (1 H, m), 8.11-8.22 (3 H, m), 8.37 (1 H, dd, J = 8.3, 1.1 Hz).

[2298]

Example 524

Production of tert-butyl [4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexyl]carbamate

[2299]



[2300]

In the same manner as in Example 25, the title compound was obtained as a white powder from the compound of Reference Example 28 (400 mg, 1.02 mmol) and tert-butyl (4-aminocyclohexyl)carbamate (285 mg, 1.33 mmol).

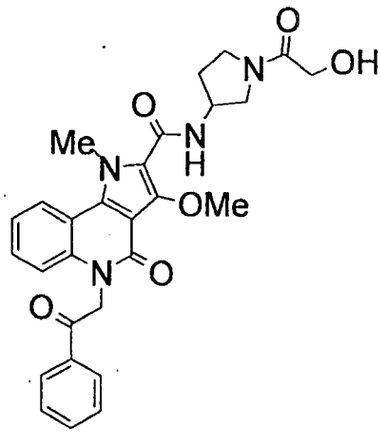
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.16-1.69 (13H, m), 1.72-1.96 (4H, m), 3.16-3.29 (1H, m), 3.65-3.80 (1H, m, J = 11.1 Hz), 3.95 (2.5H, s), 4.07 (0.5H, s), 4.30 (2.5H, s), 4.39 (0.5H, s), 5.97 (2H, s), 6.70-6.81 (0.8H, m), 6.85-6.94 (0.2H, m), 7.25-7.42 (2H, m), 7.43-7.53 (1H, m), 7.58-7.68 (2H, m), 7.72-7.86 (2H, m), 8.14-8.22 (2H, m), 8.36 (1H, dd, J = 8.3, 1.1 Hz).

[2301]

Example 525

Production of N-[1-(hydroxyacetyl)pyrrolidin-3-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2302]



[2303]

A mixture of the compound of Example 523, ethyl acetate (2 mL) and 4N hydrogen chloride ethyl acetate solution (2 mL) was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, saturated aqueous sodium hydrogen carbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure to give 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-pyrrolidin-3-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide (153 mg, 27%) as a white powder.

To a mixture of the thus-obtained 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-pyrrolidin-3-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide (153 mg, 0.327 mmol), triethylamine (99.7 μL, 0.720 mmol) and THF (3 mL) was added acetoxyacetyl chloride (38.7 μL, 0.360 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). The obtained oil was dissolved in THF (4 mL) and ethanol (12 mL), 8N aqueous sodium hydroxide solution (1 mL) was added and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with water, acidified with 1N

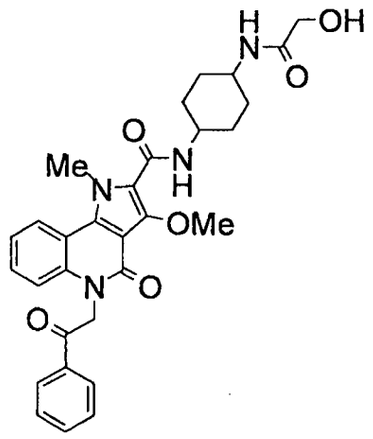
hydrochloric acid (8.5 mL), and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=10/0 - 9/1). Recrystallization of the obtained solid from ethyl acetate-THF gave the title compound (121 mg, 72%) as a white powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.86-2.31 (2H, m), 3.33-3.56 (3H, m), 3.58-3.72 (1H, m), 3.94 (3H, s), 4.02 (2H, dd, J = 10.2, 5.7 Hz), 4.29 (3H, d, J = 2.1 Hz), 4.40-4.64 (2H, m), 5.97 (2H, s), 7.27-7.41 (2H, m), 7.43-7.52 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.72-7.81 (1H, m), 8.12-8.23 (3H, m), 8.37 (1H, d, J = 7.9 Hz).

[2304]

Example 526

Production of N-{4-[(hydroxyacetyl)amino]cyclohexyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2305]



[2306]

To a mixture of the compound of Example 88 (190 mg, 0.363 mmol), triethylamine (151 μL, 1.09 mmol) and THF (7 mL) was added acetoxyacetyl chloride (46.9 μL, 0.436 mmol) at 0°C, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and

concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). The obtained oil was dissolved in THF (2.5 mL) and ethanol (5 mL), 8N aqueous sodium hydroxide solution (0.5 mL) was added and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was diluted with water, acidified with 1N hydrochloric acid (4.5 mL), and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/THF=10/0 - 0/10). Recrystallization of the obtained solid from ethyl acetate-THF gave the title compound (91.1 mg, 46%) as a white powder.

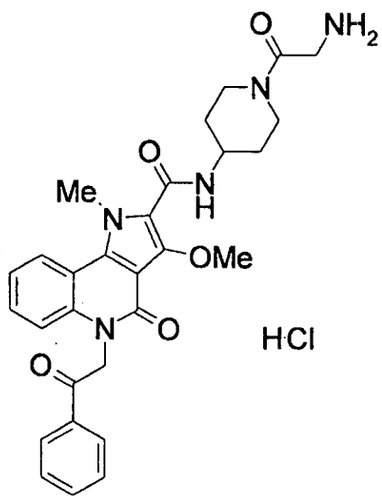
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44 (4H, t, J = 10.1 Hz), 1.67-1.85 (2H, m), 1.88-2.02 (2H, m), 3.55-3.84 (4H, m), 3.96 (3H, s), 4.30 (3H, s), 5.43 (1H, t, J = 5.8 Hz), 5.97 (2H, s), 7.23-7.40 (2H, m), 7.43-7.55 (2H, m), 7.63 (2H, t, J = 7.6 Hz), 7.71-7.89 (2H, m), 8.11-8.23 (2H, m), 8.36 (1H, dd, J = 8.3, 1.1 Hz).

[2307]

Example 527

Production of N-(1-glycylpiperidin-4-yl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2308]



[2309]

To a solution of the compound of Example 77 (250 mg, 0.529 mmol), N-Boc-glycine (111 mg, 0.635 mmol) and HOBt (107 mg, 0.794 mmol) in DMF (5 mL) was added WSCD (152 mg, 0.794 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 mL), 4N hydrogen chloride ethyl acetate solution (2 mL) was added, and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, washed with ethyl acetate, and recrystallized ethanol-ethyl acetate to give the title compound (236 mg, 79%) as white crystals.

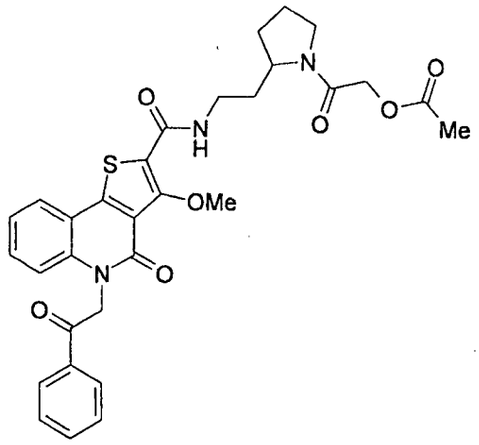
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.70 (2H, m), 1.85-2.00 (2H, m), 2.95-3.10 (1H, m), 3.15-3.30 (1H, m), 3.60-3.75 (1H, m), 3.80-3.95 (2H, m), 3.97 (3H, s), 4.05-4.30 (2H, m), 4.31 (3H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.45-7.51 (1H, m), 7.63 (2H, t, J = 7.5 Hz), 7.73-7.79 (1H, m), 7.99 (1H, d, J = 7.8 Hz), 8.08-8.21 (5H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2310]

Example 528

Production of 2-{2-[2-({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)ethyl]pyrrolidin-1-yl}-2-oxoethyl acetate

[2311]



[2312]

In the same manner as in Example 504, the title compound (200 mg, 89%) was obtained as a white solid from the compound of Example 82 (200 mg, 0.38 mmol) and acetoxyacetyl chloride (57 mg, 0.42 mmol).

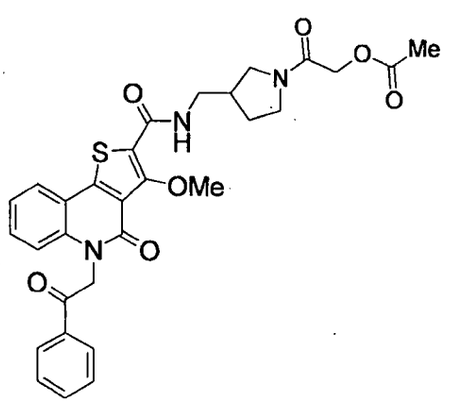
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-2.00 (6H, m), 2.08 (3H, s), 2.90-3.10 (1H, m), 3.38-3.49 (2H, m), 3.50-3.65 (1H, m), 4.05 (3H, s), 4.10-4.20 (1H, m), 4.73 (2H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 7.2 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.77 (1H, t, J = 7.5 Hz), 8.04 (1H, d, J = 7.8 Hz), 8.18 (2H, d, J = 7.5 Hz), 8.45 (1H, t, J = 6.0 Hz).

[2313]

Example 529

Production of 2-{3-[({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]pyrrolidin-1-yl}-2-oxoethyl acetate

[2314]



[2315]

In the same manner as in Example 504, the title compound (160 mg, 71%) was obtained as a white solid from the compound of Example 669 (200 mg, 0.39 mmol) and acetoxyacetyl chloride (87 mg, 0.86 mmol).

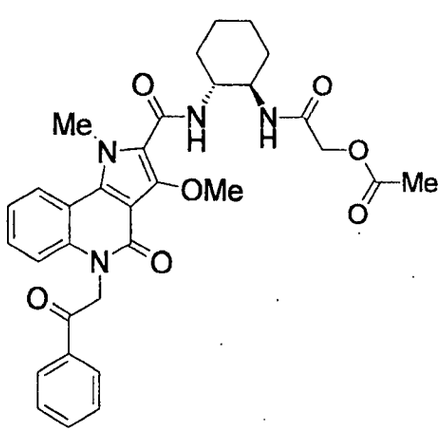
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.60-1.78 (2H, m), 1.84-1.95 (1H, m), 2.07 (3H, s), 2.50-2.70 (1H, m), 3.07-3.57 (6H, m), 4.03 (1.5H, m), 4.04 (1.5H, s), 4.65 (2H, m), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.58-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, d, J = 7.8 Hz), 8.16-8.23 (2H, m).

[2316]

Example 530

Production of 2-{[trans-2-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexyl]amino}-2-oxoethyl acetate

[2317]



[2318]

In the same manner as in Example 504, the title compound (190 mg, 85%) was obtained as a white solid from the compound of Example 85 (200 mg, 0.38 mmol) and acetoxyacetyl chloride (63 mg, 0.46 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.41 (4H, m), 1.71 (2H, br s), 1.80-1.90 (1H, br d), 2.04 (3H, s), 2.41-2.45 (1H, m), 3.72-3.85 (2H, m), 3.95 (3H, s), 4.26 (3H, s), 4.40 (2H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.48 (1H, t, J = 7.8 Hz), 7.64 (2H,

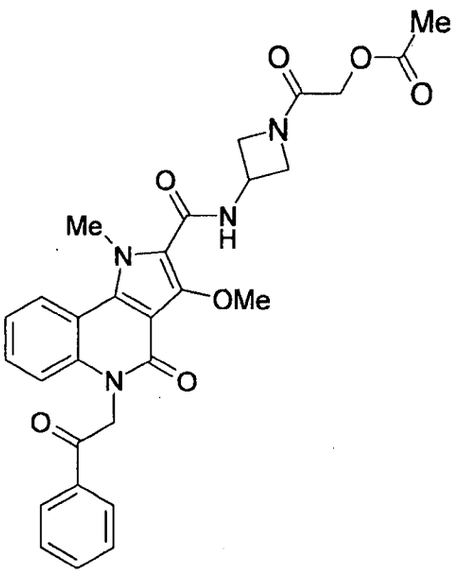
t, J = 7.5 Hz), 7.74-7.82 (2H, m), 7.95 (1H, d, J = 8.1 Hz), 8.16-8.19 (2H, m), 8.38 (1H, d, J = 6.9 Hz).

[2319]

Example 531

Production of 2-[3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)azetidin-1-yl]-2-oxoethyl acetate

[2320]



[2321]

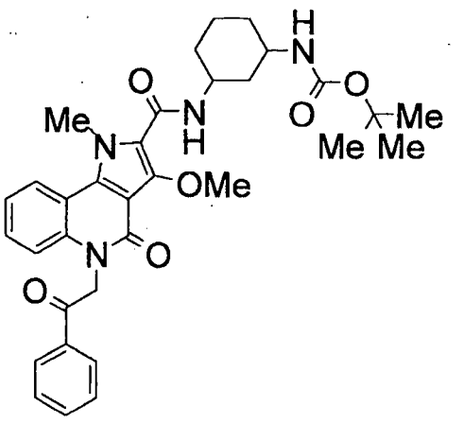
In the same manner as in Example 123, N-azetidin-3-yl-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride (600 mg) was obtained as a white powder from the compound of Reference Example 670 (610 mg, 1.12 mmol). The title compound (121 mg, 17%) was obtained as a white solid from the thus-obtained white powder by a method similar to that in Example 504. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.09 (3H, s), 3.30-3.50 (2H, m), 3.86 (3H, s), 4.16 (1H, s), 4.36 (3H, s), 4.40-4.42 (2H, m), 4.48 (2H, m), 5.97 (2H, s), 7.30-7.40 (2H, m), 7.48 (1H, d, J = 8.3 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.16-8.23 (3H, m), 8.40 (1H, d, J = 7.5 Hz).

[2322]

Example 532

Production of tert-butyl [3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexyl]carbamate

[2323]



[2324]

In the same manner as in Example 25, the title compound (395 mg, 66%) was obtained as a white powder from the compound of Reference Example 7 (400 mg, 1.02 mmol) and tert-butyl (3-aminocyclohexyl)carbamate (285 mg, 1.33 mmol).

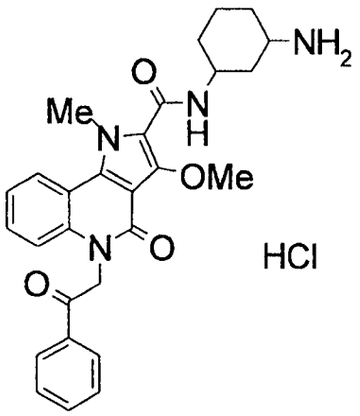
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.98-1.46 (13H, m), 1.65-1.90 (3H, m), 2.00-2.12 (1H, m), 3.23-3.42 (1H, m), 3.73-3.88 (1H, m), 3.96 (2H, s), 4.04 (1H, s), 4.30 (2H, s), 4.35 (1H, s), 5.97 (2H, s), 6.76-6.94 (1H, m), 7.24-7.42 (2H, m), 7.43-7.53 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.71-7.80 (1H, m), 7.86 (1H, d, J = 7.9 Hz), 8.12-8.22 (2H, m), 8.31-8.42 (1H, m).

[2325]

Example 533

Production of N-(3-aminocyclohexyl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2326]



[2327]

To a mixture of the compound of Example 532 (380 mg, 0.648) and ethyl acetate (4 mL) was added 4N hydrogen chloride ethyl acetate solution (4 mL), and the mixture was stirred at room temperature for 2 hr. The precipitated solid was collected by filtration, and washed with ethyl acetate to give the title compound (305 mg, 90%) as a white powder.

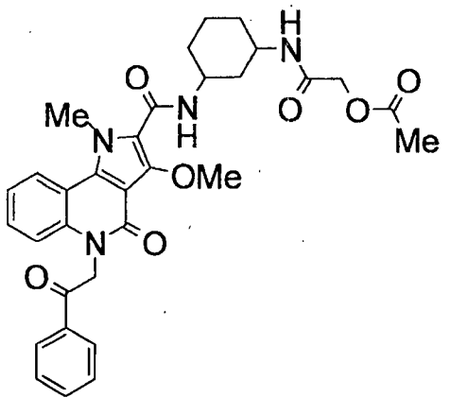
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.09-2.03 (7H, m), 2.17-2.32 (1H, m), 3.05-3.24 (1H, m), 3.80-4.10 (4H, m), 4.28 (2.5H, s), 4.32 (0.5H, s), 5.97 (2H, s), 7.26-7.53 (3H, m), 7.63 (2H, t, J = 7.4 Hz), 7.76 (1H, t, J = 7.4 Hz), 7.95-8.22 (6H, m), 8.37 (1H, d, J = 8.3 Hz).

[2328]

Example 534

Production of 2-{[3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexyl]amino}-2-oxoethyl acetate

[2329]



[2330]

In the same manner as in Example 504, the title compound (223 mg, 70%) was obtained as a white solid from the compound of Example 533 (285 mg, 0.546 mmol) and acetoxyacetyl chloride (70.4 μL, 0.655 mmol).

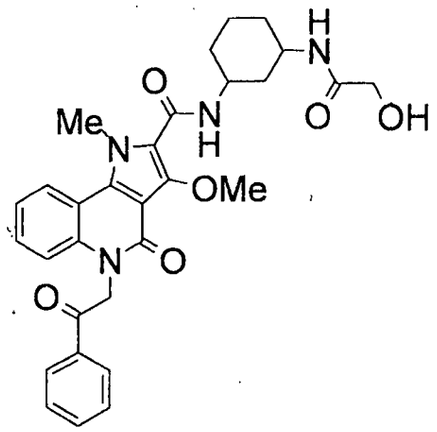
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.06-1.48 (4H, m), 1.67-1.93 (3H, m), 2.00-2.12 (4H, m), 3.59-3.76 (1H, m), 3.78-3.91 (1H, m), 3.95 (2.7H, s), 4.03 (0.3H, s), 4.29 (2.7H, s), 4.35 (0.3H, s), 4.41 (1.8H, s), 4.45 (0.2H, s), 5.97 (2H, s), 7.26-7.40 (2H, m), 7.43-7.52 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.72-7.80 (1H, m), 7.85-7.99 (2H, m), 8.11-8.23 (2H, m), 8.36 (1H, dd, J = 8.4, 1.2 Hz).

[2331]

Example 535

Production of N-{3-[(hydroxyacetyl)amino]cyclohexyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2332]



[2333]

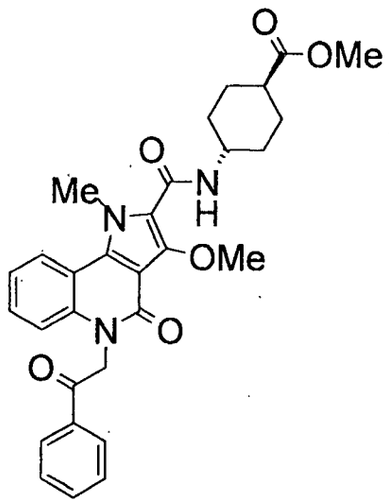
In the same manner as in Example 508, the title compound (173 mg, 93%) was obtained as a white powder from the compound of Example 534 (200 mg, 0.34 mmol), 8N aqueous sodium hydroxide solution (0.5 mL), THF (2.5 mL) and ethanol (5 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.12-1.50 (4H, m), 1.66-1.82 (2H, m), 1.84-1.94 (1H, m), 1.98-2.10 (1H, m), 3.65-3.91 (4H, m), 3.95 (2.7H, s), 4.06 (0.3H, s), 4.30 (2.7H, s), 4.35 (0.3H, s), 5.39 (1H, d, J = 5.1 Hz), 5.98 (2H, s), 7.24-7.41 (2H, m), 7.46 (1H, d, J = 7.8 Hz), 7.54-7.69 (3H, m), 7.76 (1H, t, J =.3 Hz), 7.87 (1H, d, J = 7.9 Hz), 8.17 (2H, d, J = 7.7 Hz), 8.37 (1H, d, J = 8.3 Hz).

[2334]

Example 536

Production of methyl trans-4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexanecarboxylate

[2335]



[2336]

In the same manner as in Example 25, the title compound (535 mg, 79%) was obtained as a white powder from the compound of Reference Example 7 (500 mg, 1.28 mmol), triethylamine (230 μL, 1.66 mmol) and methyl trans-4-aminocyclohexanecarboxylate hydrochloride (321 mg, 1.66 mmol).

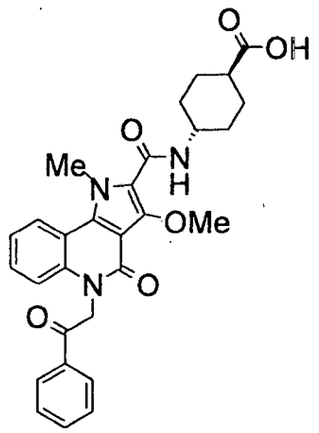
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.27-1.60 (4H, m), 1.87-2.07 (4H, m), 2.25-2.41 (1H, m), 3.60 (3H, s), 3.69-3.86 (1H, m), 3.96 (3H, s), 4.30 (3H, s), 5.96 (2H, s), 7.25-7.41 (2H, m), 7.43-7.53 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.71-7.88 (2H, m), 8.11-8.23 (2H, m), 8.36 (1H, dd, J = 8.3, 1.1 Hz).

[2337]

Example 537

Production of trans-4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexanecarboxylic acid

[2338]



[2339]

A mixture of the compound of Example 536 (300 mg, 0.566 mmol), 8N aqueous sodium hydroxide solution (1 mL) and ethanol (7 mL) was stirred at room temperature for 6 hr. The reaction mixture was acidified with 6N hydrochloric acid (1.5 mL), and the precipitated solid was collected by filtration. The obtained solid was washed with water, and dried under reduced pressure to give the title compound (225 mg, 81%) as a white powder.

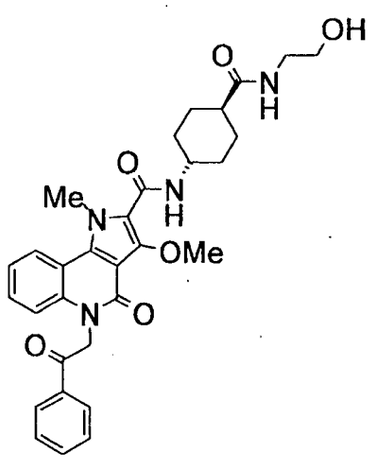
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25-1.57 (4H, m), 1.85-2.05 (4H, m), 2.10-2.26 (1H, m), 3.67-3.85 (1H, m), 3.98 (3H, s), 4.29 (3H, s), 5.97 (2H, s), 7.25-7.41 (2H, m), 7.42-7.52 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.71-7.88 (2H, m), 8.12-8.24 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz), 12.23 (1H, br s).

[2340]

Example 538

Production of N-{trans-4-[(2-hydroxyethyl)carbamoyl]cyclohexyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2341]



[2342]

To a solution of the compound of Example 537 (215 mg, 0.417 mmol), 2-aminoethanol (32.5 μL, 0.542 mmol) and HOBt (84.6 mg, 0.626 mmol) in DMF (5 mL) was added WSCD (120 mg, 0.626 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=10/0 - 8/2). Recrystallization of the obtained solid from ethyl acetate-THF gave the title compound (131 mg, 56%) as a white powder.

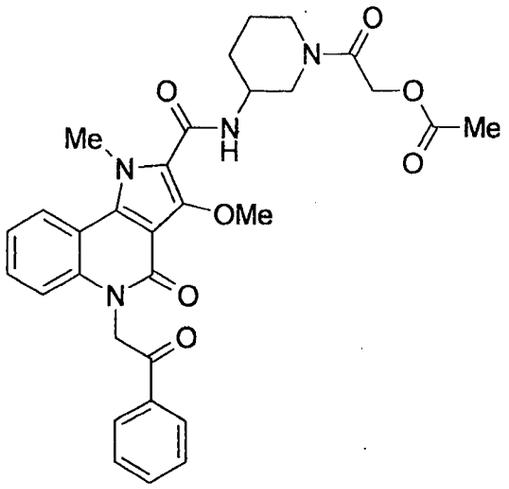
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.22-1.58 (4H, m), 1.71-1.86 (2H, m), 1.90-2.03 (2H, m), 2.05-2.20 (1H, m), 3.03-3.18 (2H, m), 3.34-3.44 (2H, m), 3.65-3.84 (1H, m), 3.98 (3H, s), 4.30 (3H, s), 4.63 (1H, t, J = 5.6 Hz), 5.97 (2H, s), 7.25-7.41 (2H, m), 7.47 (1H, t, J = 7.7 Hz), 7.58-7.68 (2H, m), 7.70-7.88 (3H, m), 8.17 (2H, d, J = 7.6 Hz), 8.37 (1H, d, J = 8.1 Hz).

[2343]

Example 539

Production of 2-[3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2344]



[2345]

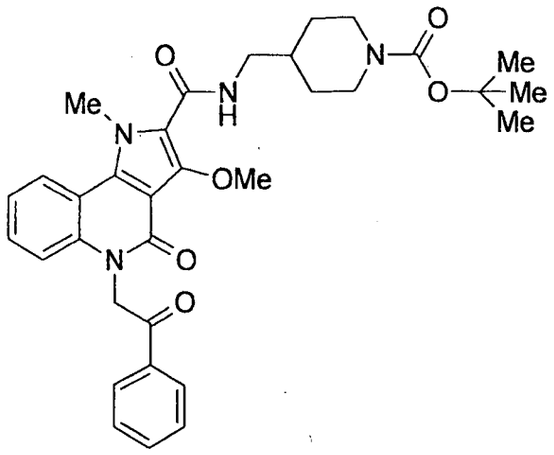
In the same manner as in Example 25, the title compound (284 mg, 39%) was obtained as a white solid from the compound of Reference Example 28 (500 mg, 1.3 mmol), tert-butyl 3-aminopiperidine-1-carboxylate (257 mg, 1.3 mmol), HOBt (203 mg, 1.5 mmol), WSCD (294 mg, 1.5 mmol), DMF (15 mL), 4N hydrogen chloride ethyl acetate solution (4.0 mL), THF (4.0 mL), methanol (4.0 mL), acetoxyacetyl chloride (0.098 mL, 0.91 mmol), triethylamine (0.28 mL, 2.0 mmol) and THF (16 mL).
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.64-1.88 (3H, m), 1.93-2.09 (1H, m), 2.16 (3H, s), 3.24-3.59 (2H, m), 3.67-3.82 (2H, m), 4.04-4.24 (4H, m), 4.47 (3H, s), 4.67-4.88 (2H, m), 5.79-5.97 (2H, m), 7.05 (1H, d, J = 7.9 Hz), 7.20-7.34 (1H, m), 7.37-7.46 (1H, m), 7.55 (2H, t, J = 7.6 Hz), 7.61-7.71 (1H, m), 7.82 (1H, d, J = 7.0 Hz), 8.07-8.16 (2H, m), 8.26 (1H, dd, J = 8.2, 1.4 Hz).

[2346]

Example 540

Production of tert-butyl 4-[({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]piperidine-1-carboxylate

[2347]



[2348]

In the same manner as in Example 25, the title compound (521 mg, 69%) was obtained as a white solid from the compound of Reference Example 28 (500 mg, 1.3 mmol), tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (302 mg, 1.4 mmol), HOBt (208 mg, 1.5 mmol), WSC (294 mg, 1.5 mmol) and DMF (15 mL).

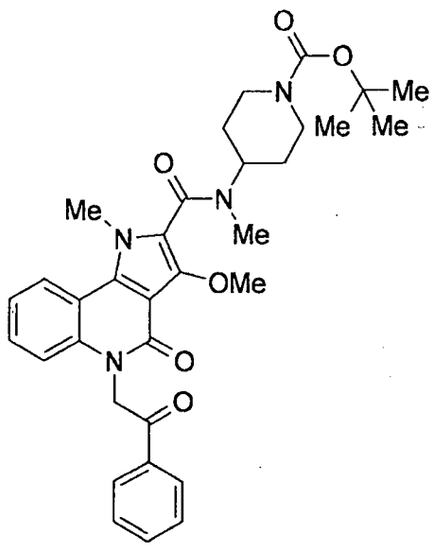
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.14-1.33 (2H, m), 1.41-1.51 (9H, m), 1.70-1.85 (3H, m), 2.63-2.80 (2H, m), 3.37 (2H, t, J = 6.1 Hz), 4.03-4.25 (5H, m), 4.47 (3H, s), 5.89 (2H, s), 7.05 (1H, d, J = 8.5 Hz), 7.21-7.31 (1H, m), 7.36-7.46 (1H, m), 7.50-7.60 (2H, m), 7.62-7.70 (1H, m), 7.76 (1H, t, J = 5.9 Hz), 8.05-8.16 (2H, m), 8.26 (1H, dd, J = 8.3, 1.3 Hz).

[2349]

Example 541

Production of tert-butyl 4-[{[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]piperidine-1-carboxylate

[2350]



[2351]

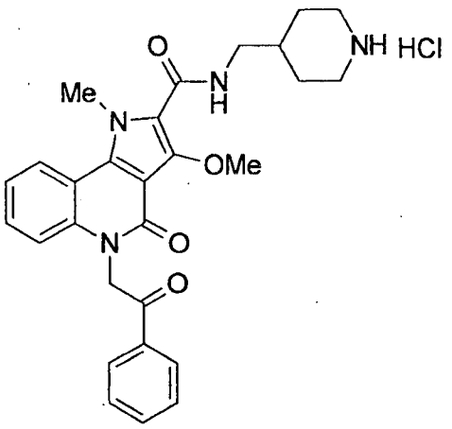
In the same manner as in Example 25, the title compound (565 mg, 75%) was obtained as a white solid from the compound of Reference Example 28 (500 mg, 1.3 mmol), tert-butyl 4-(methylamino)piperidine-1-carboxylate (274 mg, 1.3 mmol), HOBt (208 mg, 1.5 mmol), WSCD (294 mg, 1.5 mmol) and DMF (15 mL). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42-1.52 (9 H, m), 1.65-1.86 (4H, m), 2.56-2.97 (2H, m), 3.03 (3H, s), 3.97-4.20 (7H, m), 4.22-4.37 (1H, m), 4.61-4.81 (1H, m), 5.89 (2H, s), 7.05 (1H, d, J = 8.5 Hz), 7.19-7.30 (1H, m), 7.33-7.43 (1H, m), 7.49-7.59 (2H, m), 7.60-7.70 (1H, m), 8.05-8.15 (2H, m), 8.18 (1H, d, J = 7.4 Hz).

[2352]

Example 542

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(piperidin-4-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2353]



[2354]

A mixed solution of the compound of Example 540 (500 mg, 0.85 mmol) and 4N hydrogen chloride ethyl acetate solution (4.0 mL) in THF (4.0 mL)-methanol (4.0 mL) was stirred at room temperature for 2 hr. 4N hydrogen chloride ethyl acetate solution (4.0 mL) and methanol (8.0 mL) were added, and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure, and recrystallized from methanol-diethyl ether to give the title compound (356 mg, 80%) as a pale-yellow solid.

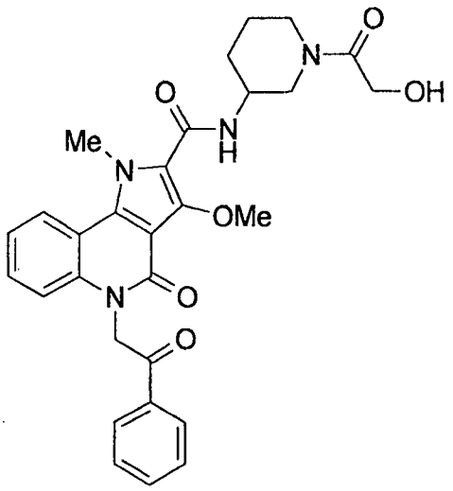
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.29-1.48 (2H, m), 1.75-1.95 (3H, m), 2.78-2.94 (2H, m), 3.18-3.38 (4H, m), 4.00 (3H, s), 4.31 (3H, s), 5.98 (2H, s), 7.27-7.42 (2H, m), 7.44-7.53 (1H, m), 7.59-7.69 (2H, m), 7.72-7.81 (1H, m), 8.07-8.22 (3H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz), 8.51 (2H, br s).

[2355]

Example 543

Production of N-[1-(hydroxyacetyl)piperidin-3-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2356]



[2357]

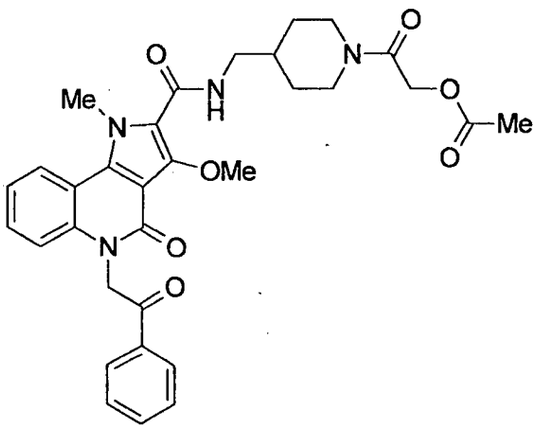
In the same manner as in Example 511, the title compound (69 mg, 43%) was obtained as a white solid from the compound of Example 539 (174 mg, 0.30 mmol), 8N aqueous sodium hydroxide solution (1.6 mL), THF (3.2 mL) and ethanol (11 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44-1.81 (3H, m), 1.84-1.96 (1H, m), 3.29-3.61 (3H, m), 3.80-3.90 (1H, m), 3.91-4.02 (4H, m), 4.04-4.17 (2H, m), 4.35 (3H, s), 4.54 (1H, t, J = 5.4 Hz), 5.97 (2H, s), 7.27-7.42 (2H, m), 7.44-7.53 (1H, m), 7.59-7.69 (2H, m), 7.71-7.81 (1H, m), 7.89-8.01 (1H, m), 8.12-8.21 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz).

[2358]

Example 544

Production of 2-{4-[({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]piperidin-1-yl}-2-oxoethyl acetate

[2359]



[2360]

To a solution of the compound of Example 542 (400 mg, 0.76 mmol) and triethylamine (0.29 mL, 2.1 mmol) in THF (17 mL) was added acetoxyacetyl chloride (0.10 mL, 0.95 mmol) under ice-cooling, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with saturated brine, dried over magnesium sulfate, and filtered through aminosilica gel. The filtrate was concentrated, and the residue was recrystallized from ethanol-hexane to give the title compound (321 mg, 71%) as a white solid.

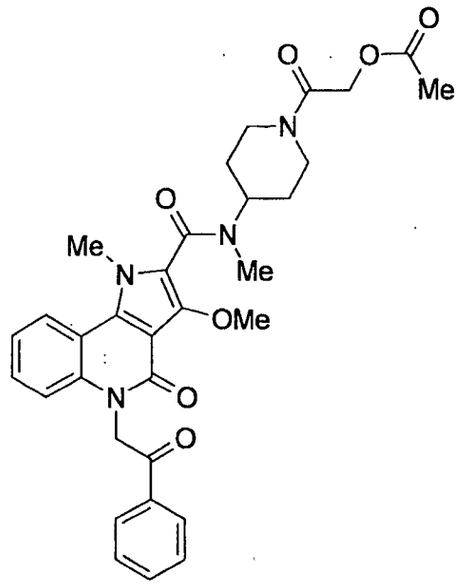
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.16-1.37 (2H, m), 1.78-1.99 (3H, m), 2.18 (3H, s), 2.58-2.71 (1H, m), 2.99-3.15 (1H, m), 3.31-3.43 (2H, m), 3.63-3.76 (1H, m), 4.17 (3H, s), 4.47 (3H, s), 4.57-4.66 (1H, m), 4.73 (2H, s), 5.89 (2H, s), 7.01-7.08 (1H, m), 7.20-7.33 (1H, m), 7.37-7.47 (1H, m), 7.50-7.60 (2H, m), 7.62-7.71 (1H, m), 7.79 (1H, t, J = 5.9 Hz), 8.07-8.17 (2H, m), 8.26 (1H, dd, J = 8.3, 1.3 Hz).

[2361]

Example 545

Production of 2-{4-[{[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}(methyl)amino]piperidin-1-yl}-2-oxoethyl acetate

[2362]



[2363]

In the same manner as in Example 123, the title compound (226 mg, 40%) was obtained as a white solid from the compound of Example 541 (565 mg, 0.96 mmol), 4N hydrogen chloride ethyl acetate solution (4.0 mL), THF (4.0 mL), methanol (4.0 mL), acetoxyacetyl chloride (0.077 mL, 0.71 mmol), triethylamine (0.22 mL, 1.6 mmol) and THF (13 mL).

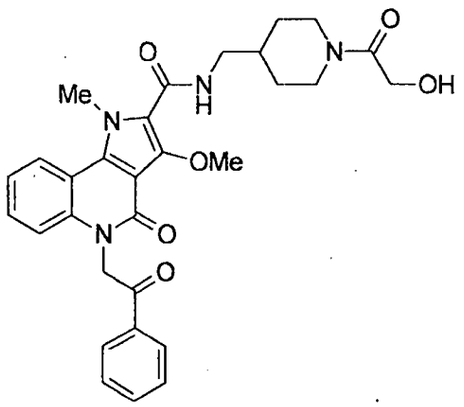
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.70-1.97 (4H, m), 2.15-2.24 (3H, m), 2.50-2.83 (1H, m), 3.03 (3H, s), 3.10-3.33 (1H, m), 3.63-3.86 (1H, m), 4.02 (3H, s), 4.04-4.11 (3H, m), 4.60-4.87 (4H, m), 5.89 (2H, s), 7.02-7.10 (1H, m), 7.17-7.32 (1H, m), 7.35-7.44 (1H, m), 7.47-7.60 (2H, m), 7.61-7.71 (1H, m), 8.07-8.15 (2H, m), 8.19 (1H, dd, J = 8.1, 1.3 Hz).

[2364]

Example 546

Production of N-{[1-(hydroxyacetyl)piperidin-4-yl]methyl}-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2365]



[2366]

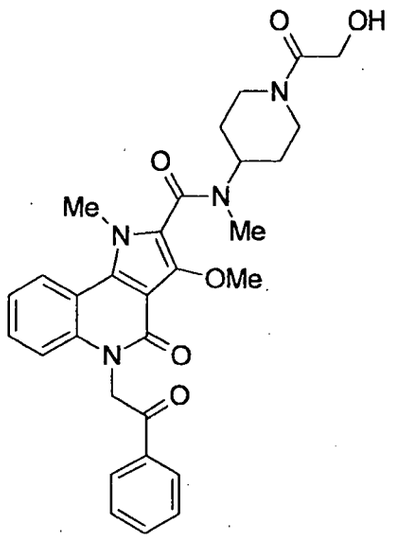
In the same manner as in Example 511, the title compound (77 mg, 41%) was obtained as a white solid from the compound of Example 544 (200 mg, 0.34 mmol), 8N aqueous sodium hydroxide solution (1.8 mL), THF (3.6 mL) and ethanol (13 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.99-1.26 (2H, m), 1.65-1.93 (3H, m), 2.57-2.71 (1H, m), 2.87-3.01 (1H, m), 3.18-3.27 (2H, m), 3.65-3.75 (1H, m), 3.98 (3H, s), 4.07 (2H, t, J = 5.4 Hz), 4.27-4.40 (4H, m), 4.41-4.50 (1H, m), 5.97 (2H, s), 7.25-7.42 (2H, m), 7.44-7.53 (1H, m), 7.59-7.68 (2H, m), 7.71-7.81 (1H, m), 8.07 (1H, t, J = 6.0 Hz), 8.13-8.21 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2367]

Example 547

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-N,1-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2368]



[2369]

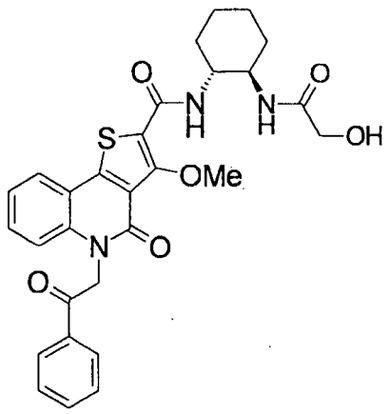
In the same manner as in Example 511, the title compound (117 mg, 62%) was obtained as a white solid from the compound of Example 545 (205 mg, 0.35 mmol), 8N aqueous sodium hydroxide solution (1.8 mL), THF (3.6 mL) and ethanol (13 mL). ^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.65-2.01 (4H, m), 2.78-2.92 (1H, m), 2.99-3.09 (3H, m), 3.12-3.27 (1H, m), 3.48-3.69 (2H, m), 3.99-4.04 (3H, m), 4.04-4.11 (3H, m), 4.14-4.30 (2H, m), 4.61-4.88 (2H, m), 5.89 (2H, s), 7.06 (1H, d, J = 8.7 Hz), 7.22-7.32 (1H, m), 7.35-7.44 (1H, m), 7.54 (2H, t, J = 7.6 Hz), 7.62-7.72 (1H, m), 8.11 (2H, d, J = 7.6 Hz), 8.19 (1H, dd, J = 8.3, 1.3 Hz).

[2370]

Example 548

Production of N-{trans-2-[(hydroxyacetyl)amino]cyclohexyl}-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2371]



[2372]

In the same manner as in Example 508, the title compound (88 mg, 58%) was obtained as white crystals from the compound of Example 530 (150 mg, 0.26 mmol).

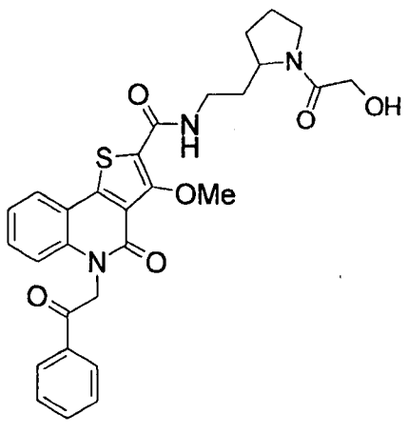
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.20-1.50 (6H, m), 1.70 (2H, br s), 1.87 (1H, d, J = 11.1 Hz), 2.05 (1H, d, J = 9.6 Hz), 3.72-3.94 (7H, m), 4.31 (3H, s), 5.48 (1H, t, J = 5.7 Hz), 5.97 (2H, s), 7.28-7.39 (2H, m), 7.47 (1H, t, J = 7.8 Hz), 7.61-7.67 (3H, m), 7.76 (1H, t, J = 7.5 Hz), 7.83 (1H, d, J = 7.8 Hz), 8.15-8.18 (2H, m), 8.137 (1H, d, J = 7.2 Hz).

[2373]

Example 549

Production of N-{2-[1-(hydroxyacetyl)pyrrolidin-2-yl]ethyl}-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2374]



[2375]

In the same manner as in Example 508, the title compound (70 mg, 51%) was obtained as white crystals from the compound of Example 528 (150 mg, 0.25 mmol).

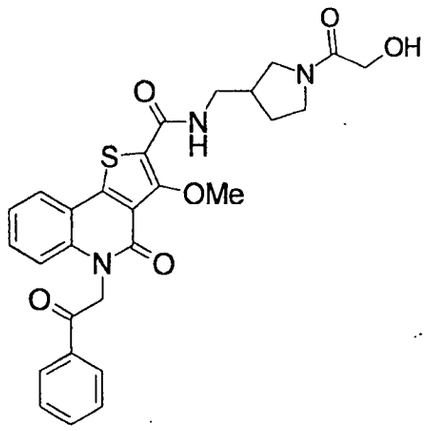
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-2.00 (7H, m), 3.00-3.15 (1H, m), 3.30-3.45 (1H, m), 3.55-3.70 (1H, m), 4.02-4.25 (7H, m), 4.52 (1H, t, J = 5.3 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.56-7.67 (2H, m), 7.77 (1H, t, J = 7.2 Hz), 8.05 (1H, d, J = 7.8 Hz), 8.18 (2H, d, J = 7.8 Hz), 8.46 (1H, t, J = 5.3 Hz).

[2376]

Example 550

Production of N-{[1-(hydroxyacetyl)pyrrolidin-3-yl]methyl}-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2377]



[2378]

In the same manner as in Example 508, the title compound (31 mg, 29%) was obtained as white crystals from the compound of Example 529 (120 mg, 0.20 mmol).

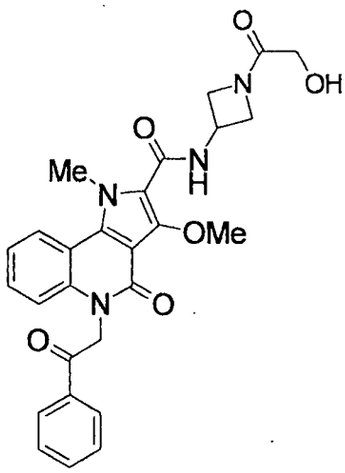
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58-1.76 (1H, m), 1.90-2.10 (1H, m), 2.50-2.65 (1H, m), 3.11-3.17 (1H, m), 3.30-3.65 (5H, m), 3.99 (2H, d, J = 4.2 Hz), 4.03 (3H, d, J = 0.9 Hz), 4.46 (1H, t, J = 4.8 Hz), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.56-7.67 (3H, m), 7.77 (1H, t, J = 7.5 Hz), 8.05 (1H, d, J = 7.5 Hz), 8.18 (3H, d, J = 7.5 Hz).

[2379]

Example 551

Production of N-[1-(hydroxyacetyl)azetidin-3-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2380]



[2381]

In the same manner as in Example 508, the title compound (58 mg, 64%) was obtained as white crystals from the compound of Example 531 (100 mg, 0.18 mmol).

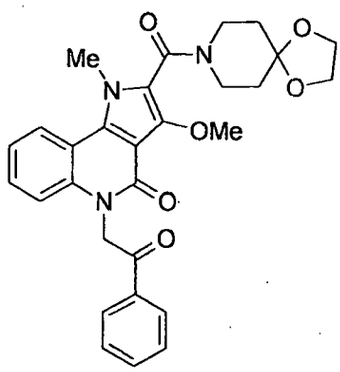
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.28-3.44 (2H, m), 3.84-3.86 (5H, tm), 4.22 (1H, t, J = 6.3 Hz), 4.36 (3H, s), 4.39-4.43 (2H, m), 5.55 (1H, t, J = 5.7 Hz), 5.96 (2H, s), 7.30-7.40 (2H, m), 7.48 (1H, t, J = 7.5 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 7.90 (1H, t, J = 6.2 Hz), 8.16-8.19 (2H, m), 8.40 (1H, dd, J = 8.1, 0.9 Hz).

[2382]

Example 552

Production of 2-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylcarbonyl)-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one

[2383]



[2384]

In the same manner as in Example 25, the title compound (279 mg, 60%) was obtained as a white solid from the compound of Reference Example 28 (350 mg, 0.90 mmol), 1,4-dioxa-8-azaspiro[4.5]decane (154 mg, 1.1 mmol), HOBt (146 mg, 1.1 mmol), WSCD (206 mg, 1.1 mmol) and DMF (10 mL).

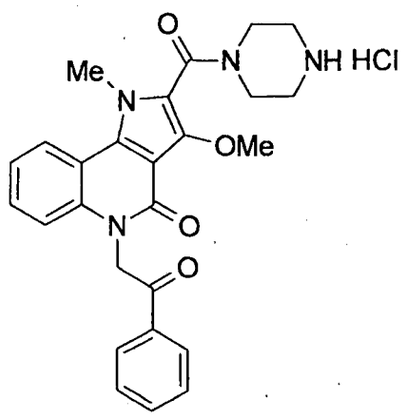
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.72-1.88 (4H, m), 3.64-3.77 (2H, m), 3.82-3.96 (2H, m), 3.98-4.02 (4H, m), 4.03 (3H, s), 4.09 (3H, s), 5.89 (2H, br s), 7.01-7.10 (1H, m), 7.19-7.30 (1H, m), 7.34-7.42 (1H, m), 7.49-7.58 (2H, m), 7.61-7.69 (1H, m), 8.06-8.14 (2H, m), 8.19 (1H, dd, J = 8.3, 1.3 Hz).

[2385]

Example 553

Production of 3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-2-(piperazin-1-ylcarbonyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one hydrochloride

[2386]



[2387]

In the same manner as in Example 542, the title compound (478 mg, 95%) was obtained as a pale-yellow solid from the compound of Example 680 (571 mg, 1.0 mmol), 4N hydrochloric acid ethyl acetate solution (11 mL), ethyl acetate (8.0 mL) and methanol (8.0 mL).

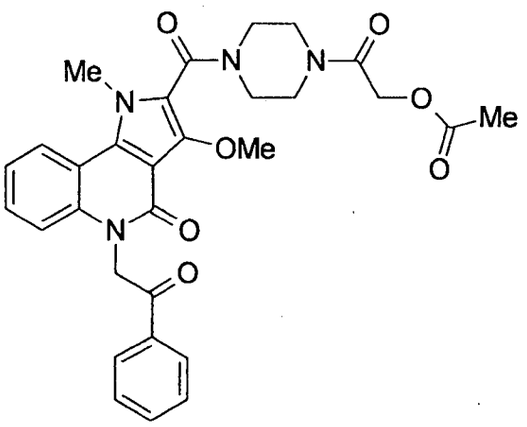
^{1}H-NMR (300 MHz, DMSO-d_6) δ:3.07-3.27 (4H, m), 3.65-3.78 (2H, m), 3.81-3.96 (5H, m), 4.05 (3H, s), 5.98 (2H, s), 7.24-7.52 (3H, m), 7.57-7.68 (2H, m), 7.71-7.81 (1H, m), 8.08-8.24 (2H, m), 8.35 (1H, dd, J = 8.2, 1.0 Hz), 9.20 (2H, br s).

[2388]

Example 554

Production of 2-(4-{[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}piperazin-1-yl)-2-oxoethyl acetate

[2389]



[2390]

In the same manner as in Example 544, the title compound (34 mg, 10%) was obtained as a white solid from the compound of Example 553 (300 mg, 0.61 mmol), acetoxyacetyl chloride (0.081 mL, 0.76 mmol), triethylamine (0.23 mL, 1.7 mmol) and THF (13 mL).

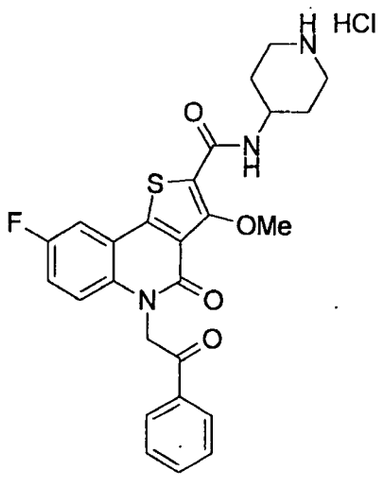
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.09 (3H, s), 3.43-3.79 (8H, m), 3.91 (3H, s), 4.03 (3H, s), 4.76-4.88 (2H, m), 5.98 (2H, s), 7.25-7.51 (3H, m), 7.59-7.68 (2H, m), 7.71-7.80 (1H, m), 8.13-8.22 (2H, m), 8.30-8.38 (1H, m).

[2391]

Example 555

Production of 8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[2392]



[2393]

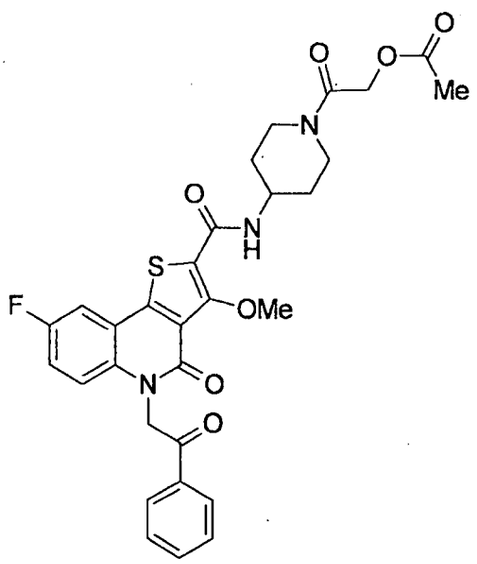
In the same manner as in Example 542, the title compound (335 mg, 83%) was obtained as a white solid from the compound of Example 673 (452 mg, 0.76 mmol), 4N hydrogen chloride ethyl acetate solution (6.0 mL), THF (4.0 mL) and methanol (4.0 mL). ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.70-1.91 (2H, m), 1.95-2.12 (2H, m), 2.93-3.13 (2H, m), 3.19-3.52 (2H, m), 3.95-4.22 (4H, m), 6.00 (2H, s), 7.41-7.52 (1H, m), 7.53-7.71 (3H, m), 7.72-7.84 (1H, m), 7.86-8.03 (2H, m), 8.11-8.25 (2H, m), 8.63 (2H, br s).

[2394]

Example 556

Production of 2-[4-({[8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2395]



[2396]

In the same manner as in Example 544, the title compound (161 mg, 80%) was obtained as a white solid from the compound of Example 555 (180 mg, 0.34 mmol), acetoxyacetyl chloride (0.046 mL, 0.42 mmol), triethylamine (0.13 mL, 0.93 mmol) and THF (7.5 mL).

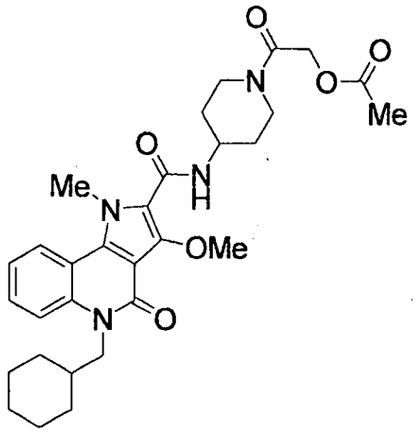
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.45-1.64 (2H, m), 2.01-2.26 (5H, m), 2.89-3.05 (1H, m), 3.15-3.34 (1H, m), 3.60-3.77 (1H, m), 4.15 (3H, s), 4.20-4.34 (1H, m), 4.41-4.54 (1H, m), 4.67-4.84 (2H, m), 5.85 (2H, s), 6.95-7.04 (1H, m), 7.16-7.24 (1H, m), 7.51-7.62 (4H, m), 7.64-7.74 (1H, m), 8.06-8.14 (2H, m).

[2397]

Example 557

Production of 2-[4-({[5-(cyclohexylmethyl)-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2398]



[2399]

A mixture of the compound of Example 672 (110 mg, 0.24 mmol), bromomethylcyclohexane (108 mg, 0.60 mmol), potassium carbonate (72 mg, 0.60 mmol) and DMF (3 mL) was stirred at 80°C for 24 hr. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate: ethyl acetate) to give the title compound (34 mg, 16%) as a colorless oil.

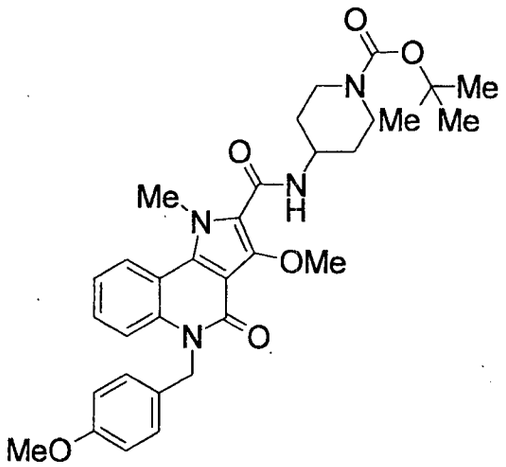
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.05-1.20 (5H, m), 1.35-2.00 (9H, m), 2.09 (3H, s), 2.90 (1H, t, J = 11.4 Hz), 3.19 (1H, t, J = 12.2 Hz), 3.70 (1H, d, J = 13.5 Hz), 3.97 (3H, s), 4.10-4.40 (8H, m), 4.80 (2H, d, J = 2.1 Hz), 7.30 (1H, t, J = 7.5 Hz), 7.54-7.62 (2H, m), 7.96 (1H, d, J = 7.8 Hz), 8. 32 (1H, d, J = 7.8 Hz).

[2400]

Example 558

Production of tert-butyl 4-({[3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[2401]



[2402]

In the same manner as in Example 25, the title compound (6.09 g, 74%) was obtained as white crystals from the compound of Reference Example 107 (5.65 g, 14.4 mmol) and 1-Boc-4-aminopiperidine (5.77 g, 28.80 mmol).

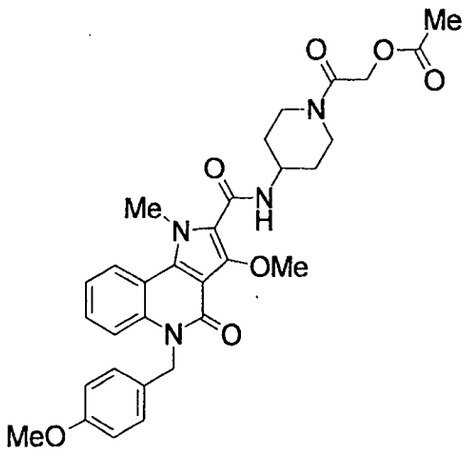
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32-1.53 (11H, m), 1.85 (2H, d, J = 10.2 Hz), 2.85-3.10 (2H, m), 3.69 (3H, s), 3.88 (2H, d, J = 13.2 Hz), 3.95-4.05 (4H, m), 4.27 (3H, s), 5.52 (2H, br s), 6.85 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz), 7.27 (1H, t, J = 7.1 Hz), 7.41-7.48 (2H, m), 7.96 (1H, d, J = 7.8 Hz), 8.32 (1H, d, J = 8.1 Hz).

[2403]

Example 559

Production of 2-[4-({[3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2404]



[2405]

In the same manner as in Example 123, the title compound (360 mg, 73%) was obtained as a white solid from the compound of Example 681 (440 mg, 0.87 mmol).

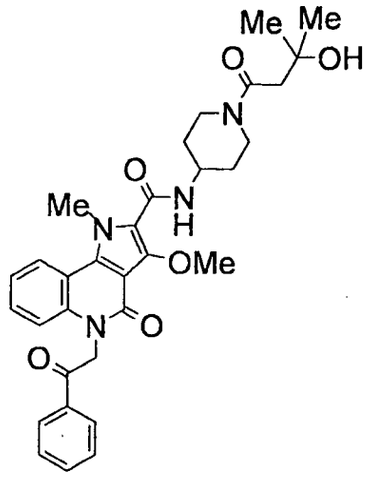
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.65 (2H, m), 1.72-1.95 (2H, m), 2.09 (3H, s), 2.91 (1H, t, J = 11.7 Hz), 3.20 (1H, t, J = 12.0 Hz), 3.58-3.75 (4H, m), 4.00-4.20 (5H, m), 4.27 (3H, s), 4.80 (2H, d, J = 2.4 Hz), 5.40-5.60 (2H, br), 6.86 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz), 7.27 (1H, td, J = 7.1, 2.1 Hz), 7.41-7.49 (2H, m), 8.00 (1H, d, J = 8.1 Hz), 8.33 (1H, d, J = 8.1 Hz).

[2406]

Example 560

Production of N-[1-(3-hydroxy-3-methylbutanoyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2407]



[2408]

In the same manner as in Example 518, the title compound (109 mg, 60%) was obtained as a white powder from the compound of Example 77 (150 mg, 0.317 mmol) and 3-hydroxy-3-methylbutanoic acid (45.0 mg, 0.381 mmol).

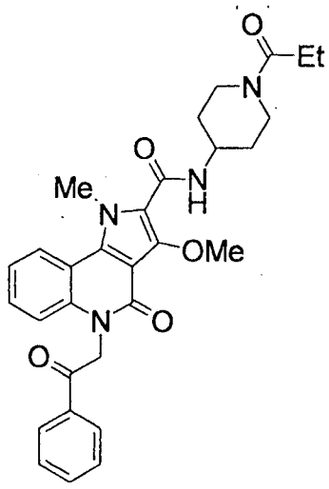
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (6H, s), 1.33-1.63 (2H, m), 1.79-1.97 (2H, m), 2.43-2.52 (2H, m), 2.81-2.96 (1H, m), 3.14-3.29 (1H, m), 3.90-4.00 (4H, m), 4.02-4.16 (1H, m), 4.22-4.36 (4H, m), 4.89 (1H, s), 5.97 (2H, s), 7.26-7.41 (2H, m), 7.48 (1H, t, J = 7.6 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.72-7.81 (1H, m), 7.95 (1H, d, J = 7.9 Hz), 8.17 (2H, d, J = 7.7 Hz), 8.37 (1H, d, J = 8.3 Hz).

[2409]

Example 561

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-propanoylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2410]



[2411]

In the same manner as in Example 123, the title compound (90.2, 81%) was obtained as a white powder from the compound of Example 77 (100 mg, 0.212 mmol) and propionyl chloride (20.2 μL, 0.233 mmol).

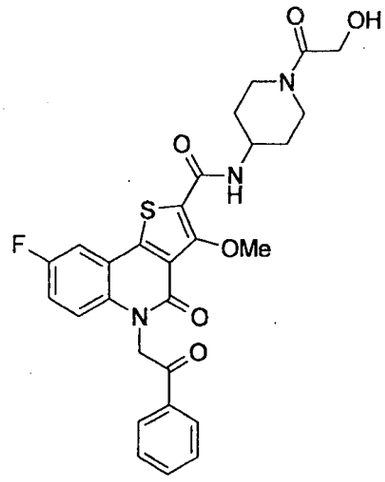
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.00 (3H, t, J = 7.5 Hz), 1.31-1.61 (2H, m), 1.77-1.96 (2H, m), 2.34 (2H, q, J = 7.4 Hz), 2.77-2.92 (1H, m), 3.10-3.25 (1H, m), 3.76-3.88 (1H, m), 3.97 (3H, s), 4.01-4.14 (1H, m), 4.19-4.29 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.63 (2H, t, J = 7.6 Hz), 7.71-7.81 (1H, m), 7.94 (1H, d, J = 7.7 Hz), 8.12-8.22 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2412]

Example 562

Production of 8-fluoro-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2413]



[2414]

In the same manner as in Example 511, the title compound (59 mg, 39%) was obtained as a pale-yellow solid from the compound of Example 556 (164 mg, 0.28 mmol).

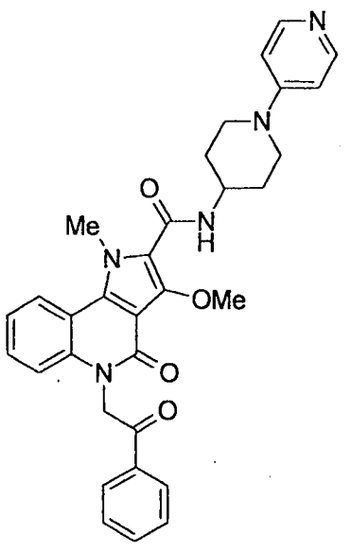
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.42-1.63 (2H, m), 2.08-2.25 (2H, m), 2.97-3.26 (2H, m), 3.47-3.59 (1H, m), 3.62 (1H, t, J = 4.2 Hz), 4.14 (3H, s), 4.20 (2H, d, J = 4.0 Hz), 4.23-4.34 (1H, m), 4.45-4.58 (1H, m), 5.85 (2H, s), 6.94-7.04 (1H, m), 7.15-7.25 (1H, m), 7.50-7.63 (4H, m), 7.64-7.77 (1H, m), 8.04-8.15 (2H, m).

[2415]

Example 563

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyridin-4-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2416]



[2417]

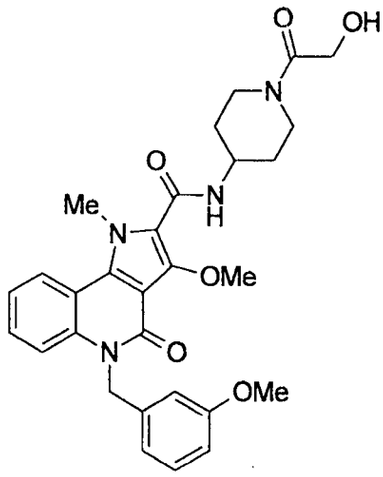
To a solution of the compound of Reference Example 28 (200 mg, 0.51 mmol), 1-pyridin-4-ylpiperidin-4-amine hydrochloride (128 mg, 0.51 mmol) and HOBt (83 mg, 0.61 mmol) in DMF (5.0 mL) were added WSCD (118 mg, 0.61 mmol) and triethylamine (0.23 ml, 1.6 mmol) under ice-cooling, and the mixture was stirred at room temperature for 67 hr. The reaction mixture was diluted with brine, and extracted 4 times with ethyl acetate. The extracts were combined and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=40/60 - 100/0) and recrystallized from THF to give the title compound (121 mg, 43%) as a pale-purple solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.52-1.68 (2H, m), 1.87-1.98 (2H, m), 3.08 (2H, m), 3.89 (2H, m), 3.95 (3H, s), 4.04-4.17 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.85 (2H, d, J = 6.4 Hz), 7.26-7.41 (2H, m), 7.43-7.53 (1H, m), 7.63 (2H, m), 7.71-7.80 (1H, m), 7.98 (1H, d, J = 7.7 Hz), 8.10-8.21 (4H, m), 8.37 (1H, d, J = 7.4 Hz).

[2418]

Example 564

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-5-(3-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2419]



[2420]

A mixture of the compound of Example 672 (110 mg, 0.24 mmol), 3-methoxybenzyl chloride (150 mg, 0.96mmol), potassium carbonate (55 mg, 0.40 mmol) and DMF (5 mL) was stirred at 80°C for 5 hr. After cooling to room temperature, 2N aqueous sodium hydroxide solution (1 mL) was added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate:ethyl acetate - ethyl acetate/methanol=10/1) and reprecipitated from ethyl acetate-hexane to give the title compound (14 mg, 10%) as a white powder.

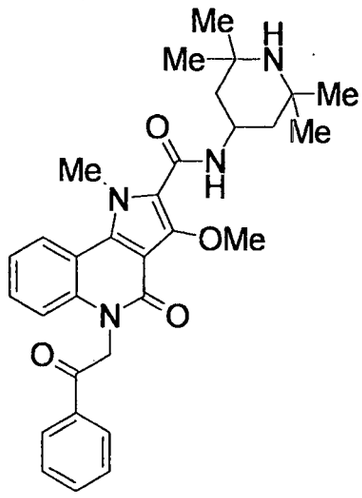
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.65 (2H, m), 1.90 (2H, d, J = 10.2 Hz), 2.93 (1H, t, J = 10.2 Hz), 3.19 (1H, t, J = 14.3 Hz), 3.60-3.70 (4H, m), 4.00-4.04 (4H, m), 4.04-4.10 (2H, m), 4.30-4.36 (4H, m), 4.52 (1H, t, J = 5.4 Hz), 5.58 (2H, br s), 6.69 (1H, d, J = 8.4 Hz), 6.79 (2H, d, J = 6.3 Hz), 7.20 (1H, t, J = 8.4 Hz), 7.28 (1H, t, J = 6.3 Hz), 7.34-7.48 (2H, m), 7.89 (1H, d, J = 8.1 Hz), 8. 34 (1H, d, J = 8.4 Hz).

[2421]

Example 565

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2422]



[2423]

In the same manner as in Example 25, the title compound (410 mg, 76%) was obtained as a white solid from the compound of Reference Example 28 (400 mg, 1.02 mmol) and 4-amino-2,2,6,6-tetramethylpiperidine (320 mg, 2.04 mmol).

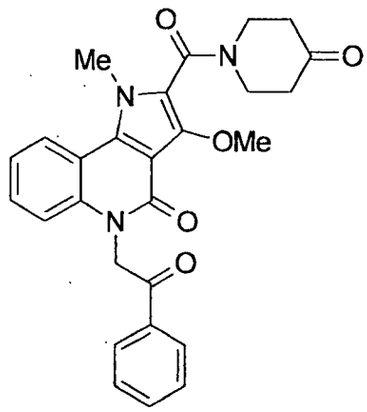
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.86-1.24 (14H, m), 1.78 (2H, dd, J = 12.6, 2.4 Hz), 3.96 (3H, s), 4.28-4.31 (4H, m), 5.97 (2H, s), 7.29-7.47 (3H, m), 7.63 (2H, t, J = 7.5 Hz), 7.76 (2H, t, J = 6.9 Hz), 8.17 (2H, d, J = 7.5 Hz), 8.37 (1H, d, J = 8.4 Hz).

[2424]

Example 566

Production of 3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-2-[(4-oxopiperidin-1-yl)carbonyl]-1,5-dihydro-4H-pyrrolo[3,2-c]quinolin-4-one

[2425]



[2426]

A solution of the compound of Example 552 (285 mg, 0.55 mmol) and 5N hydrochloric acid (3.0 mL) in THF (6.0 mL) was stirred at room temperature for 2 hr. 5N Hydrochloric acid (1.5 mL) was added, and the mixture was stirred at room temperature for 2 hr. 5N Hydrochloric acid (1.5 mL) was added, and the mixture was stirred at room temperature for 3.5 hr and concentrated under reduced pressure. The residue was basified with saturated sodium hydrogen carbonate solution and extracted twice with ethyl acetate. The extracts were combined, washed with brine, and concentrated under reduced pressure. The residue was washed with water, and recrystallized from methanol-diethyl ether to give the title compound (123 mg, 47%) as a white solid.

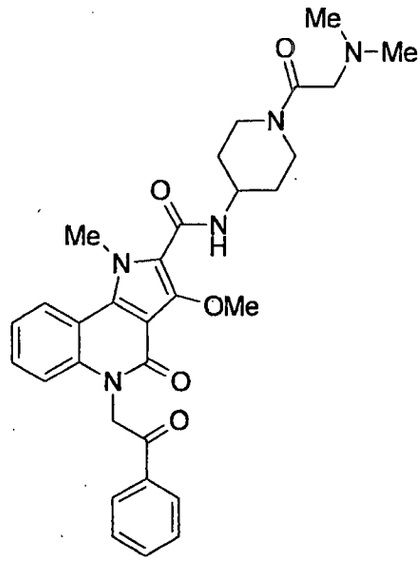
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.78-1.93 (3H, m), 1.95-1.99 (1H, m), 3.58-3.73 (2H, m), 3.79-3.94 (2H, m), 4.03 (3H, s), 4.07-4.11 (3H, m), 5.90 (2H, s), 7.02-7.11 (1H, m), 7.19-7.30 (1H, m), 7.34-7.43 (1H, m), 7.49-7.58 (2H, m), 7.61-7.70 (1H, m), 8.07-8.14 (2H, m), 8.16-8.26 (1H, m).

[2427]

Example 567

Production of N-[1-(N,N-dimethylglycyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2428]



[2429]

In the same manner as in Example 25, the title compound (125 mg, 57%) was obtained as a pale-purple solid from the compound of Example 77 (200 mg, 0.39 mmol) and N,N-dimethylglycine (49 mg, 0.47 mmol).

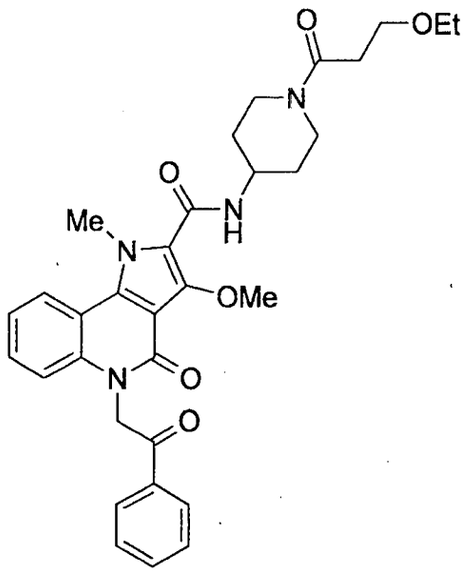
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.40-1.64 (2H, m), 1.99-2.17 (2H, m), 2.31 (6H, s), 2.90-3.05 (1H, m), 3.08-3.21 (2H, m), 3.22-3.36 (1H, m), 3.99-4.11 (1H, m), 4.14 (3H, s), 4.18-4.29 (1H, m), 4.36-4.45 (1H, m), 4.47 (3H, s), 5.88 (2H, d, J = 4.2 Hz), 7.05 (1H, d, J = 7.7 Hz), 7.20-7.32 (1H, m), 7.37-7.46 (1H, m), 7.50-7.59 (2H, m), 7.62-7.73 (2H, m), 8.06-8.16 (2H, m), 8.26 (1H, dd, J = 8.3, 1.3 Hz).

[2430]

Example 568

Production of N-[1-(3-ethoxypropanoyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2431]



[2432]

In the same manner as in Example 25, the title compound (159 mg, 70%) was obtained as a pale-purple solid from the compound of Example 77 (200 mg, 0.39 mmol) and 3-ethoxypropanoic acid (56 mg, 0.47 mmol).

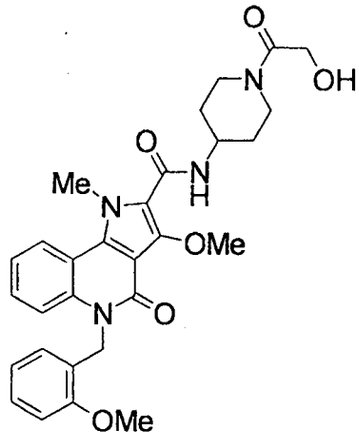
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.09 (3H, t, J = 7.0 Hz), 1.36-1.60 (2H, m), 1.80-1.96 (2H, m), 2.54-2.63 (2H, m), 2.78-2.92 (1H, m), 3.13-3.26 (1H, m), 3.42 (2H, q, J = 6.9 Hz), 3.59 (2H, t, J = 6.7 Hz), 3.81-3.91 (1H, m), 3.96 (3H, s), 4.02-4.14 (1H, m), 4.18-4.27 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.26-7.41 (2H, m), 7.44-7.53 (1H, m), 7.58-7.68 (2H, m), 7.72-7.80 (1H, m), 7.94 (1H, d, J = 7.9 Hz), 8.12-8.21 (2H, m), 8.37 (1H, dd, J = 8.3, 1.3 Hz).

[2433]

Example 569

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-5-(2-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2434]



[2435]

To a solution of the compound of Example 570 (40 mg, 0.07 mmol) in THF (1 mL)-methanol (1 ml) was added 2N sodium hydroxide solution (1 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Recrystallization from ethyl acetate-hexane gave the title compound (30 mg, 80 %) as white crystals.

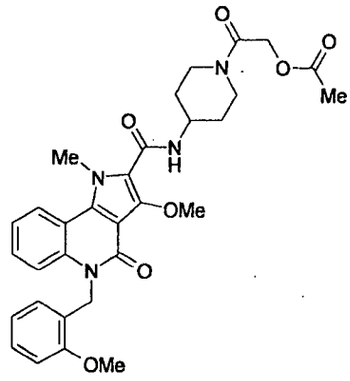
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.60 (2H, m), 1.90 (2H, d, J = 10.2 Hz), 2.93 (1H, t, J = 12.5 Hz), 3.15 (1H, t, J = 12.5 Hz), 3.67 (1H, d, J = 13.2 Hz), 3.95 (3H, s), 4.00 (3H, s), 4.05-4.20 (3H, m), 4.20-4.30 (4H, m), 4.51 (1H, t, J = 5.4 Hz), 5.47 (2H, s), 6.50 (1H, d, J = 7.5 Hz), 6.75 (1H, t, J = 7.5 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.21-7.31 (3H, m), 7.44 (1H, t, J = 7.8 Hz), 7.97 (1H, d, J = 7.8 Hz), 8. 36 (1H, d, J = 8.1 Hz).

[2436]

Example 570

Production of 2-[4-({[3-methoxy-5-(2-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2437]



[2438]

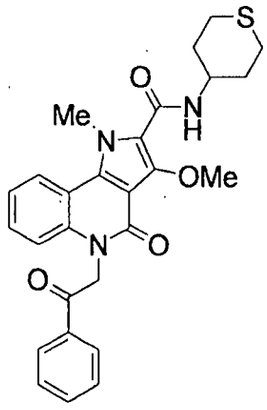
In the same manner as in Example 557, an amorphous solid (90 mg) was obtained from the compound of Example 672 (120 mg, 0.24 mmol), 2-methoxybenzyl chloride (50% dichloromethane solution; 0.1 mL, 0.79 mmol) and potassium carbonate (110 mg, 0.79 mmol). Recrystallization from ethyl acetate-diisopropyl ether gave the title compound (44 mg, 29 %) as white crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.70 (2H, m), 2.07-2.28 (5H, m), 3.04 (1H, t, J = 11.1 Hz), 3.29 (1H, t, J = 11.1 Hz), 3.70 (1H, d, J = 14.4 Hz), 3.99 (3H, s), 4.21-4.28 (4H, m), 4.40-4.56 (4H, m), 4.78 (2H, s), 5.62 (2H, br s), 6.77 (2H, d, J = 4.2 Hz), 6.95 (1H, d, J = 10.8 Hz), 7.19-7.42 (4H, m), 7.77 (1H, d, J = 7.8 Hz), 8. 25 (1H, dd, J = 8.4, 1.2 Hz).

[2439]

Example 571

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydro-2H-thiopyran-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2440]



[2441]

In the same manner as in Example 25, the title compound (2.51 g, 90%) was obtained as a white solid from the compound of Reference Example 28 (2.22 g, 5.69 mmol) and tetrahydrothiopyran-4-ylamine (1.0 g, 8.53 mmol).

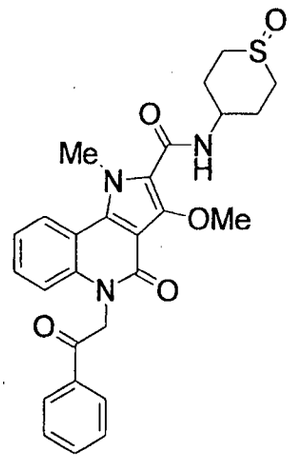
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.63-1.77 (2H, m), 1.99-2.17 (2H, m), 2.66-2.78 (4H, m), 3.87-3.97 (4H, m), 4.30 (3H, s), 5.97 (2H, s), 7.28-7.39 (2H, m), 7.47 (1H, td, J = 7.8, 1.2 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 8.1 Hz), 7.97 (1H, d, J = 8.1 Hz), 8.16-8.18 (2H, m), 8.36 (1H, dd, J = 8.4, 1.2 Hz).

[2442]

Example 572

Production of 3-methoxy-1-methyl-N-(1-oxidotetrahydro-2H-thiopyran-4-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2443]



[2444]

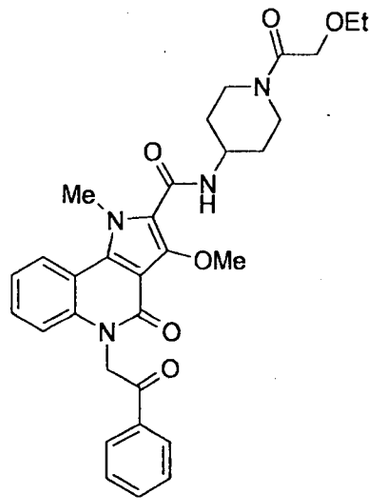
A solution of the compound of Example 571 (200 mg, 0.41 mmol) and mCPBA (70% containing water; 106 mg, 0.43 mmol) in ethyl acetate (25 mL) was stirred at 0°C for 1 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization of the residue from ethyl acetate-hexane gave the title compound (54 mg, 26 %) as white crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.88 (2H, d, J = 12.9 Hz), 2.20 (2H, q, J = 12.7 Hz), 2.70-3.00 (4H, m), 3.97-4.06 (4H, m), 4.29 (3H, s), 5.97 (2H, s), 7.29-7.40 (2H, m), 7.48 (1H, t, J = 7.5 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.05 (1H, d, J = 8.1 Hz), 8.16-8.19 (2H, m), 8.37 (1H, d, J = 7.5 Hz).

[2445]

Example 573

Production of N-[1-(ethoxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2446]



[2447]

In the same manner as in Example 25, the title compound (134 mg, 61%) was obtained as a white solid from the compound of Example 77 (200 mg, 0.39 mmol) and ethoxyacetic acid (0.045 mL, 0.47 mmol).

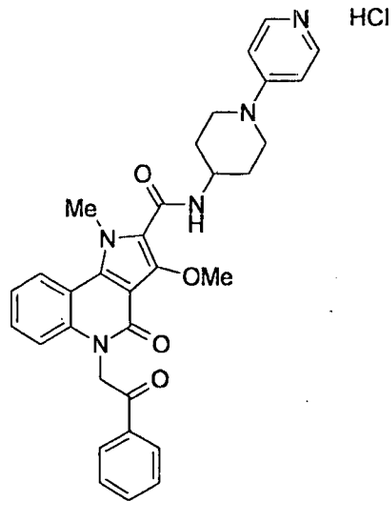
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.14 (3H, t, J = 7.0 Hz), 1.35-1.64 (2H, m), 1.81-1.97 (2H, m), 2.81-2.95 (1H, m), 3.09-3.24 (1H, m), 3.42-3.55 (2H, m), 3.73-3.85 (1H, m), 3.96 (3H, s), 4.02-4.25 (4H, m), 4.31 (3H, s), 5.97 (2H, s), 7.26-7.41 (2H, m), 7.43-7.53 (1H, m), 7.58-7.68 (2H, m), 7.71-7.81 (1H, m), 7.95 (1H, d, J = 7.7 Hz), 8.12-8.22 (2H, m), 8.37 (1H, dd, J = 8.2, 1.2 Hz).

[2448]

Example 574

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyridin-4-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2449]



[2450]

A solution of the compound of Example 563 (250 mg, 0.46 mmol) and 4N hydrogen chloride ethyl acetate solution (0.114 mL, 0.46 mmol) in methanol (3.0 mL)-ethyl acetate (3.0 mL) was stirred at room temperature for 10 min. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from methanol-diethyl ether to give the title compound (45 mg, 17%) as a white solid.

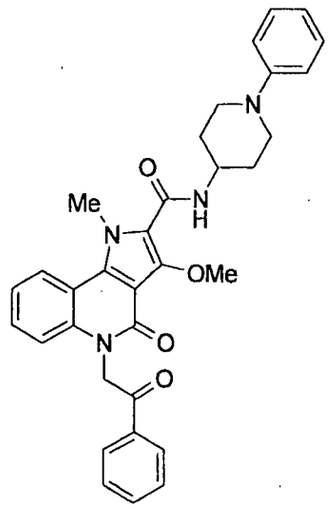
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.54-1.74 (2H, m), 1.95-2.10 (2H, m), 3.36-3.48 (2H, m), 3.96 (3H, s), 4.11-4.36 (6H, m), 5.97 (2H, s), 7.17-7.27 (2H, m), 7.28-7.42 (2H, m), 7.43-7.53 (1H, m), 7.58-7.69 (2H, m), 7.71-7.82 (1H, m), 8.00 (1H, d, J = 7.7 Hz), 8.12-8.19 (2H, m), 8.21-8.28 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 13.40 (1H, br s).

[2451]

Example 575

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-phenylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2452]



[2453]

A solution of the compound of Example 77 (200 mg, 0.42 mmol), iodobenzene (0.50 mL), tris(dibenzylideneacetone)dipalladium (0) (38 mg, 0.042 mmol), x-phos (40 mg, 0.085 mmol) and sodium tert-butoxide (102 mg, 1.1 mmol) in tert-butanol (4.0 mL) was stirred under microwave irradiation at 130°C for 35 min. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=30/70 - 100/0) and recrystallized from ethyl acetate to give the title compound (70 mg, 30%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.67-1.85 (2H, m), 2.09-2.25 (2H, m), 2.92-3.08 (2H, m), 3.53-3.69 (2H, m), 4.06-4.25 (4H, m), 4.48 (3H, s), 5.88 (2H, s), 6.82-6.92 (1H, m), 6.94-7.09 (3H, m), 7.20-7.32 (3H, m), 7.35-7.46 (1H, m), 7.49-7.59 (2H, m), 7.61-7.81 (2H, m), 8.03-8.16 (2H, m), 8.26 (1H, dd, J = 8.3, 1.3 Hz).

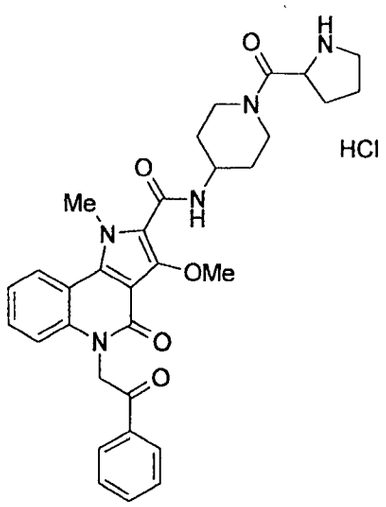
[2454]

Example 576

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-prolylpiperidin-4-yl)-4,5-dihydro-1H-

pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2455]



[2456]

To a solution of the compound of Example 77 (300 mg, 0.59 mmol), 1-(tert-butoxycarbonyl)proline (152 mg, 0.71 mmol) and HOBt (96 mg, 0.71 mmol) in DMF (7.5 mL) were added WSCD (136 mg, 0.71 mmol) and triethylamine (0.18 ml, 1.3 mmol) under ice-cooling, and the mixture was stirred at room temperature for 17 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=20/80 - 100/0). The obtained compound was dissolved in methanol (4.5 mL), 4N hydrogen chloride ethyl acetate solution (4.5 mL) was added, and the mixture was stirred at room temperature for 7 hr. The reaction mixture was concentrated under reduced pressure and recrystallized from methanol-diethyl ether to give the title compound (234 mg, 65%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.37-1.69 (2H, m), 1.69-1.84 (1H, m), 1.84-2.05 (4H, m), 2.29-2.46 (1H, m), 2.91-3.27 (4H, m), 3.75-3.91 (1H, m), 3.97 (3H, d, J = 1.5 Hz), 4.06-4.29 (2H, m), 4.32 (3H, d, J = 3.2 Hz), 4.48-4.67 (1H, m), 5.97 (2H, s),

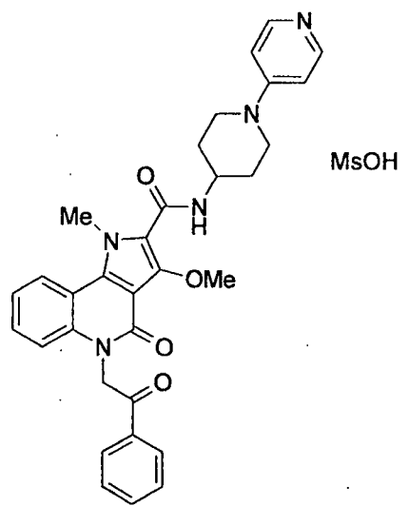
7.27-7.43 (2H, m), 7.44-7.54 (1H, m), 7.56-7.70 (2H, m), 7.70-7.83 (1H, m), 7.97 (1H, dd, J = 11.8, 7.8 Hz), 8.08-8.26 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz), 8.93 (2H, br s).

[2457]

Example 577

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyridin-4-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide methanesulfonate

[2458]



[2459]

In the same manner as in Example 574, the title compound (142 mg, 36%) was obtained as a pale-yellow solid from the compound of Example 563 (333 mg, 0.61 mmol), methanesulfonic acid (0.041 mL, 0.64 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-1.73 (2H, m), 1.96-2.09 (2H, m), 2.30 (3H, s), 3.36-3.49 (2H, m), 3.96 (3H, s), 4.14-4.37 (6H, m), 5.97 (2H, s), 7.17-7.27 (2H, m), 7.28-7.42 (2H, m), 7.43-7.52 (1H, m), 7.57-7.68 (2H, m), 7.71-7.81 (1H, m), 8.00 (1H, d, J = 7.9 Hz), 8.11-8.19 (2H, m), 8.21-8.28 (2H, m), 8.38 (1H, dd, J = 8.2, 1.2 Hz), 13.22 (1H, br s).

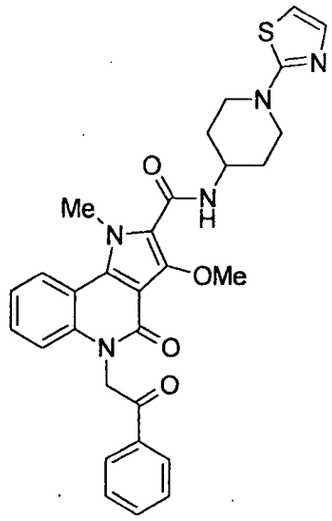
[2460]

Example 578

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-[1-(1,3-thiazol-2-yl)piperidin-4-yl]-4,5-

dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2461]



[2462]

In the same manner as in Example 25, the title compound (152 mg, 53%) was obtained as a white solid from the compound of Reference Example 28 (200 mg, 0.51 mmol) and 1-(1,3-thiazol-2-yl)piperidin-4-amine hydrochloride (124 mg, 0.56 mmol).

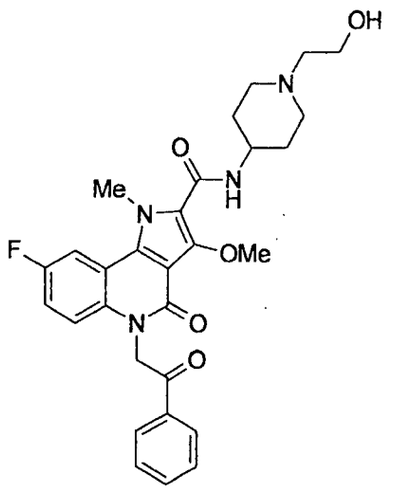
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58-1.79 (2H, m), 1.90-2.04 (2H, m), 3.15-3.28 (2H, m), 3.81-3.92 (2H, m), 3.96 (3H, s), 4.03-4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.83 (1H, d, J = 3.6 Hz), 7.16 (1H, d, J = 3.6 Hz), 7.27-7.41 (2H, m), 7.44-7.52 (1H, m), 7.58-7.68 (2H, m), 7.70-7.82 (1H, m), 8.00 (1H, d, J = 7.9 Hz), 8.10-8.23 (2H, m), 8.37 (1H, dd, J = 8.3, 1.3 Hz).

[2463]

Example 579

Production of 8-fluoro-N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2464]



[2465]

A solution of the compound of Example 675 (300 mg, 0.57 mmol), potassium carbonate (629 mg, 4.6 mmol) and triethylamine (0.11 mL, 0.76 mmol) in DMF (13 mL) was stirred at 100°C for 5 min, and 2-bromoethanol (0.16 mL, 2.3 mmol) was added. After stirring at 100°C for 1.5 hr, the reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with water, and extracted 3 times with ethyl acetate. The extracts were combined, washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; methanol/ethyl acetate=0/100 - 5/95) and recrystallized from THF-diethyl ether to give the title compound (205 mg, 51%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.47-1.67 (2H, m), 1.75-1.89 (2H, m), 2.08-2.25 (2H, m), 2.40 (2H, t, J = 6.3 Hz), 2.70-2.86 (2H, m), 3.49 (2H, q, J = 6.1 Hz), 3.74-3.89 (1H, m), 3.97 (3H, s), 4.31 (3H, s), 4.38 (1H, t, J = 5.4 Hz), 5.97 (2H, s), 7.28-7.40 (1H, m), 7.40-7.49 (1H, m), 7.58-7.68 (2H, m), 7.71-7.82 (1H, m), 7.92 (1H, d, J = 7.7 Hz), 8.05-8.23 (3H, m).

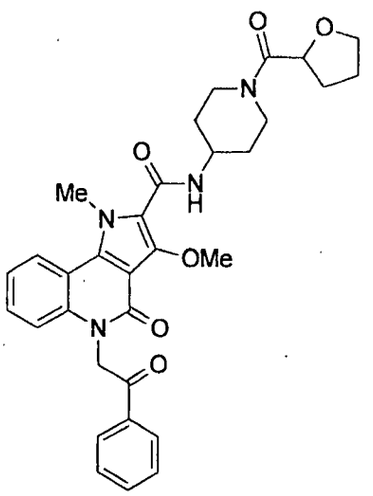
[2466]

Example 580

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-[1-(tetrahydrofuran-2-ylcarbonyl)piperidin-4-

yl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2467]



[2468]

In the same manner as in Example 25, the title compound (41 mg, 17%) was obtained as a white solid from the compound of Reference Example 77 (200 mg, 0.42 mmol) and tetrahydrofuran-2-carboxylic acid (0.049 mL, 0.51 mmol).

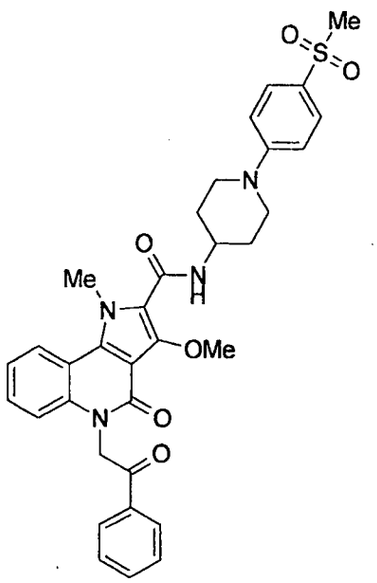
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34-1.63 (2H, m), 1.74-1.95 (4H, m), 1.96-2.12 (2H, m), 2.78-2.97 (1H, m), 3.09-3.28 (1H, m), 3.68-3.86 (2H, m), 3.88-4.02 (4H, m), 4.03-4.27 (2H, m), 4.28-4.35 (3H, m), 4.68 (1H, dd, J = 7.4, 5.9 Hz), 5.97 (2H, s), 7.26-7.41 (2H, m), 7.43-7.53 (1H, m), 7.58-7.68 (2H, m), 7.71-7.81 (1H, m), 7.89-8.03 (1H, m), 8.12-8.22 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2469]

Example 581

Production of 3-methoxy-1-methyl-N-{1-[4-(methylsulfonyl)phenyl]piperidin-4-yl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2470]



[2471]

In the same manner as in Example 575, the title compound (28 mg, 8.0%) was obtained as a white solid from the compound of Example 77 (260 mg, 0.55 mmol) and 1-bromo-4-(methylsulfonyl)benzene (259 mg, 1.1 mmol).

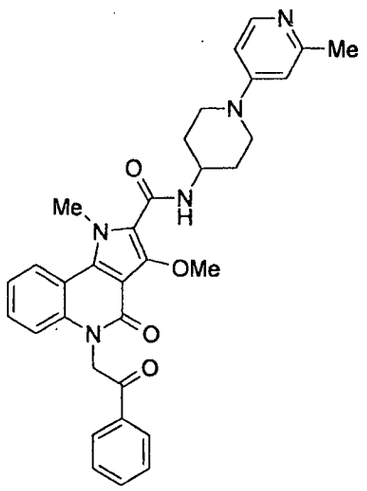
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.54-1.72 (2H, m), 1.88-2.04 (2H, m), 3.05-3.20 (5H, m), 3.85-3.99 (5H, m), 4.04-4.22 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.06-7.17 (2H, m), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.57-7.71 (4H, m), 7.72-7.82 (1H, m), 7.99 (1H, d, J = 7.9 Hz), 8.14-8.23 (2H, m), 8.37 (1H, dd, J = 8.1, 1.1 Hz).

[2472]

Example 582

Production of 3-methoxy-1-methyl-N-[1-(2-methylpyridin-4-yl)piperidin-4-yl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2473]



[2474]

In the same manner as in Example 575, the title compound (51 mg, 14%) was obtained as a white solid from the compound of Reference Example 77 (300 mg, 0.64 mmol) and 4-bromo-2-methylpyridine (0.15 mL, 1.3 mmol).

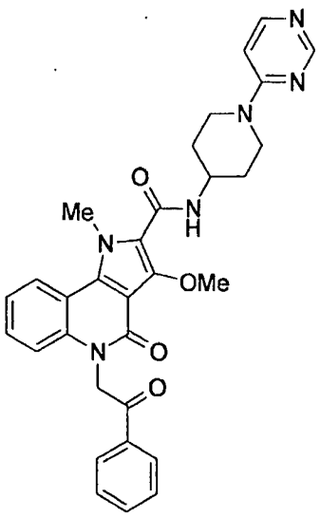
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.48-1.68 (2H, m), 1.84-1.98 (2H, m), 2.32 (3H, s), 2.95-3.14 (2H, m), 3.80-3.91 (2H, m), 3.95 (3H, s), 4.02-4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.62-6.70 (1H, m), 6.71-6.75 (1H, m), 7.24-7.41 (2H, m), 7.43-7.52 (1H, m), 7.58-7.67 (2H, m), 7.70-7.81 (1H, m), 7.92-8.06 (2H, m), 8.12-8.22 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2475]

Example 583

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyrimidin-4-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2476]



[2477]

A solution of the compound of Example 77 (200 mg, 0.42 mmol), 4-chloropyrimidine (58 mg, 0.51 mmol) and triethylamine (0.12 mL, 0.85 mmol) in 2-propanol (4.0 mL) was heated under reflux for 23 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with a mixed solvent of ethyl acetate-methanol. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/methanol=0/100 - 5/95) and recrystallized from THF to give the title compound (97 mg, 42%) as a white solid.

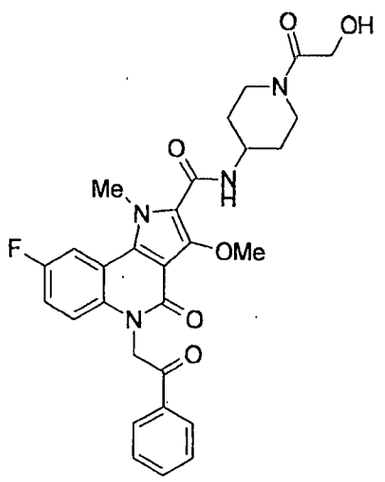
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44-1.65 (2H, m), 1.88-2.02 (2H, m), 3.10-3.24 (2H, m), 3.95 (3H, s), 4.08-4.23 (1H, m), 4.25-4.39 (5H, m), 5.97 (2H, s), 6.88 (1H, dd, J = 6.4, 1.1 Hz), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.58-7.68 (2H, m), 7.72-7.81 (1H, m), 7.97 (1H, d, J = 7.9 Hz), 8.11-8.23 (3H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz), 8.49 (1H, s).

[2478]

Example 584

Production of 8-fluoro-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2479]



[2480]

In the same manner as in Example 511, the title compound (103 mg, 38%) was obtained as a white solid from the compound of Example 676 (293 mg, 0.50 mmol).

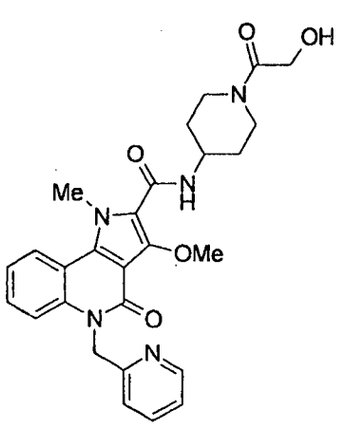
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.36-1.63 (2H, m), 1.81-1.96 (2H, m), 2.84-2.99 (1H, m), 3.06-3.20 (1H, m), 3.61-3.74 (1H, m), 3.95 (3H, s), 4.03-4.15 (3H, m), 4.17-4.27 (1H, m), 4.30 (3H, s), 4.52 (1H, t, J = 5.5 Hz), 5.97 (2H, s), 7.30-7.40 (1H, m), 7.41-7.49 (1H, m), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 8.01 (1H, d, J = 7.7 Hz), 8.07-8.21 (3H, m).

[2481]

Example 585

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2482]



[2483]

To a suspension of the compound of Example 672 (300 mg, 0.66 mmol) in DMF (5 mL) was added sodium hydride (60% in oil; 79 mg, 1.98 mmol), and the mixture was stirred at room temperature for 30 min. 2-Chloromethylpyridine hydrochloride (238 mg, 1.46 mmol) was added to the mixture, and the mixture was stirred at 60°C for 16 hr. After cooling, the reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate) to give 2-[4-({[3-methoxy-1-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (60 mg).

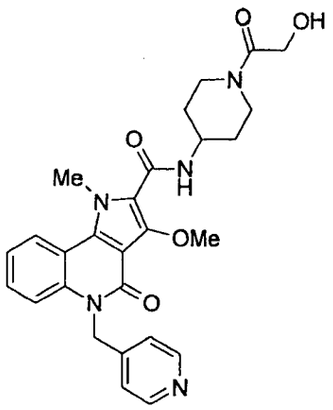
To a solution of 2-[4-({[3-methoxy-1-methyl-4-oxo-5-(pyridin-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (60 mg) in THF (2 mL)-methanol (2 ml) was added 2N sodium hydroxide solution (2 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Recrystallization from ethyl acetate-diisopropyl ether gave the title compound (25 mg, 45%) as beige crystals. ^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.60 (2H, m), 1.90 (2H, d, J = 11.4 Hz), 2.93 (1H, t, J = 11.2 Hz), 3.15 (1H, t, J = 11.9 Hz), 3.67 (1H, d, J = 13.8 Hz), 4.01-4.29 (10H, m), 4.52 (1H, t, J = 5.4 Hz), 5.66 (2H, s), 7.11 (1H, d, J = 7.8 Hz), 7.24-7.31 (2H, m), 7.40-7.44 (2H, m), 7.71 (1H, td, J = 7.5, 1.8 Hz), 7.97 (1H, d, J = 7.8 Hz), 8.34 (1H, d, J = 8.1 Hz), 8.49-8.51 (1H, m).

[2484]

Example 586

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(pyridin-4-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2485]



[2486]

In the same manner as in Example 585, the title compound (14 mg, 5%) was obtained as beige crystals from the compound of Example 672 (300 mg, 0.66 mmol) and 4-chloromethylpyridine hydrochloride (130 mg, 0.80 mmol).

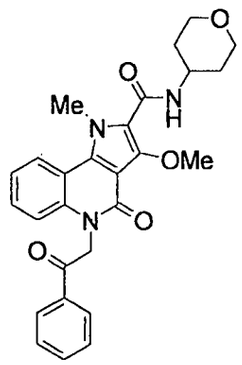
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.60 (2H, m), 1.90 (2H, d, J = 11.4 Hz), 2.93 (1H, t, J = 12.4 Hz), 3.14 (1H, t, J = 14.2 Hz), 3.60-3.75 (1H, m), 4.10-4.29 (10H, m), 4.45-4.60 (1H, br), 5.63 (2H, s), 7.16 (2H, d, J = 5.1 Hz), 7.28-7.36 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.36 (1H, d, J = 8.4 Hz), 8.48 (2H, d, J = 4.8 Hz).

[2487]

Example 587

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2488]



[2489]

In the same manner as in Example 25, the title compound (204 mg, 84%) was obtained as white crystals from the compound of Reference Example 28 (200 mg, 0.51 mmol) and 4-aminotetrahydropyran (62 mg, 0.61 mmol).

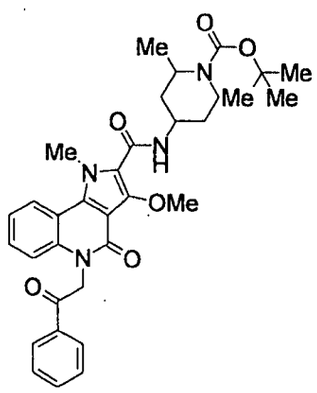
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.59 (2H, q, J = 10.0 Hz), 1.84 (2H, d, J = 13.5 Hz), 3.44 (2H, t, J = 11.0 Hz), 3.86 (2H, d, J = 11.4 Hz), 3.97 (3H, s), 4.00-4.10 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.29-7.39 (2H, m), 7.48 (1H, t, J = 7.5 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.1 Hz), 7.96 (1H, d, J = 7.8 Hz), 8.17 (2H, d, J = 7.5 Hz), 8.37 (1H, d, J = 8.1 Hz).

[2490]

Example 588

Production of tert-butyl 4-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)-2-methylpiperidine-1-carboxylate

[2491]



[2492]

In the same manner as in Example 25, the title compound

(220 mg, 75%) was obtained as white crystals from the compound of Reference Example 28 (200 mg, 0.51 mmol) and 1-Boc-4-amino-2-methylpiperidine (131 mg, 0.61 mmol).

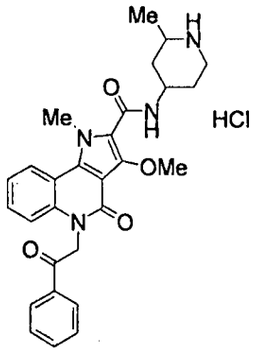
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.24 (3H, d, J = 6.9 Hz), 1.41 (9H, s), 1.65-1.95 (4H, m), 3.13 (1H, t, J = 10.7 Hz), 3.73 (1H, d, J = 13.2 Hz), 4.02 (3H, s), 4.10-4.20 (2H, m), 4.35 (3H, s), 5.98 (2H, s), 7.30-7.41 (2H, m), 7.48 (1H, t, J = 7.2 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.02 (1H, d, J = 6.6 Hz), 8.16-8.19 (2H, m), 8.38 (1H, d, J = 7.2 Hz).

[2493]

Example 589

Production of 3-methoxy-1-methyl-N-(2-methylpiperidin-4-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2494]



[2495]

In the same manner as in Example 61, the title compound (163 mg, 100%) was obtained as white crystals from the compound of Example 588 (200 mg, 0.34 mmol).

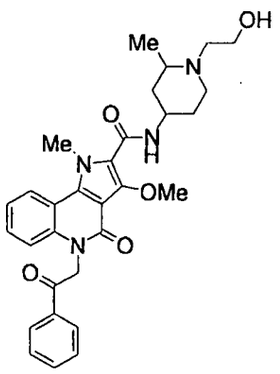
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.26 (3H, d, J = 6.3 Hz), 1.45-1.90 (3H, m), 2.08 (2H, t, J = 14.1 Hz), 3.04 (1H, t, J = 11.9 Hz), 3.96 (3H, s), 4.04-4.14 (1H, m), 4.28 (3H, s), 5.98 (2H, s), 7.29-7.40 (2H, m), 7.48 (1H, d, J = 7.8 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.09 (1H, d, J = 7.8 Hz), 8.16-8.19 (2H, m), 8.37 (1H, d, J = 8.4 Hz), 8.50-8.90 (2H, br).

[2496]

Example 590

Production of N-[1-(2-hydroxyethyl)-2-methylpiperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2497]



[2498]

In the same manner as in Example 79, the title compound (25 mg, 36%) was obtained as white crystals from the compound of Example 589 (70 mg, 0.13 mmol).

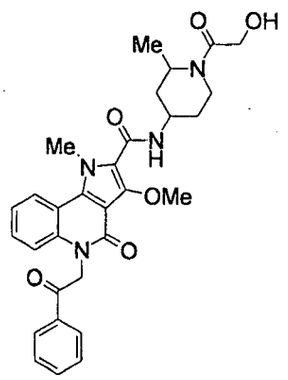
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.06 (3H, d, J = 6.3 Hz), 1.23 (1H, q, J = 11.6 Hz), 1.40-1.60 (1H, m), 1.85 (2H, d, J = 10.8 Hz), 2.21-2.32 (3H, m), 2.74-2.83 (1H, m), 2.96 (1H, t, J = 12.3 Hz), 3.45-3.51 (2H, m), 3.70-3.90 (1H, m), 3.98 (3H, s), 4.30-4.38 (4H, m), 5.97 (2H, s), 7.29-7.45 (2H, m), 7.48 (1H, d, J = 7.5 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.74-7.84 (2H, m), 8.17 (2H, d, J = 7.8 Hz), 8.37 (1H, d, J = 8.4 Hz).

[2499]

Example 591

Production of N-[1-(hydroxyacetyl)-2-methylpiperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2500]



[2501]

In the same manner as in Example 130, the title compound (35 mg, 40%) was obtained as white crystals from the compound of Example 589 (80 mg, 0.15 mmol).

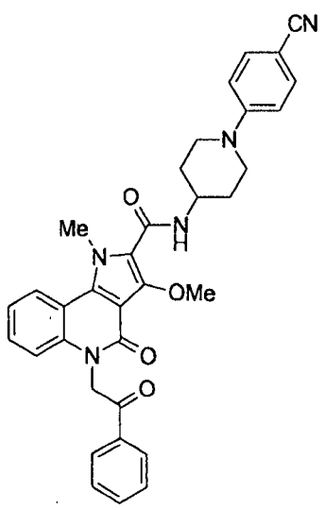
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.28 (3H, d, J = 6.9 Hz), 1.70-1.95 (4H, m), 3.10-3.25 (1H, m), 4.03-4.15 (7H, m), 4.30-4.34 (4H, m), 4.50 (1H, t, J = 5.4 Hz), 5.98 (2H, s), 7.30-7.41 (2H, m), 7.49 (1H, t, J = 8.1 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.2 Hz), 8.07 (1H, d, J = 6.6 Hz), 8.17 (2H, d, J = 7.2 Hz), 8.38 (1H, d, J = 7.5 Hz).

[2502]

Example 592

Production of N-[1-(4-cyanophenyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2503]



[2504]

A solution of the compound of Example 77 (300 mg, 0.64 mmol), 4-fluorobenzonitrile (115 mg, 0.95 mmol) and potassium carbonate (176 mg, 1.3 mmol) in N-methylpyrrolidone (3.0 mL) was stirred at 120°C for 16.5 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=30/70 - 100/0) and recrystallized from THF-diethyl ether to give the title compound (73 mg, 20%) as a pale-yellow solid.

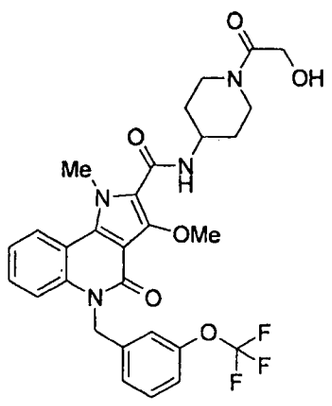
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.52-1.70 (2H, m), 1.87-2.03 (2H, m), 3.02-3.20 (2H, m), 3.81-4.00 (5H, m), 4.03-4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.98-7.12 (2H, m), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.53-7.69 (4H, m), 7.71-7.82 (1H, m), 7.98 (1H, d, J = 7.9 Hz), 8.12-8.22 (2H, m), 8.37 (1H, dd, J = 8.4, 1.2 Hz).

[2505]

Example 593

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-[3-(trifluoromethoxy)benzyl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2506]



[2507]

In the same manner as in Example 570, 2-{4-[({3-methoxy-

1-methyl-4-oxo-5-[3-(trifluoromethoxy)benzyl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl}carbonyl)amino]piperidin-1-yl}-2-oxoethyl acetate (70 mg) was obtained as a colorless amorphous solid from the compound of Example 672 (500 mg, 1.10 mmol) and 3-trifluoromethoxybenzyl bromide (1.0 g, 3.92 mmol).

A solution of 2-{4-[({3-methoxy-1-methyl-4-oxo-5-[3-(trifluoromethoxy)benzyl]-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl}carbonyl)amino]piperidin-1-yl}-2-oxoethyl acetate (70 mg) and potassium carbonate (77 mg, 0.55 mmol) in THF (2 mL)-methanol (1 mL)-water (1 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (23 mg, 4%) as white crystals.

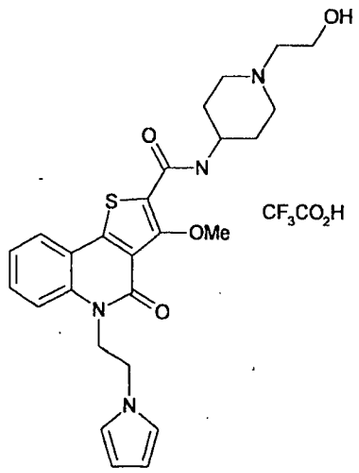
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.65 (2H, m), 1.85-1.95 (2H, m), 2.93 (1H, t, J = 11.7 Hz), 3.15 (1H, t, J = 11.7 Hz), 3.68 (1H, d, J = 12.3 Hz), 4.01-4.29 (10H, m), 4.53 (1H, t, J = 5.4 Hz), 5.50-5.70 (2H, br), 7.16-7.33 (4H, m), 7.41-7.47 (3H, m), 8.00 (1H, d, J = 8.1 Hz), 8.36 (1H, d, J = 8.1 Hz).

[2508]

Example 594

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-4-oxo-5-[2-(1H-pyrrol-1-yl)ethyl]-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide trifluoroacetate

[2509]



[2510]

To a 0.2M-DMF solution of the compound of Example 667 (500 μL, 100 μmol) was added sodium carbonate (1 mmol, 138 mg), and a 0.3M-DMF solution (500 μL, 150 μmol) of 1-(2-bromoethyl)-1H-pyrrole was added dropwise thereto. The reaction mixture was stirred at 40°C overnight. Ethyl acetate (3 mL) and water (2 mL) were added thereto, and the mixture was extracted and the organic layer was separate. Ethyl acetate was evaporated under reduced pressure and the residue was dissolved in acetonitrile (500 μl), purified (trifluoroacetic acid type) by preparative HPLC to give the title compound.

yield: 6.9 mg

LC-MS analysis: purity 84%

MS(ESI+): 495 (M+H)

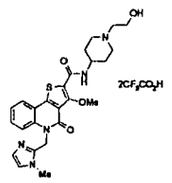
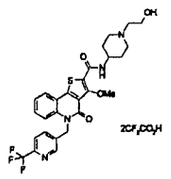
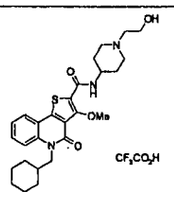
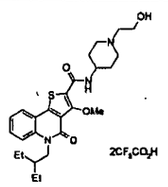
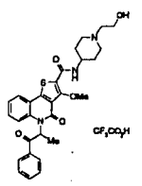
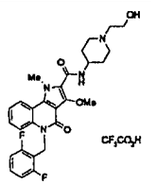
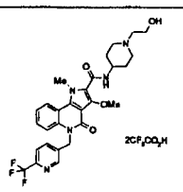
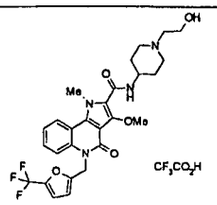
[2511]

Example 595 - Example 602

In the same manner as in Example 594, the compounds shown in Table 1 were obtained from the compound of Example 667 or Example 683 and corresponding halide.

[2512]

Table 1

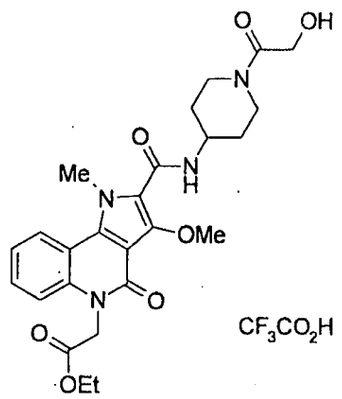
Example No.	structure	yield (mg)	purity (%)	MS (ESI+)
595		8.6	100	496
596		2.3	89	561
597		4.7	100	498
598		2.1	100	486
599		7.4	100	534
600		1.3	81	525
601		3.1	97	558
602		4.3	100	547

[2513]

Example 603

Production of ethyl (2-{[1-(hydroxyacetyl)piperidin-4-yl]carbamoyl}-3-methoxy-1-methyl-4-oxo-1,4-dihydro-5H-pyrrolo[3,2-c]quinolin-5-yl)acetate

[2514]



[2515]

To a 0.2M-DMF solution of the compound of Example 672 (500 μL, 100 μmol) was added sodium carbonate (1 mmol, 138 mg), and a 2M-DMF solution (500 μL, 1 mmol) of ethyl bromoacetate was added dropwise thereto. The reaction mixture was stirred at 80°C overnight. After completion of the reaction, DMF was evaporated using a centrifugal vacuum concentrator under heating at 60°C. Acetonitrile-DMSO (1:1, 500 μl) was added to the residue, and the insoluble material was filtered off. The filtrate was purified (ammonium carbonate type) by preparative HPLC to give the title compound.

yield: 2.9 mg

LC-MS analysis: purity 97%

MS(ESI+): 499 (M+H)

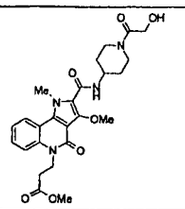
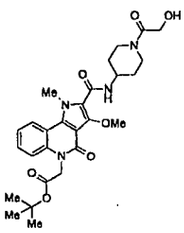
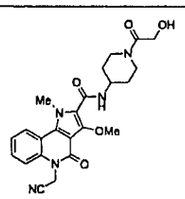
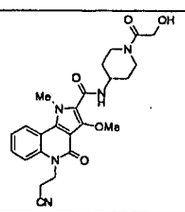
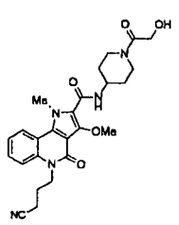
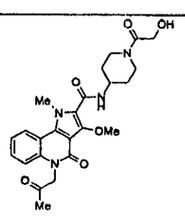
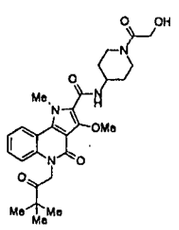
[2516]

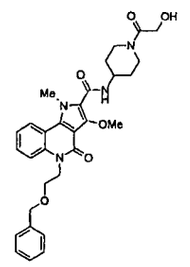
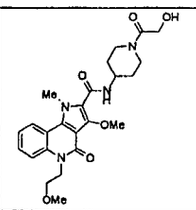
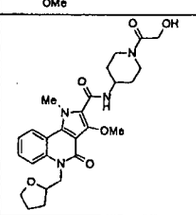
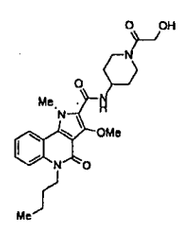
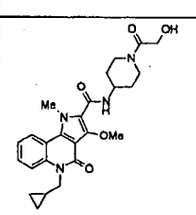
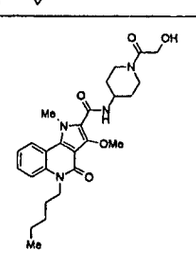
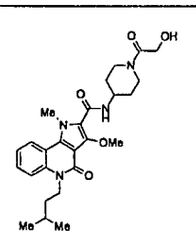
Example 604 - Example 618

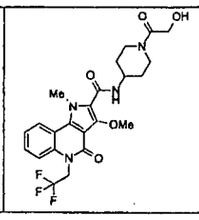
In the same manner as in Example 594, the compounds shown in Table 2 were obtained from the compound of Example 672 and corresponding halide.

[2517]

Table 2

Example No.	structure	yield (mg)	purity (%)	MS (ESI+)
604		7.3	100	499
605		8.4	100	527
606		6.2	71	452
607		16.9	100	466
608		13.2	100	480
609		10.7	100	469
610		11.7	100	511

611		17.3	100	547
612		1.6	100	471
613		11	100	497
614		7.7	100	469
615		5.3	100	467
616		12	100	483
617		6.6	100	483

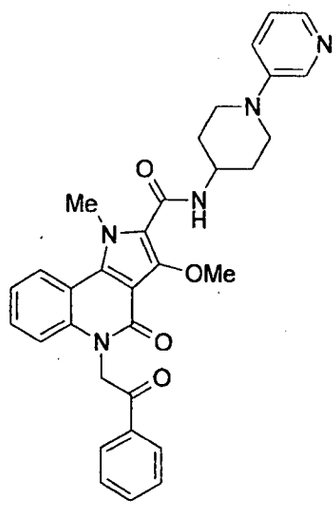
618		8.2	100	495

[2518]

Example 619

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(1-pyridin-3-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2519]



[2520]

In the same manner as in Example 575, the title compound (19 mg, 5.4%) was obtained as a white solid from the compound of Reference Example 77 (300 mg, 0.64 mmol) and 3-bromopyridine (0.50 mL, 5.2 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58-1.81 (2H, m), 1.89-2.04 (2H, m), 2.90-3.04 (2H, m), 3.64-3.77 (2H, m), 3.97 (3H, s), 4.00-4.13 (1H, m), 4.32 (3H, s), 5.97 (2H, s), 7.15-7.25 (1H, m), 7.27-7.41 (3H, m), 7.42-7.52 (1H, m), 7.57-7.68 (2H, m), 7.71-7.82 (1H, m), 7.93-8.04 (2H, m), 8.11-8.21 (2H, m), 8.30-8.43 (2H, m).

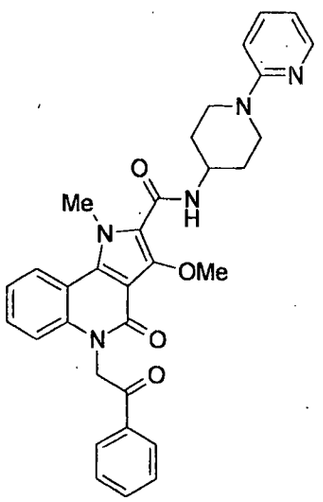
[2521]

Example 620

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-

phenylethyl)-N-(1-pyridin-2-ylpiperidin-4-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2522]



[2523]

A solution of the compound of Example 77 (284 mg, 0.60 mmol), 2-iodopyridine (0.13 mL, 1.2 mmol) and potassium carbonate (208 mg, 1.5 mmol) in DMF (3.0 mL) was stirred at 90°C for 5.5 hr. 2-Bromopyridine (0.23 mL, 2.5 mmol) and triethylamine (0.49 mL, 3.5 mmol) were added to the reaction mixture, and the mixture was stirred under microwave irradiation at 165°C for 1 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=30/70 - 100/0) and recrystallized from THF-diethyl ether to give the title compound (38 mg, 12%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.45-1.65 (2H, m), 1.86-2.00 (2H, m), 2.99-3.14 (2H, m), 3.95 (3H, s), 4.03-4.14 (1H, m), 4.16-4.26 (2H, m), 4.31 (3H, s), 5.97 (2H, s), 6.61 (1H, dd, J = 6.8, 5.1 Hz), 6.87 (1H, d, J = 8.7 Hz), 7.26-7.42 (2H, m), 7.43-7.57 (2H, m), 7.59-7.68 (2H, m), 7.70-7.81 (1H, m), 7.97 (1H, d, J = 7.9 Hz), 8.08-8.21 (3H, m), 8.37 (1H, d, J = 7.7

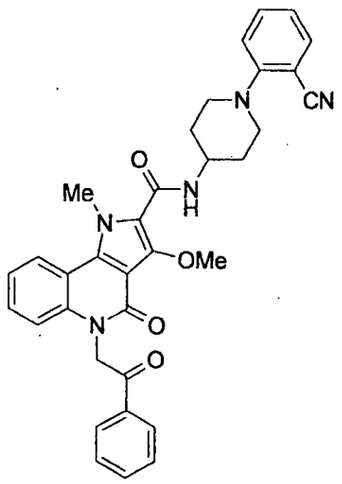
Hz).

[2524]

Example 621

Production of N-[1-(2-cyanophenyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2525]



[2526]

A solution of the compound of Example 77 (300 mg, 0.59 mmol), 2-fluorobenzonitrile (0.50 mL, 4.6 mmol) and triethylamine (0.50 mL, 3.6 mmol) in DMF (3.5 mL) was stirred under microwave irradiation at 130°C for 30 min. 2-Bromobenzonitrile (143 mg, 1.2 mmol) and potassium carbonate (208 mg, 1.5 mmol) were added to the reaction mixture, and the mixture was stirred under microwave irradiation at 165°C for 30 min. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=50/50 - 100/0) and recrystallized from ethyl acetate-hexane to give the title compound (74 mg, 22%) as a pale-yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.72-1.89 (2H, m), 1.97-2.10 (2H, m), 2.94-3.08 (2H, m), 3.43-3.54 (2H, m), 3.95-4.14 (4H, m),

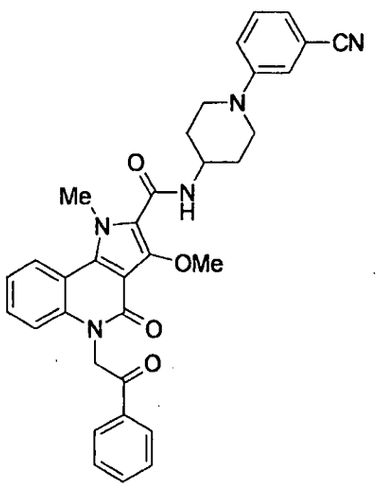
4.32 (3H, s), 5.98 (2H, s), 7.05-7.13 (1H, m), 7.22 (1H, d, J = 8.1 Hz), 7.28-7.42 (2H, m), 7.44-7.52 (1H, m), 7.56-7.81 (5H, m), 8.06 (1H, d, J = 7.9 Hz), 8.14-8.23 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz).

[2527]

Example 622

Production of N-[1-(3-cyanophenyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2528]



[2529]

A solution of the compound of Example 77 (300 mg, 0.59 mmol), 3-bromobenzonitrile (143 mg, 1.2 mmol), tris(dibenzylideneacetone)dipalladium (0) (54 mg, 0.059 mmol), x-phos (56 mg, 0.12 mmol), sodium tert-butoxide (142 mg, 1.5 mmol) and triethylamine (0.082 mL, 0.59 mmol) in 2-butanone (4.0 mL) was stirred under microwave irradiation at 130°C for 40 min. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=40/60 - 100/0) and recrystallized from ethyl acetate-hexane to give the title compound (25 mg, 7.4%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58-1.74 (2H, m), 1.88-2.01 (2H,

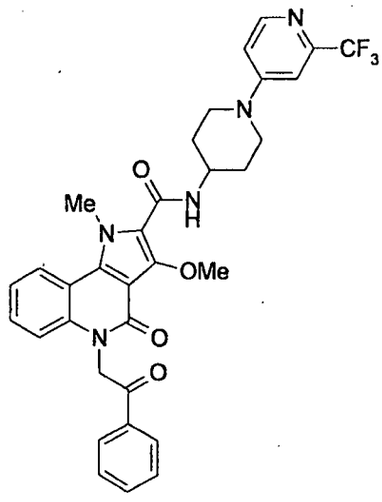
m), 2.94-3.07 (2H, m), 3.71-3.83 (2H, m), 3.96 (3H, s), 4.00-4.12 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.10-7.16 (1H, m), 7.27-7.42 (5H, m), 7.44-7.52 (1H, m), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 7.99 (1H, d, J = 7.9 Hz), 8.11-8.22 (2H, m), 8.38 (1H, dd, J = 8.3, 1.1 Hz).

[2530]

Example 623

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-{1-[2-(trifluoromethyl)pyridin-4-yl]piperidin-4-yl}-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2531]



[2532]

A solution of the compound of Example 77 (300 mg, 0.59 mmol), potassium carbonate (204 mg, 1.5 mmol) and triethylamine (0.082 mL, 0.59 mmol) in DMF (3.0 mL) was heated to 80°C, 4-bromo-2-(trifluoromethyl)pyridine (133 mg, 0.59 mmol) was added, and the mixture was stirred at 100°C for 23 hr. The reaction mixture was diluted with water, and extracted 3 times with ethyl acetate. The extract was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=50/50 - 100/0) and recrystallized from ethyl acetate-hexane to give the title compound (126 mg, 35%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.52-1.70 (2H, m), 1.89-2.02 (2H,

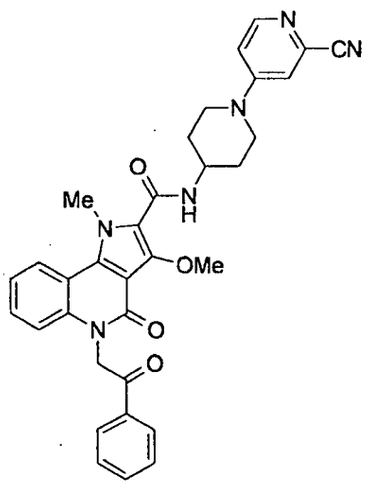
m), 3.11-3.25 (2H, m), 3.90-4.07 (5H, m), 4.10-4.24 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.08 (1H, dd, J = 6.1, 2.5 Hz), 7.21-7.27 (1H, m), 7.27-7.41 (2H, m), 7.43-7.52 (1H, m), 7.57-7.67 (2H, m), 7.72-7.80 (1H, m), 7.98 (1H, d, J = 7.9 Hz), 8.13-8.21 (2H, m), 8.27 (1H, d, J = 5.9 Hz), 8.37 (1H, dd, J = 8.2, 1.2 Hz).

[2533]

Example 624

Production of N-[1-(2-cyanopyridin-4-yl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2534]



[2535]

In the same manner as in Example 623, the title compound (70 mg, 21%) was obtained as a white solid from the compound of Example 77 (300 mg, 0.59 mmol) and 4-iodopyridine-2-carbonitrile (136 mg, 0.59 mmol).

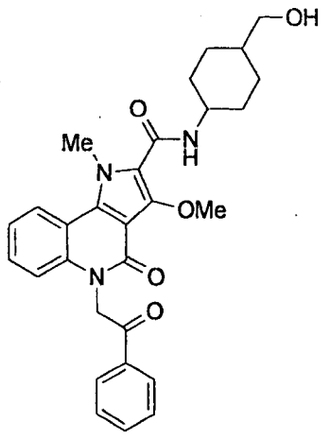
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.69 (2H, m), 1.86-1.98 (2H, m), 3.10-3.25 (2H, m), 3.90-4.05 (5H, m), 4.08-4.24 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.10 (1H, dd, J = 6.1, 2.7 Hz), 7.25-7.42 (2H, m), 7.43-7.55 (2H, m), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 7.97 (1H, d, J = 7.7 Hz), 8.11-8.27 (3H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2536]

Example 625

Production of N-[4-(hydroxymethyl)cyclohexyl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2537]



[2538]

In the same manner as in Example 25, the title compound (165 mg, 64%) was obtained as a white solid from the compound of Reference Example 28 (200 mg, 0.51 mmol) and (4-aminocyclohexyl)methanol (130 mg, 1.0 mmol).

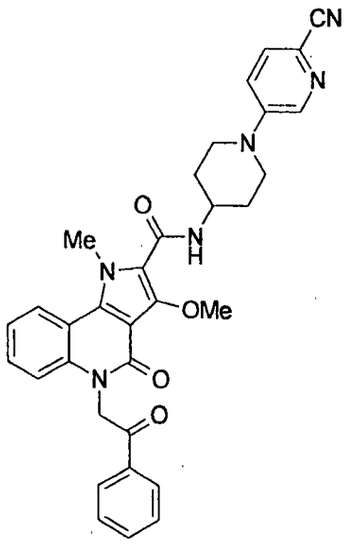
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.92-1.10 (2H, m), 1.21-1.43 (3H, m), 1.72-1.86 (2H, m), 1.89-2.02 (2H, m), 3.24 (2H, t, J = 5.8 Hz), 3.66-3.83 (1H, m), 3.96 (3H, s), 4.31 (3H, s), 4.42 (1H, t, J = 5.3 Hz), 5.97 (2H, s), 7.25-7.41 (2H, m), 7.42-7.53 (1H, m), 7.58-7.68 (2H, m), 7.71-7.85 (2H, m), 8.10-8.22 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2539]

Example 626

Production of N-[1-(6-cyanopyridin-3-yl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2540]



[2541]

In the same manner as in Example 623, the title compound (52 mg, 15%) was obtained as a pale-yellow solid from the compound of Example 77 (300 mg, 0.59 mmol) and 5-bromopyridine-2-carbonitrile (119 mg, 0.65 mmol).

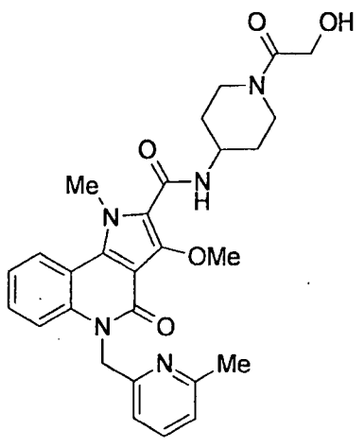
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.56-1.74 (2H, m), 1.88-2.02 (2H, m), 3.10-3.25 (2H, m), 3.91-4.04 (5H, m), 4.06-4.22 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.25-7.52 (4H, m), 7.58-7.68 (2H, m), 7.71-7.81 (2H, m), 7.98 (1H, d, J = 7.9 Hz), 8.12-8.21 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz), 8.46 (1H, d, J = 2.8 Hz).

[2542]

Example 627

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-5-[(6-methylpyridin-2-yl)methyl]-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2543]



[2544]

In the same manner as in Example 570, 2-{4-[({3-methoxy-1-methyl-5-[(6-methylpyridin-2-yl)methyl]-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl}carbonyl)amino]piperidin-1-yl}-2-oxoethyl acetate (80 mg) was obtained as a colorless amorphous solid from the compound of Example 672 (300 mg, 0.66 mmol), 2-(chloromethyl)-6-methylpyridine hydrochloride (940 mg, 5.28 mmol) and cesium carbonate (2.18 g, 6.60 mmol).

A solution of 2-{4-[({3-methoxy-1-methyl-5-[(6-methylpyridin-2-yl)methyl]-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl}carbonyl)amino]piperidin-1-yl}-2-oxoethyl acetate (80 mg) and potassium carbonate (100 mg, 0.71 mmol) in THF (2 mL)-methanol (1 mL)-water (1 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (37 mg, 11%) as white crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.60 (2H, m), 1.90 (2H, d, J = 9.6 Hz), 2.47 (3H, s), 2.93 (1H, t, J = 11.7 Hz), 3.14 (1H, t, J = 11.6 Hz), 3.67 (1H, d, J = 12.9 Hz), 3.99-4.29 (10H, m), 4.52 (1H, t, J = 5.4 Hz), 5.59 (2H, s), 6.71 (1H, d, J = 7.8 Hz), 7.12 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.5 Hz), 7.37-7.48 (2H, m), 7.55 (1H, t, J = 7.8 Hz), 7.98 (1H, d, J = 7.8

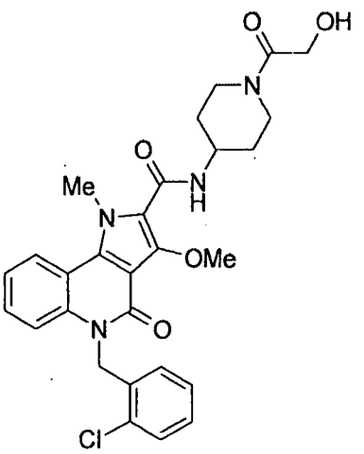
Hz), 8.35 (1H, d, J = 7.2 Hz).

[2545]

Example 628

Production of 5-(2-chlorobenzyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2546]



[2547]

In the same manner as in Example 570, 2-[4-({[5-(2-chlorobenzyl)-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (80 mg) was obtained as a colorless amorphous solid from the compound of Example 672 (300 mg, 0.66 mmol), 2-chlorobenzyl chloride (1.06 g, 6.60 mmol) and cesium carbonate (2.18 g, 6.60 mmol).

A solution of 2-[4-({[5-(2-chlorobenzyl)-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (80 mg) and potassium carbonate (100 mg, 0.71 mmol) in THF (2 mL)-methanol (1 mL)-water (1 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to

give the title compound (8 mg, 2%) as white crystals.

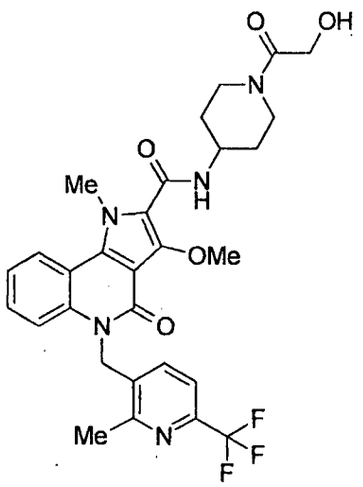
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.60 (2H, m), 1.90 (2H, d, J = 12.3 Hz), 2.93 (1H, t, J = 11.0 Hz), 3.15 (1H, t, J = 11.6 Hz), 3.68 (1H, d, J = 13.5 Hz), 3.99-4.34 (10H, m), 4.52 (1H, t, J = 5.4 Hz), 5.58 (2H, s), 6.59 (1H, d, J = 7.5 Hz), 7.14-7.20 (2H, m), 7.27-7.34 (2H, m), 7.47 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.39 (1H, d, J = 8.4 Hz).

[2548]

Example 629

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-5-{[2-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2549]



[2550]

In the same manner as in Example 570, 2-(4-{[(3-methoxy-1-methyl-5-{[2-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxoethyl acetate (50 mg) was obtained as a colorless amorphous solid from the compound of Example 672 (300 mg, 0.66 mmol), 3-chloromethyl-2-methyl-6-trifluoromethylpyridine (980 mg, 4.68 mmol) and cesium carbonate (1.09 g, 3.30 mmol).

A solution of 2-(4-{[(3-methoxy-1-methyl-5-{[2-methyl-6-(trifluoromethyl)pyridin-3-yl]methyl}-4-oxo-4,5-dihydro-1H-

pyrrolo[3,2-c]quinolin-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxoethyl acetate (50 mg) and potassium carbonate (55 mg, 0.40 mmol) in THF (2 mL)-methanol (1 mL)-water (1 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (19 mg, 5%) as white crystals.

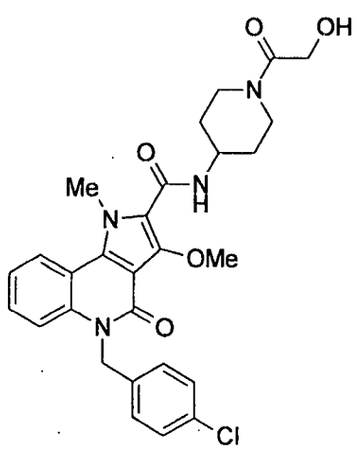
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.60 (2H, m), 1.89 (2H, d, J = 13.5 Hz), 2.77 (3H, s), 2.92 (1H, t, J = 9.9 Hz), 3.14 (1H, t, J = 11.4 Hz), 3.68 (1H, d, J = 12.9 Hz), 3.98 (3H, s), 4.00-4.33 (7H, m), 4.52 (1H, t, J = 5.4 Hz), 5.62 (2H, s), 6.99 (1H, d, J = 7.8 Hz), 7.29-7.36 (2H, m), 7.47 (1H, t, J = 7.5 Hz), 7.54 (1H, d, J = 8.1 Hz), 7.99 (1H, d, J = 7.5 Hz), 8.40 (1H, d, J = 6.9 Hz).

[2551]

Example 630

Production of 5-(4-chlorobenzyl)-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2552]



[2553]

In the same manner as in Example 570, 2-[4-({[5-(4-chlorobenzyl)-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-

pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (60 mg) was obtained as a white solid from the compound of Example 672 (200 mg, 0.44 mmol), 4-chlorobenzyl chloride (708 mg, 4.40 mmol) and cesium carbonate (572 g, 1.76 mmol).

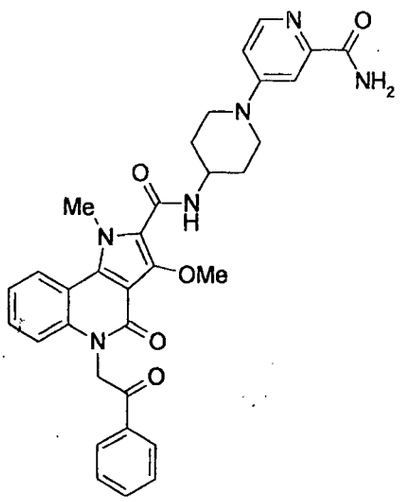
A solution of 2-[4-({[5-(4-chlorobenzyl)-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (60 mg) and potassium carbonate (72 mg, 0.52 mmol) in THF (2 mL)-methanol (1 mL)-water (1 mL) was stirred at room temperature for 3 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (7 mg, 2%) as white crystals.
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40-1.60 (2H, m), 1.90 (2H, d, J = 10.8 Hz), 2.93 (1H, t, J = 12.0 Hz), 3.15 (1H, t, J = 12.0 Hz), 3.68 (1H, d, J = 13.5 Hz), 4.01-4.34 (10H, m), 4.52 (1H, t, J = 5.4 Hz), 5.59 (2H, br s), 7.20-7.49 (7H, m), 7.99 (1H, d, J = 5.4 Hz), 8.35 (1H, d, J = 8.1 Hz).

[2554]

Example 631

Production of N-[1-(2-carbamoylpyridin-4-yl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2555]



[2556]

In the same manner as in Example 623, the title compound (58 mg, 17%) was obtained as a pale-red solid from the compound of Example 77 (300 mg, 0.59 mmol) and 4-bromopyridine-2-carboxamide (119 mg, 0.59 mmol).

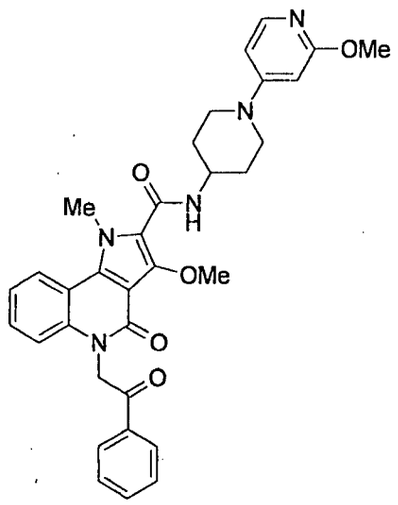
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.52-1.72 (2H, m), 1.88-2.05 (2H, m), 3.07-3.24 (2H, m), 3.86-4.03 (5H, m), 4.07-4.22 (1H, m), 4.31 (3H, s), 5.96 (2H, s), 6.93-7.08 (1H, m), 7.25-7.41 (2H, m), 7.43-7.54 (3H, m), 7.56-7.68 (2H, m), 7.70-7.82 (1H, m), 7.91-8.04 (2H, m), 8.10-8.25 (3H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2557]

Example 632

Production of 3-methoxy-N-[1-(2-methoxypyridin-4-yl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2558]



[2559]

In the same manner as in Example 575, the title compound (51 mg, 15%) was obtained as a white solid from the compound of Example 77 (300 mg, 0.59 mmol) and 4-bromo-2-methoxypyridine (122 mg, 0.65 mmol).

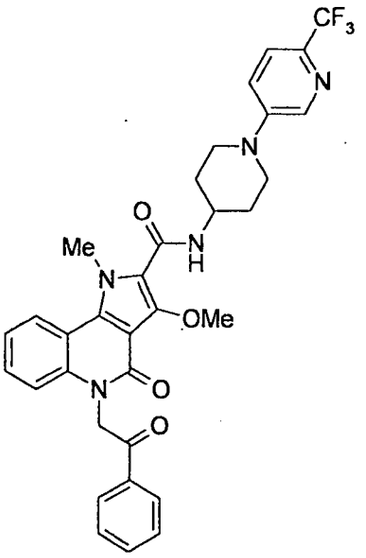
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.49-1.70 (2H, m), 1.85-2.00 (2H, m), 2.98-3.12 (2H, m), 3.73-3.88 (5H, m), 3.95 (3H, s), 4.03-4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.15 (1H, d, J = 2.3 Hz), 6.59 (1H, dd, J = 6.2, 2.3 Hz), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.57-7.68 (2H, m), 7.71-7.84 (2H, m), 7.96 (1H, d, J = 7.9 Hz), 8.09-8.23 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2560]

Example 633

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-{1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-4-yl}-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2561]



[2562]

In the same manner as in Example 623, the title compound (51 mg, 14%) was obtained as a pale-yellow solid from the compound of Example 77 (300 mg, 0.59 mmol) and 5-bromo-2-(trifluoromethyl)pyridine (147 mg, 0.65 mmol).

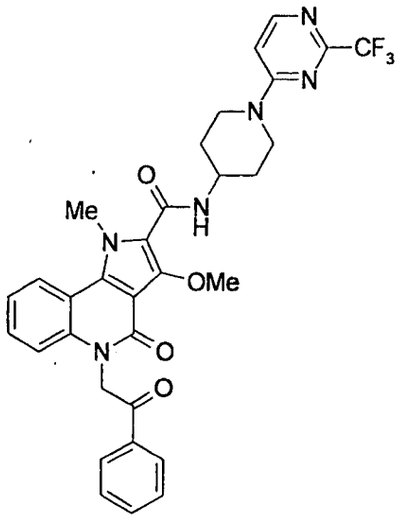
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.59-1.77 (2H, m), 1.91-2.02 (2H, m), 3.07-3.20 (2H, m), 3.86-4.00 (5H, m), 4.05-4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.27-7.41 (2H, m), 7.43-7.52 (2H, m), 7.58-7.67 (3H, m), 7.72-7.80 (1H, m), 7.98 (1H, d, J = 7.9 Hz), 8.13-8.20 (2H, m), 8.37 (1H, dd, J = 8.2, 1.0 Hz), 8.46 (1H, d, J = 2.8 Hz).

[2563]

Example 634

Production of 3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-{1-[2-(trifluoromethyl)pyrimidin-4-yl]piperidin-4-yl}-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2564]



[2565]

In the same manner as in Example 623, the title compound (210 mg, 58%) was obtained as a pale-red solid from the compound of Example 77 (300 mg, 0.59 mmol) and 4-chloro-2-(trifluoromethyl)pyrimidine (129 mg, 0.71 mmol).

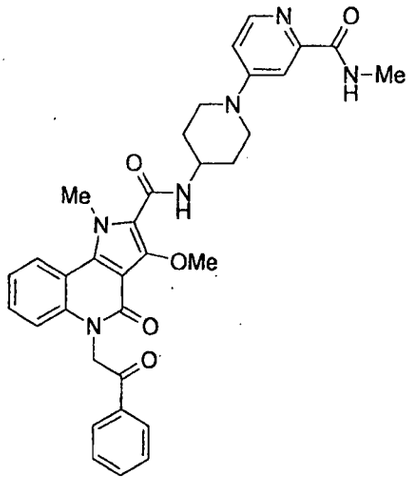
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.48-1.69 (2H, m), 1.91-2.07 (2H, m), 3.17-3.30 (2H, m), 3.96 (3H, s), 4.10-4.52 (6H, m), 5.97 (2H, s), 7.12 (1H, d, J = 6.4 Hz), 7.26-7.41 (2H, m), 7.43-7.52 (1H, m), 7.57-7.68 (2H, m), 7.71-7.81 (1H, m), 7.97 (1H, d, J = 7.9 Hz), 8.11-8.22 (2H, m), 8.27-8.45 (2H, m).

[2566]

Example 635

Production of 3-methoxy-1-methyl-N-{1-[2-(methylcarbamoyl)pyridin-4-yl]piperidin-4-yl}-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2567]



[2568]

To a solution of 4-chloropyridine-2-carboxylic acid (200 mg, 1.3 mmol), methylamine hydrochloride (103 mg, 1.5 mmol), HOBt (205 mg, 1.5 mmol) and triethylamine (0.42 mL, 3.0 mmol) in DMF (3.0 mL) was added WSCD (292 mg, 1.5 mmol) under ice-cooling, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extracts were combined, washed with brine, dried over magnesium sulfate, filtered through aminosilica gel, and the filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (3.0 mL), the compound of Example 77 (300 mg, 0.59 mmol), potassium carbonate (204 mg, 1.5 mmol) and triethylamine (0.082 mL, 0.59 mmol) were added, and the mixture was stirred at 100°C for 16 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with a mixed solvent of ethyl acetate-THF. The extract was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=40/60 - 100/0) and recrystallized from ethyl acetate-hexane to give the title compound (40 mg, 11%) as a pale-yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.52-1.72 (2H, m), 1.90-2.05 (2H, m), 2.79 (3H, d, J = 4.9 Hz), 3.09-3.22 (2H, m), 3.88-4.02 (5H,

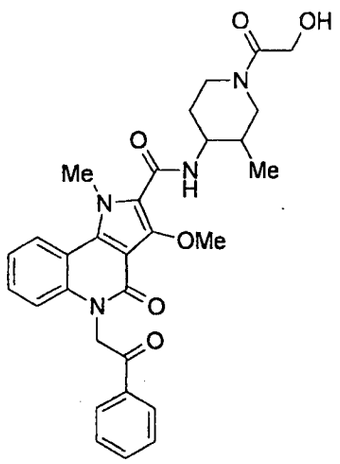
m), 4.07-4.22 (1H, m), 4.31 (3H, s), 5.96 (2H, s), 7.01 (1H, dd, J = 6.0, 2.8 Hz), 7.25-7.41 (2H, m), 7.43-7.52 (2H, m), 7.57-7.68 (2H, m), 7.70-7.81 (1H, m), 7.98 (1H, d, J = 7.9 Hz), 8.11-8.24 (3H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz), 8.53-8.70 (1H, m).

[2569]

Example 636

Production of N-[1-(hydroxyacetyl)-3-methylpiperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2570]



[2571]

In the same manner as in Example 130, the title compound (21 mg, 22%) was obtained as a white solid from the compound of Example 678 (83 mg, 0.17 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.82-1.02 (3H, m), 1.55-2.40 (3H, m), 3.14-3.77 (4H, m), 3.93-4.05 (3H, m), 4.07-4.17 (2H, m), 4.20-4.41 (4H, m), 4.45-4.57 (1H, m), 5.98 (2H, s), 7.25-7.42 (2H, m), 7.43-7.53 (1H, m), 7.58-7.68 (2H, m), 7.71-7.80 (1H, m), 7.85-8.05 (1H, m), 8.10-8.24 (2H, m), 8.38 (1H, dd, J = 8.4, 1.2 Hz).

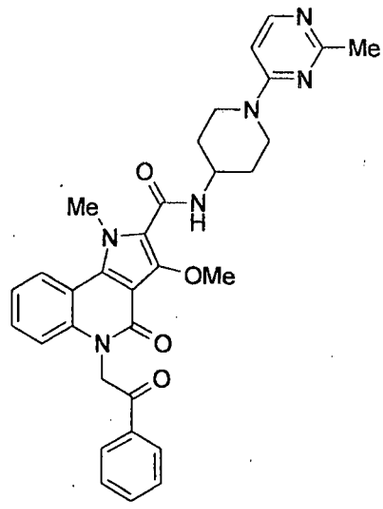
[2572]

Example 637

Production of 3-methoxy-1-methyl-N-[1-(2-methylpyrimidin-4-yl)piperidin-4-yl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-

1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2573]



[2574]

In the same manner as in Example 623, the title compound (130 mg, 59%) was obtained as a pale-brown solid from the compound of Example 77 (200 mg, 0.39 mmol) and 4-chloro-2-methylpyrimidine (61 mg, 0.47 mmol).

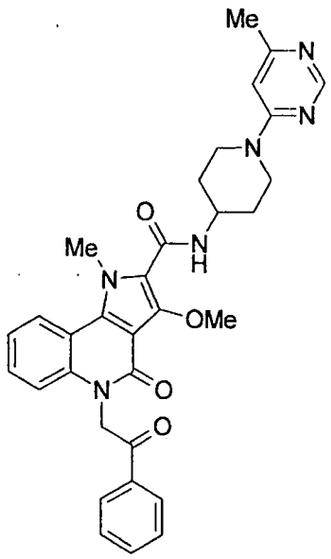
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44-1.62 (2H, m), 1.85-2.01 (2H, m), 2.36 (3H, s), 3.06-3.23 (2H, m), 3.96 (3H, s), 4.06-4.23 (1H, m), 4.24-4.41 (5H, m), 5.97 (2H, s), 6.68 (1H, d, J = 6.4 Hz), 7.25-7.42 (2H, m), 7.43-7.53 (1H, m), 7.57-7.69 (2H, m), 7.71-7.82 (1H, m), 7.96 (1H, d, J = 7.9 Hz), 8.08 (1H, d, J = 6.2 Hz), 8.13-8.22 (2H, m), 8.37 (1H, d, J = 7.6 Hz).

[2575]

Example 638

Production of 3-methoxy-1-methyl-N-[1-(6-methylpyrimidin-4-yl)piperidin-4-yl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2576]



[2577]

In the same manner as in Example 623, the title compound (137 mg, 62%) was obtained as a pale-brown solid from the compound of Example 77 (200 mg, 0.39 mmol) and 4-chloro-6-methylpyrimidine (61 mg, 0.47 mmol).

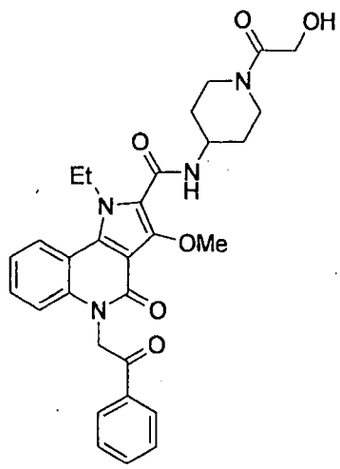
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.44-1.64 (2H, m), 1.85-2.01 (2H, m), 2.26 (3H, s), 3.05-3.23 (2H, m), 3.95 (3H, s), 4.07-4.23 (1H, m), 4.24-4.39 (5H, m), 5.97 (2H, s), 6.77 (1H, s), 7.25-7.42 (2H, m), 7.43-7.53 (1H, m), 7.57-7.69 (2H, m), 7.70-7.82 (1H, m), 7.96 (1H, d, J = 7.9 Hz), 8.11-8.23 (2H, m), 8.32-8.45 (2H, m).

[2578]

Example 639

Production of 1-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2579]



[2580]

In the same manner as in Example 140, the title compound (42 mg, 22%) was obtained as a white solid from the compound of Reference Example 120 (140 mg, 0.35 mmol) and 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (81 mg, 0.42 mmol).

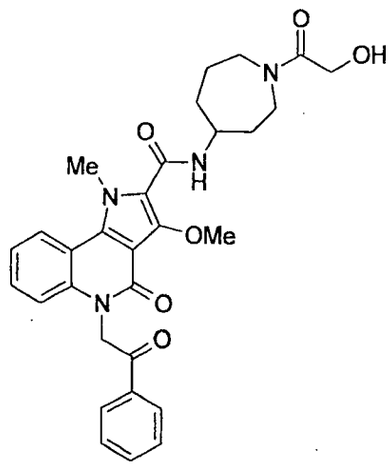
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.39-1.61 (5H, m), 1.82-1.98 (2H, m), 2.84-3.01 (1H, m), 3.06-3.21 (1H, m), 3.59-3.74 (1H, m), 3.96 (3H, s), 4.03-4.14 (3H, m), 4.16-4.28 (1H, m), 4.51 (1H, t, J = 5.4 Hz), 4.82 (2H, q, J = 7.1 Hz), 5.98 (2H, s), 7.30-7.42 (2H, m), 7.43-7.52 (1H, m), 7.59-7.68 (2H, m), 7.71-7.81 (1H, m), 8.03 (1H, d, J = 7.7 Hz), 8.12-8.25 (3H, m).

[2581]

Example 640

Production of N-[1-(hydroxyacetyl)azepan-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2582]



[2583]

A mixed solution of the compound of Reference Example 123 (220 mg, 0.70 mmol) and 8N aqueous sodium hydroxide solution (0.36 mL) in ethanol (3.0 mL)-water (3.0 mL) was stirred for 30 min under ice-cooling. The reaction mixture was neutralized with 1N hydrochloric acid, stirred for 10 min under ice-cooling and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2.0 mL), and 4N hydrogen chloride ethyl acetate solution (2.0 mL) was added. The mixture was stirred at room temperature for 2 hr, and concentrated under reduced pressure. To a solution of the residue, the compound of Reference Example 28 (200 mg, 0.51 mmol), HOBt (90 mg, 0.67 mol) and triethylamine (0.22 mL, 1.6 mmol) in DMF (5.0 mL) was added WSCD (128 mg, 0.67 mmol) under ice-cooling, and the mixture was stirred at room temperature for 62 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=80/20 - 100/0) and recrystallized from THF-diethyl ether to give the title compound (122 mg, 44%) as a white solid.

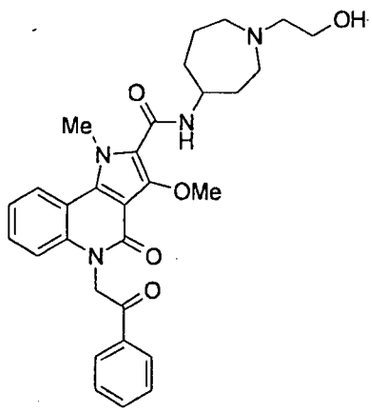
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-1.92 (5H, m), 1.93-2.11 (1H, m), 3.25-3.45 (2H, m), 3.47-3.55 (1H, m), 3.63-3.80 (1H, m), 3.92-4.06 (4H, m), 4.07-4.18 (2H, m), 4.25-4.36 (3H, m), 4.43 (1H, t, J = 4.7 Hz), 5.97 (2H, s), 7.24-7.42 (2H, m), 7.43-7.52 (1H, m), 7.58-7.67 (2H, m), 7.71-7.81 (1H, m), 7.94 (1H, d, J = 8.1 Hz), 8.12-8.22 (2H, m), 8.37 (1 H, d, J = 7.9 Hz).

[2584]

Example 641

Production of N-[1-(2-hydroxyethyl)azepan-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2585]



[2586]

A solution of the compound of Reference Example 122 (157 mg, 0.73 mmol) and potassium carbonate (607 mg, 4.4 mmol) in DMF (6.0 mL) was stirred at 100°C for 5 min, 2-bromoethanol (0.16 mL, 2.2 mmol) was added to the reaction mixture, and the mixture was stirred at 100°C for 1 hr. The reaction mixture was diluted with water, brine was added, and the mixture was extracted 4 times with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; methanol/ethyl acetate=0/100 - 5/95). The residue was dissolved in ethyl acetate (2.0 mL), and 4N hydrogen chloride ethyl acetate solution (2.0 mL) was added. The reaction mixture was stirred at room temperature for 30

min, and concentrated under reduced pressure. To a solution of the residue, the compound of Reference Example 28 (200 mg, 0.51 mmol) and triethylamine (0.27 mL, 1.9 mmol)* in DMF (5.0 mL) was added DMT-MM (167 mg, 0.61 mmol) under ice-cooling, and the mixture was stirred at room temperature for 62 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution and water, and extracted twice with ethyl acetate. The extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=50/50 - 100/0) and recrystallized from ethanol-hexane to give the title compound (75 mg, 28%) as a pale-yellow solid.

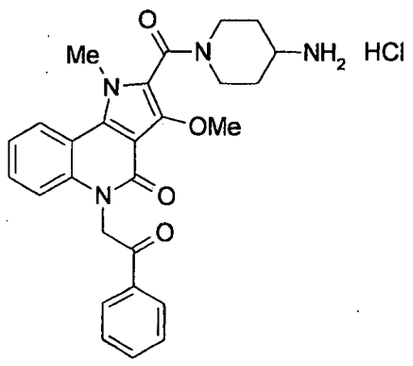
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.49-2.01 (6H, m), 2.53-2.84 (6H, m), 3.44-3.56 (2H, m), 3.90-4.03 (3H, m), 4.14-4.41 (5H, m), 5.97 (2H, s), 7.25-7.42 (2H, m), 7.43-7.53 (1 H, m), 7.57-7.69 (2H, m), 7.71-7.82 (1H, m), 8.04 (1H, d, J = 8.3 Hz), 8.11-8.23 (2H, m), 8.37 (1H, dd, J = 8.3, 1.1 Hz).

[2587]

Example 642

Production of 2-[(4-aminopiperidin-1-yl)carbonyl]-3-methoxy-1-methyl-5-(2-oxo-2-phenylethyl)-1,5-dihydro-4H-pyrrolo[3,2-c]quinoline-4-one hydrochloride

[2588]



[2589]

In the same manner as in Example 542, the title compound (119 mg, 79%) was obtained as a white solid from the compound

of Example 679 (170 mg, 0.30 mmol).

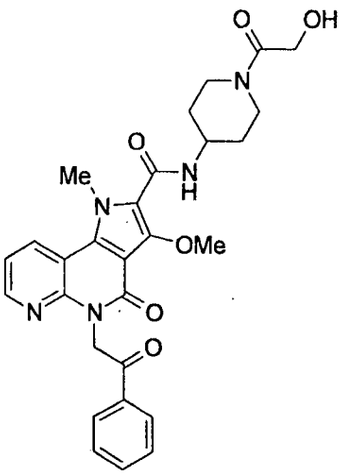
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.36-1.73 (2H, m), 1.84-2.15 (2H, m), 2.83-3.04 (1H, m), 3.08-3.30 (2H, m), 3.77-3.95 (4H, m), 4.00 (3H, s), 4.45-4.68 (1H, m), 5.98 (2H, s), 7.24-7.52 (3H, m), 7.58-7.70 (2H, m), 7.71-7.81 (1H, m), 8.00 (3H, br s), 8.13-8.23 (2H, m), 8.33 (1H, dd, J = 8.2, 1.0 Hz).

[2590]

Example 643

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,8]naphthyridine-2-carboxamide

[2591]



[2592]

In the same manner as in Example 141, the title compound (141 mg, 69%) was obtained as a white solid from the compound of Reference Example 131 (150 mg, 0.38 mmol).

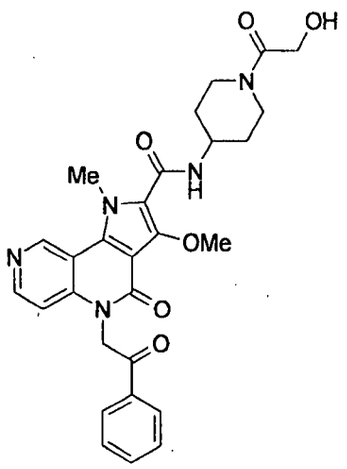
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.32-1.65 (2H, m), 1.81-1.97 (2H, m), 2.81-3.01 (1H, m), 3.04-3.22 (1H, m), 3.63-3.74 (1H, m), 3.98 (3H, s), 4.04-4.16 (3H, m), 4.17-4.28 (1H, m), 4.32 (3H, s), 4.51 (1H, t, J = 5.4 Hz), 5.99 (2H, s), 7.35 (1H, dd, J = 8.1, 4.7 Hz), 7.54-7.68 (2H, m), 7.69-7.80 (1H, m), 8.00 (1H, d, J = 7.9 Hz), 8.08-8.22 (2H, m), 8.44 (1H, dd, J = 4.7, 1.5 Hz), 8.73 (1H, dd, J = 8.3, 1.5 Hz).

[2593]

Example 644

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxamide

[2594]



[2595]

In the same manner as in Example 141, the title compound (97 mg, 48%) was obtained as a white solid from the compound of Reference Example 139 (150 mg, 0.38 mmol).

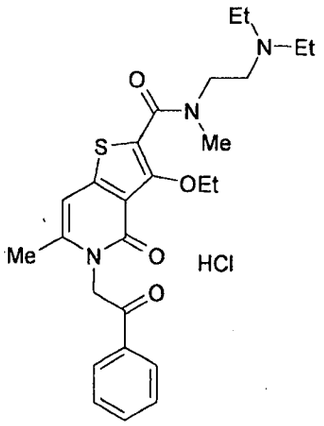
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.34-1.63 (2H, m), 1.79-1.97 (2H, m), 2.83-3.01 (1H, m), 3.05-3.22 (1H, m), 3.59-3.74 (1H, m), 3.95 (3H, s), 4.01-4.17 (3H, m), 4.17-4.28 (1H, m), 4.35 (3H, s), 4.50 (1H, t, J = 5.4 Hz), 5.95 (2H, s), 7.42 (1H, d, J = 6.2 Hz), 7.57-7.69 (2H, m), 7.71-7.82 (1H, m), 7.99 (1H, d, J = 7.7 Hz), 8.10-8.22 (2H, m), 8.48 (1H, d, J = 6.0 Hz), 9.51 (1H, s).

[2596]

Example 645

Production of N-[2-(diethylamino)ethyl]-3-ethoxy-N,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide hydrochloride

[2597]



[2598]

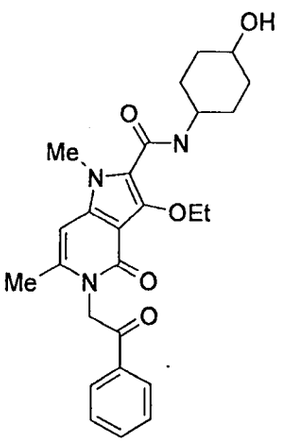
To a solution of the compound of Example 146 (150 mg, 0.310 mmol) in ethyl acetate (20 mL) was added 4N hydrogen chloride ethyl acetate solution (93.0 μL, 0.372 mmol). The mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL) and ethanol (5 mL). Hexane (10 mL) was added, and the mixture was stirred at room temperature for 15 hr. The precipitated solid was collected by filtration, and washed with ethyl acetate to give the title compound (90.0 mg, 56%) as a white solid.
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.10-1.35 (9H, m), 2.30 (3H, s), 3.08 (3H, s), 3.00-3.40 (6H, m), 3.79 (2H, t, J = 7.2 Hz), 4.08 (2H, q, J = 7.0 Hz), 5.67 (2H, s), 6.84 (1H, d, J = 0.6 Hz), 7.62 (2H, t, J = 7.5 Hz), 7.72-7.78 (1H, m), 8.10-8.13 (2H, m), 10.03 (1H, s).

[2599]

Example 646

Production of 3-ethoxy-N-(4-hydroxycyclohexyl)-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2600]



[2601]

In the same manner as in Example 25, the title compound (106 mg, 60%) was obtained as a white powder from the compound of Reference Example 44 (140 mg, 0.380 mmol) and 4-aminocyclohexanol (53 mg, 0.456 mmol).

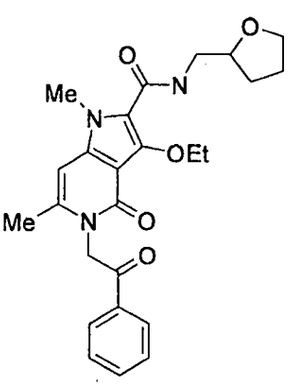
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19-1.35 (7H, m), 1.86 (4H, d, J = 12.8 Hz), 2.27 (3H, s), 3.45 (1H, br s), 3.71 (1H, br s), 3.86 (3H, s), 4.33 (2H, q, J = 6.9 Hz), 4.56 (1H, d, J = 4.3 Hz), 5.61 (2H, s), 6.57 (1H, s), 7.48-7.67 (3H, m), 7.72 (1H, d, J = 7.2 Hz), 8.10 (2H, d, J = 7.4 Hz).

[2602]

Example 647

Production of 3-ethoxy-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydrofuran-2-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2603]



[2604]

In the same manner as in Example 25, the title compound

(114 mg, 66%) was obtained as a white powder from the compound of Reference Example 35 (140 mg, 0.380 mmol) and 2-tetrahydrofurfurylamine (47 µl, 0.456 mmol).

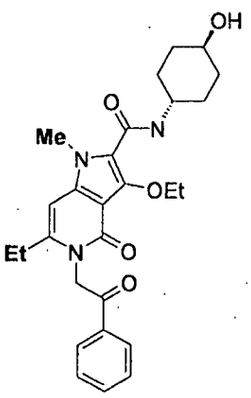
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.29 (3H, t, J = 6.8 Hz), 1.48-1.62 (1H, m), 1.78-1.99 (3H, m), 2.28 (3H, s), 3.41-3.52 (1H, m), 3.60-3.71 (1H, m), 3.75-3.84 (1H, m), 3.89 (3H, s), 3.91-4.02 (2 H, m), 4.35 (2H, t, J = 7.0 Hz), 5.61 (2H, s), 6.59 (1H, s), 7.61 (2H, t, J = 7.4 Hz), 7.73 (1H, m), 7.88 (1H, br s), 8.11 (2H, d, J = 7.6 Hz).

[2605]

Example 648

Production of 3-ethoxy-6-ethyl-N-(trans-4-hydroxycyclohexyl)-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2606]



[2607]

In the same manner as in Example 25, the title compound (76 mg, 79%) was obtained as a white powder from the compound of Reference Example 42 (77 mg, 0.20 mmol) and trans-4-aminocyclohexanol (28 mg, 0.24 mmol).

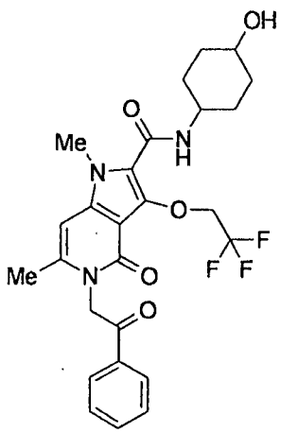
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.4 Hz), 1.22-1.36 (7H, m), 1.75-1.96 (4H, m), 2.57 (2H, q, J = 7.3 Hz), 3.44 (1H, br s), 3.71 (1H, br s), 3.89 (3H, s), 4.32 (2H, q, J = 7.1 Hz), 4.57 (1H, d, J = 4.2 Hz), 5.58 (2H, s), 6.48 (1H, s), 7.51-7.66 (3H, m), 7.67-7.78 (1H, m), 8.11 (2H, d, J = 7.2 Hz).

[2608]

Example 649

Production of N-[1-(hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c][1,6]naphthyridine-2-carboxamide

[2609]



[2610]

In the same manner as in Example 140, the title compound (132 mg, 54%) was obtained as white crystals from the compound of Reference Example 50 (200 mg, 0.47 mmol) and 4-aminocyclohexanol (82 mg, 0.71 mmol).

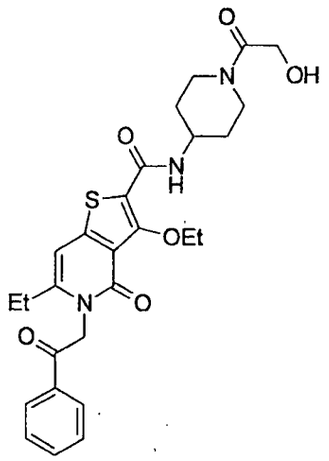
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25 (4H, t, J = 9.6 Hz), 1.80-1.90 (4H, m), 2.29 (3H, s), 3.30-3.45 (1H, br), 3.60-3.80 (1H, br), 3.83 (3H, s), 4.57 (1H, t, J = 4.5 Hz), 5.06 (2H, q, J = 9.3 Hz), 5.65 (2H, s), 6.64 (1H, s), 7.31 (1H, d, J = 7.8 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.74 (1H, t, J = 7.5 Hz), 8.09-8.12 (2H, m).

[2611]

Example 650

Production of 3-ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide

[2612]



[2613]

In the same manner as in Reference Example 7, 3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid (700 mg, 83%) was obtained as a purple powder from the compound of Reference Example 170 (900 mg, 2.25 mmol). tert-Butyl 4-({[3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridin-2-yl]carbonyl}amino)piperidine-1-carboxylate (125 mg, 15%) was obtained as a white powder from the thus-obtained 3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridine-2-carboxylic acid (550 mg, 1.4 mmol) and 4-amino-1-Boc-piperidine (361 mg, 1.8 mmol). 3-Ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (94 mg, 85%) was obtained as a white powder from the thus-obtained tert-butyl 4-({[3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridin-2-yl]carbonyl}amino)piperidine-1-carboxylate (125 mg, 0.22 mmol) by a method similar to that in Example 126. 2-[4-({[3-Ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (80 mg, 78%) was obtained as a white solid from the thus-obtained 3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]pyridine-2-carboxamide (90 mg, 0.18 mmol) by a method similar to that in Example 127.

A mixed solution of 2-[4-({[3-ethoxy-6-ethyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]pyridin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate (90 mg, 0.18 mmol) and potassium carbonate (39 mg, 0.28 mmol) in THF (8 mL)-methanol (2 mL)-water (2 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate-hexane to give the title compound (64 mg, 69%) as white crystals.

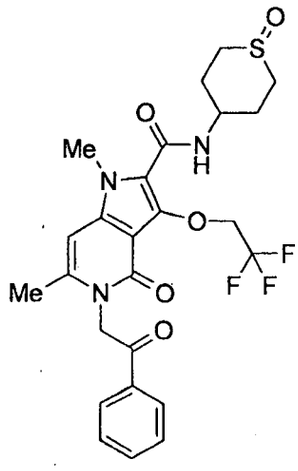
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.4 Hz), 1.30 (3H, t, J = 7.1 Hz), 1.35-1.60 (2H, m), 1.90 (2H, d, J = 9.9 Hz), 2.60 (2H, q, J = 7.4 Hz), 2.84 (1H, t, J = 12.0 Hz), 3.10 (1H, t, J = 14.0 Hz), 3.66 (1H, d, J = 13.5 Hz), 4.00-4.09 (3H, m), 4.28 (3H, q, J = 7.1 Hz), 4.50 (1H, t, J = 5.4 Hz), 5.66 (2H, s), 6.84 (1H, s), 7.60-7.68 (2H, m), 7.75 (1H, t, J = 7.5 Hz), 8.10-8.13 (2H, m).

[2614]

Example 651

Production of 1,6-dimethyl-N-(1-oxidotetrahydro-2H-thiopyran-4-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2615]



[2616]

In the same manner as in Example 571, 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydro-2H-thiopyran-4-yl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide (150 mg) was obtained as a white solid from the compound of Reference Example 50 (200 mg, 0.47 mmol). The title compound (131 mg, 51%) was obtained as white crystals from the thus-obtained 1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-(tetrahydro-2H-thiopyran-4-yl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide (150 mg) by a method similar to that in Example 571.

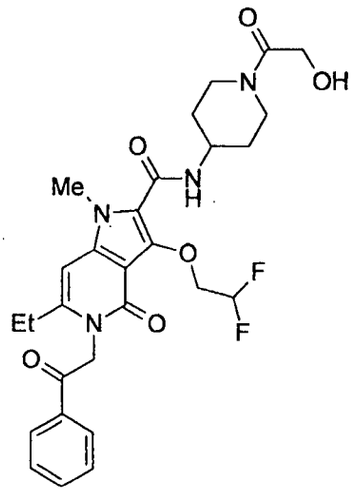
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.60-1.75 (1H, m), 1.83 (1H, d, J = 10.2 Hz), 2.06-2.29 (5H, m), 2.70-2.85 (2H, m), 2.93 (1H, d, J = 12.9 Hz), 3.81 (3H, d, J = 6.3 Hz), 3.90-4.10 (1H, m), 5.00-5.13 (2H, m), 5.65 (2H, s), 6.64 (1H, s), 7.61 (3H, t, J = 7.8 Hz), 7.74 (1H, t, J = 7.2 Hz), 8.10-8.12 (2H, m).

[2617]

Example 652

Production of 3-(2,2-difluoroethoxy)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2618]



[2619]

In the same manner as in Example 140, the title compound (340 mg, 84%) was obtained as a white amorphous solid from the compound of Reference Example 171 (300 mg, 0.72 mmol).

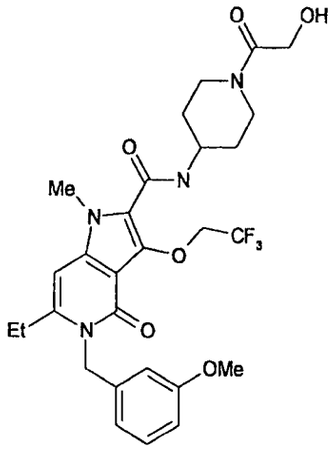
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.4 Hz), 1.20-1.50 (2H, m), 1.90 (2H, d, J = 9.9 Hz), 2.59 (2H, q, J = 7.4 Hz), 2.83 (1H, t, J = 12.2 Hz), 3.09 (1H, t, J = 11.7 Hz), 3.68 (1H, d, J = 12.9 Hz), 3.90 (3H, s), 3.95-4.20 (3H, m), 4.26 (1H, d, J = 11.7 Hz), 4.51 (1H, t, J = 5.4 Hz), 4.67 (2H, td, J = 16.1, 3.0 Hz), 5.23 (1H, s), 5.61 (2H, s), 6.33 (1H, tt, J = 54.2, 3.0 Hz), 7.49 (1H, d, J = 7.8 Hz), 7.61 (2H, t, J = 7.5 Hz), 7.73 (1H, t, J = 7.5 Hz), 8.10-8.12 (2H, m).

[2620]

Example 653

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(3-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2621]



[2622]

A mixture of the compound of Reference Example 143 (200 mg, 0.456 mmol), 2-(4-aminopiperidin-1-yl)-2-oxoethanol hydrochloride (115 mg, 0.593 mmol), HOBt (92.4 mg, 0.684 mmol), WSCD (131 mg, 0.684 mmol), triethylamine (0.126 mL, 0.912 mmol) and DMF (4.0 mL) was stirred at room temperature for 16 hr. The reaction mixture was diluted with water, and extracted twice with ethyl acetate. The extract was combined, washed

with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate). Recrystallization of the obtained solid from ethyl acetate gave the title compound (162 mg, 61%) as a white powder.

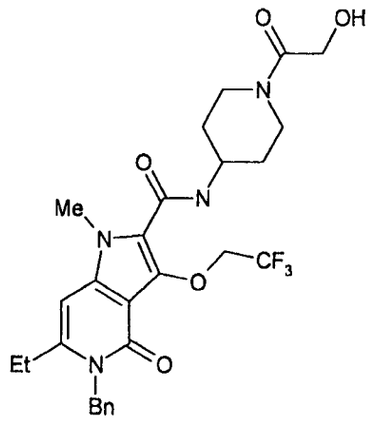
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 1.24-1.50 (2H, m), 1.81-1.95 (2H, m), 2.60 (2H, q, J = 7.3 Hz), 2.76-2.91 (1H, m), 3.01-3.18 (1H, m), 3.64-3.74 (4H, m), 3.84 (3H, s), 3.95-4.14 (3H, m), 4.20-4.33 (1H, m), 4.52 (1H, t, J = 5.4 Hz), 5.11 (2H, q, J = 9.3 Hz), 5.32 (2H, br s), 6.49-6.64 (3H, m), 6.81 (1H, dd, J = 8.0, 2.2 Hz), 7.22 (1H, t, J = 8.0 Hz), 7.53 (1H, d, J = 7.6 Hz).

[2623]

Example 654

Production of 5-benzyl-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2624]



[2625]

In the same manner as in Example 653, the title compound (182 mg, 75%) was obtained as a white powder from the compound of Reference Example 145 (180 mg, 0.441 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.2 Hz), 1.25-1.48 (2 H, m), 1.83-1.95 (2H, m), 2.60 (2H, q, J = 7.2 Hz), 2.77-2.90 (1H, m), 3.02-3.17 (1H, m), 3.63-3.75 (1H, m), 3.84 (3H, s), 3.96-4.14 (3H, m), 4.20-4.33 (1H, m), 4.52 (1H, t, J = 5.5

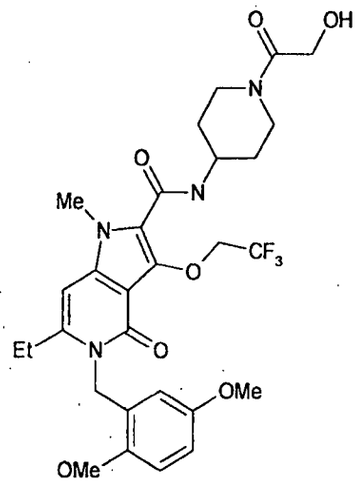
Hz), 5.10 (2H, q, J = 9.4 Hz), 5.36 (2H, br s), 6.52 (1H, s), 7.00-7.09 (2H, m), 7.19-7.36 (3H, m), 7.53 (1H, d, J = 7.7 Hz).

[2626]

Example 655

Production of 5-(2,5-dimethoxybenzyl)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2627]



[2628]

In the same manner as in Example 653, the title compound (86.0 mg, 80%) was obtained as a white powder from the compound of Reference Example 147 (82.7 mg, 0.177 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.3 Hz), 1.24-1.48 (2H, m), 1.84-1.93 (2H, m), 2.52-2.61 (2H, m), 2.77-2.90 (1H, m), 3.03-3.16 (1H, m), 3.55 (3H, s), 3.64-3.74 (1H, m), 3.83 (3H, s), 3.86 (3H, s), 3.97-4.14 (3H, m), 4.20-4.32 (1H, m), 4.52 (1H, t, J = 5.3 Hz), 5.08 (2H, q, J = 9.2 Hz), 5.21 (2H, br s), 5.89 (1H, d, J = 3.0 Hz), 6.56 (1H, s), 6.79 (1H, dd, J = 8.9, 3.0 Hz), 6.97 (1H, d, J = 8.9 Hz), 7.53 (1H, d, J = 7.9 Hz).

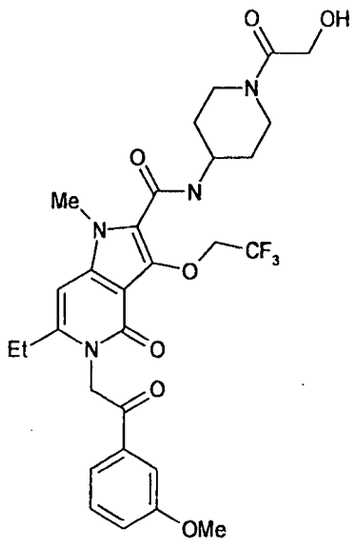
[2629]

Example 656

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-[2-(3-methoxyphenyl)-2-oxoethyl]-1-methyl-4-oxo-3-(2,2,2-

trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2630]



[2631]

In the same manner as in Example 653, the title compound (65.1 mg, 29%) was obtained as a white powder from the compound of Reference Example 151 (170 mg, 0.364 mmol).

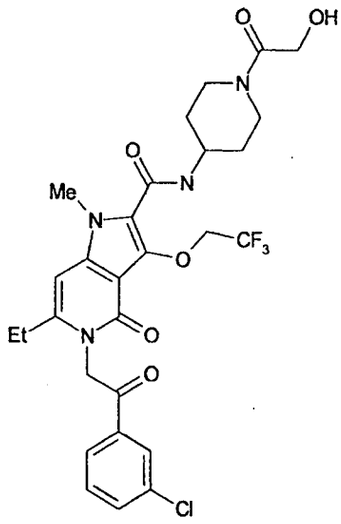
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 1.25-1.48 (2H, m), 1.82-1.95 (2H, m), 2.54-2.64 (2H, m), 2.76-2.90 (1H, m), 3.01-3.15 (1H, m), 3.62-3.74 (1H, m), 3.82-3.90 (6H, m), 3.95-4.13 (3H, m), 4.20-4.35 (1H, m), 4.52 (1H, t, J = 5.5 Hz), 5.05 (2H, q, J = 9.3 Hz), 5.62 (2H, s), 6.54 (1H, s), 7.26-7.35 (1H, m), 7.46-7.62 (3H, m), 7.69-7.76 (1H, m).

[2632]

Example 657

Production of 5-[2-(3-chlorophenyl)-2-oxoethyl]-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2633]



[2634]

In the same manner as in Example 653, the title compound (160 mg, 64%) was obtained as a white powder from the compound of Reference Example 155 (192 mg, 0.408 mmol).

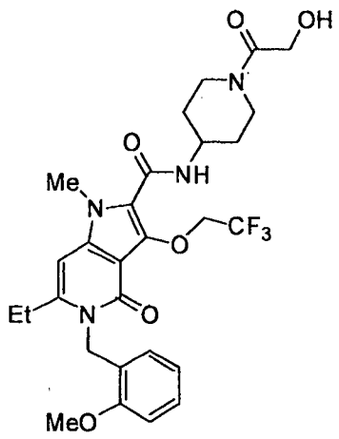
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.3 Hz), 1.25-1.49 (2H, m), 1.82-1.95 (2H, m), 2.60 (2H, q, J = 7.3 Hz), 2.76-2.90 (1H, m), 3.01-3.17 (1H, m), 3.62-3.74 (1H, m), 3.86 (3H, s), 3.96-4.15 (3H, m), 4.20-4.32 (1H, m), 4.52 (1H, t, J = 5.4 Hz), 5.05 (2H, q, J = 9.2 Hz), 5.62 (2H, s), 6.55 (1H, s), 7.50 (1H, d, J = 7.6 Hz), 7.61-7.69 (1H, m), 7.77-7.84 (1H, m), 8.03-8.09 (1H, m), 8.14 (1H, t, J = 1.8 Hz).

[2635]

Example 658

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(2-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2636]



[2637]

In the same manner as in Example 653, the title compound (120 mg, 86%) was obtained as a white powder from the compound of Reference Example 157 (104 mg, 0.237 mmol).

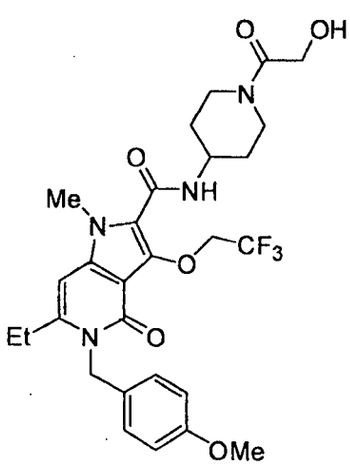
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.4 Hz), 1.26-1.49 (2H, m), 1.81-1.95 (2H, m), 2.52-2.61 (2H, m), 2.77-2.91 (1H, m), 3.00-3.19 (1H, m), 3.56-3.77 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 3.97-4.14 (3H, m), 4.19-4.33 (1H, m), 4.52 (1H, t, J = 5.4 Hz), 5.08 (2H, q, J = 9.2 Hz), 5.23 (2H, br s), 6.32-6.40 (1H, m), 6.56 (1H, s), 6.76-6.85 (1H, m), 7.01-7.09 (1H, m), 7.17-7.28 (1H, m), 7.52 (1H, d, J = 7.6 Hz).

[2638]

Example 659

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-5-(4-methoxybenzyl)-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2639]



[2640]

In the same manner as in Example 653, the title compound (147 mg, 71%) was obtained as a white powder from the compound of Reference Example 159 (157 mg, 0.358 mmol).

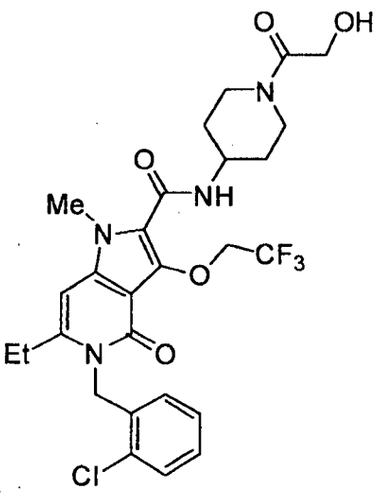
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.3 Hz), 1.24-1.48 (2H, m), 1.83-1.96 (2H, m), 2.62 (2H, q, J = 7.3 Hz), 2.76-2.91 (1H, m), 3.02-3.17 (1H, m), 3.63-3.76 (4H, m), 3.83 (3H, s), 3.95-4.14 (3H, m), 4.20-4.33 (1H, m), 4.52 (1H, t, J = 5.4 Hz), 5.11 (2H, q, J = 9.4 Hz), 5.28 (2H, br s), 6.50 (1H, s), 6.83-6.90 (2H, m), 6.96-7.05 (2H, m), 7.52 (1H, d, J = 7.7 Hz).

[2641]

Example 660

Production of 5-(2-chlorobenzyl)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2642]



[2643]

In the same manner as in Example 653, the title compound (119 mg, 66%) was obtained as a white powder from the compound of Reference Example 161 (138 mg, 0.312 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.18 (3H, t, J = 7.3 Hz), 1.26-1.47 (2H, m), 1.82-1.94 (2H, m), 2.53-2.61 (2H, m), 2.76-2.90 (1H, m), 3.02-3.17 (1H, m), 3.61-3.76 (1H, m), 3.86 (3H, s), 3.95-4.14 (3H, m), 4.19-4.33 (1H, m), 4.46-4.56 (1H, m), 5.06 (2H,

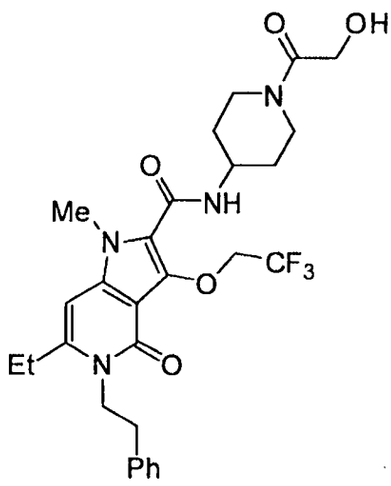
q, J = 9.4 Hz), 5.33 (2H, s), 6.45-6.55 (1H, m), 6.60 (1H, s), 7.21-7.32 (2H, m), 7.45-7.60 (2H, m).

[2644]

Example 661

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2645]



[2646]

In the same manner as in Example 653, the title compound (123 mg, 65%) was obtained as a white powder from the compound of Reference Example 165 (143 mg, 0.339 mmol).

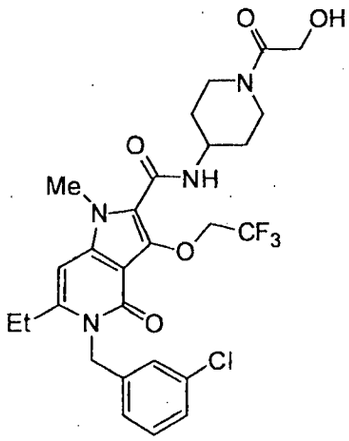
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.21 (3H, t, J = 7.2 Hz), 1.25-1.49 (2H, m), 1.82-1.94 (2H, m), 2.66 (2H, q, J = 7.2 Hz), 2.77-2.95 (3H, m), 3.02-3.17 (1H, m), 3.62-3.75 (1H, m), 3.82 (3H, s), 3.95-4.35 (6H, m), 4.52 (1H, t, J = 5.5 Hz), 5.12 (2H, q, J = 9.4 Hz), 6.44 (1H, s), 7.16-7.35 (5H, m), 7.49 (1H, d, J = 7.6 Hz).

[2647]

Example 662

Production of 5-(3-chlorobenzyl)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2648]



[2649]

In the same manner as in Example 653, the title compound (261 mg, 71%) was obtained as a white powder from the compound of Reference Example 167 (281 mg, 0.635 mmol).

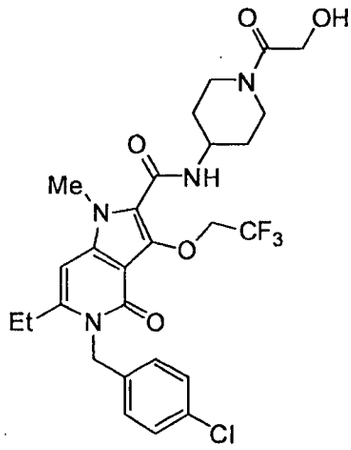
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.17 (3H, t, J = 7.2 Hz), 1.23-1.50 (2H, m), 1.81-1.95 (2H, m), 2.60 (2H, q, J = 7.2 Hz), 2.76-2.92 (1H, m), 3.02-3.17 (1H, m), 3.64-3.76 (1H, m), 3.85 (3H, s), 3.95-4.15 (3H, m), 4.19-4.36 (1H, m), 4.52 (1H, t, J = 5.4 Hz), 5.09 (2H, q, J = 9.4 Hz), 5.35 (2H, br s), 6. 55 (1H, s), 6.95-7.03 (1H, m), 7.07-7.15 (1H, m), 7.25-7.40 (2H, m), 7.55 (1H, d, J = 7.6 Hz).

[2650]

Example 663

Production of 5-(4-chlorobenzyl)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2651]



[2652]

In the same manner as in Example 653, the title compound (160 mg, 65%) was obtained as a white powder from the compound of Reference Example 169 (188 mg, 0.425 mmol).

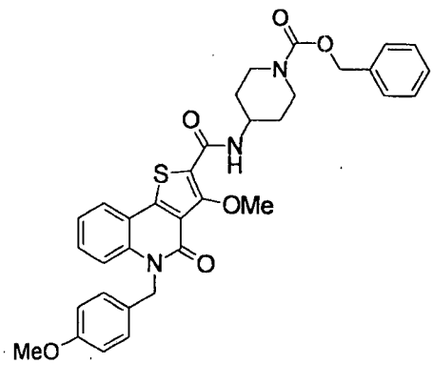
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.16 (3H, t, J = 7.2 Hz), 1.23-1.49 (2H, m), 1.82-1.95 (2H, m), 2.59 (2H, q, J = 7.2 Hz), 2.77-2.90 (1H, m), 3.00-3.17 (1H, m), 3.62-3.76 (1H, m), 3.84 (3H, s), 3.95-4.14 (3H, m), 4.21-4.34 (1H, m), 4.52 (1H, t, J = 5.5 Hz), 5.09 (2H, q, J = 9.4 Hz), 5.33 (2H, br s), 6. 53 (1H, s), 7.03-7.12 (2H, m), 7.34-7.42 (2H, m), 7.53 (1H, d, J = 7.6 Hz).

[2653]

Example 664

Production of Benzyl 4-({[3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[2654]



[2655]

In the same manner as in Example 25, the title compound

(3.07 g, 79%) was obtained as a white powder from the compound of Reference Example 13 (2.5 g, 6.31 mmol) and benzyl 4-aminopiperidine-1-carboxylate hydrochloride (2.56 g, 9.46 mmol).

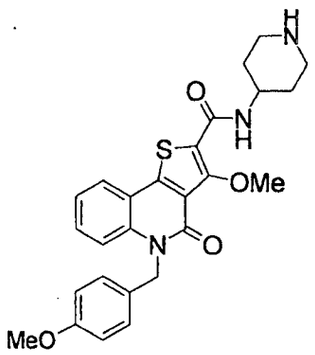
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.15-1.64 (2H, m), 1.87 (2H, br d, J = 9.6 Hz), 2.90-3.10 (2H, br), 3.69 (3H, s), 4.00 (2H, d, J = 11.4 Hz), 4.09 (4H, s), 5.10 (2H, s), 5.53 (2H, br s), 6.87 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.28-7.40 (6H, m), 7.49-7.56 (2H, m), 7.80 (1H, d, J = 8.1 Hz), 8.00 (1H, d, J = 8.4 Hz).

[2656]

Example 665

Production of 3-methoxy-5-(4-methoxybenzyl)-4-oxo-N-piperidin-4-yl-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2657]



[2658]

A mixture of the compound of Example 664 (300 mg, 0.49 mmol), 10% Pd-C (60 mg) and THF (20 mL)-methanol (10 mL) was stirred at room temperature for 24 hr under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated and recrystallized from methanol-diethyl ether to give the title compound (154 mg, 66%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.48 (2H, q, J = 11.0 Hz), 1.82 (2H, d, J = 9.6 Hz), 1.95-2.15 (1H, br), 2.56 (2H, t, J = 8.4 Hz), 2.93 (2H, d, J = 12.6 Hz), 3.33 (3H, s), 3.70 (3H, s), 3.80-4.00 (1H, br), 4.10 (3H, s), 5.53 (2H, br s), 6.86 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.4 Hz), 7.30 (1H, t, J = 7.1 Hz),

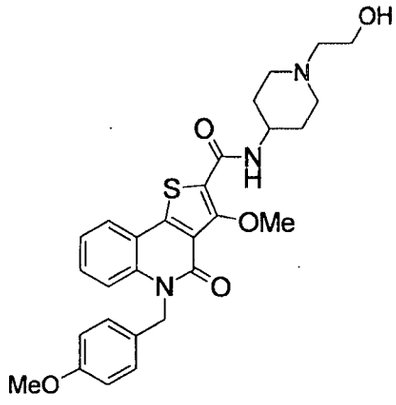
7.49-7.58 (2H, m), 7.72 (1H, d, J = 8.1 Hz), 8.00 (1H, d, J = 7.8 Hz).

[2659]

Example 666

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-5-(4-methoxybenzyl)-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2660]



[2661]

In the same manner as in Example 79, the title compound (110 mg, 68%) was obtained as a white solid from the compound of Example 665 (150 mg, 0.31 mmol).

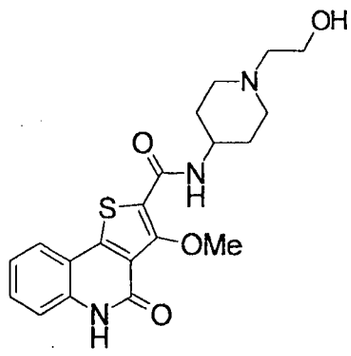
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.55-1.74 (2H, m), 2.00-2.11 (2H, m), 2.36 (2H, t, J = 11.6 Hz), 2.58 (2H, t, J = 5.4 Hz), 2.84 (3H, br s), 3.65 (2H, t, J = 5.4 Hz), 3.75 (3H, s), 4.05-4.20 (1H, br), 4.20 (3H, s), 5.53 (2H, br s), 6.83 (2H, dd, J = 6.9, 1.8 Hz), 7.17-7.26 (3H, m), 7.35 (1H, d, J = 8.1 Hz), 7.41-7.46 (1H, m), 7.64 (1H, d, J = 7.8 Hz), 7.85 (1H, dd, J = 7.8, 1.5 Hz).

[2662]

Example 667

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-4-oxo-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide

[2663]



[2664]

A solution of the compound of Example 666 (110 mg, 0.21 mmol), anisole (91 mg, 0.84 mmol) and trifluoromethanesulfonic acid (0.5 mL) in trifluoroacetic acid (2 mL) was stirred at 80°C for 1 hr. After cooling, the reaction mixture was concentrated, and the residue was partitioned between ethyl acetate and saturated sodium hydrogen carbonate solution. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluate; ethyl acetate/hexane=1/1 to 2/1) to give the title compound (60 mg, 71%) as a white solid.

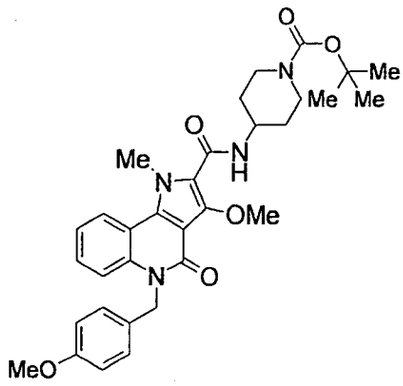
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.60-1.76 (2H, m), 2.07 (2H, d, J = 14.4 Hz), 2.36 (2H, t, J = 10.1 Hz), 2.59 (2H, t, J = 5.4 Hz), 2.88 (2H, d, J = 11.4 Hz), 3.65 (2H, t, J = 5.4 Hz), 3.70-3.80 (2H, br), 4.00-4.15 (1H, m), 4.22 (3H, s), 6.76-6.85 (1H, m), 7.32 (1H, t, J = 8.1 Hz), 7.51 (1H, t, J = 8.4 Hz), 7.85 (1H, d, J = 8.1 Hz), 10.20-10.50 (1H, br).

[2665]

Example 668

Production of tert-butyl 4-({[3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[2666]



[2667]

In the same manner as in Example 25, the title compound (3.45 g, 95%) was obtained as a beige solid from the compound of Reference Example 107 (2.49 g, 6.35 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (2.54 g, 12.69 mmol).

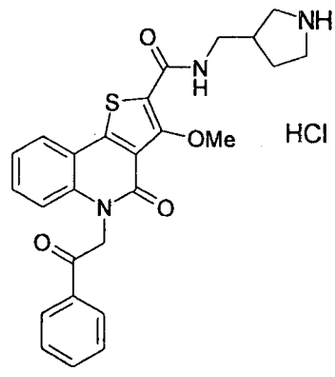
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.35-1.49 (11H, m), 1.85 (2H, dd, J = 12.6, 2.7 Hz), 2.89-2.96 (2H, m), 3.69 (3H, s), 3.88 (2H, d, J = 13.5 Hz), 3.96-4.09 (4H, m), 4.27 (3H, s), 5.40-5.60 (2H, br), 6.83-6.88 (2H, m), 7.14 (2H, d, J = 8.7 Hz), 7.24-7.30 (1H, m), 7.41-7.49 (2H, m), 7.97 (1H, d, J = 8.1 Hz), 8.33 (1H, d, J = 8.1 Hz).

[2668]

Example 669

Production of 3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-N-(pyrrolidin-3-ylmethyl)-4,5-dihydrothieno[3,2-c]quinoline-2-carboxamide hydrochloride

[2669]



[2670]

In the same manner as in Example 25, tert-butyl 3-[({[3-

methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]pyrrolidine-1-carboxylate (530 mg, 72%) was obtained as a white powder from the compound of Reference Example 7 (500 mg, 1.27 mmol) and 3-(aminomethyl)-1-Boc-pyrrolidine (381 mg, 1.90 mmol).

In the same manner as in Example 500, the title compound (456 mg, 97%) was obtained as a white powder from tert-butyl 3-[({[3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)methyl]pyrrolidine-1-carboxylate (530 mg, 0.92 mmol).

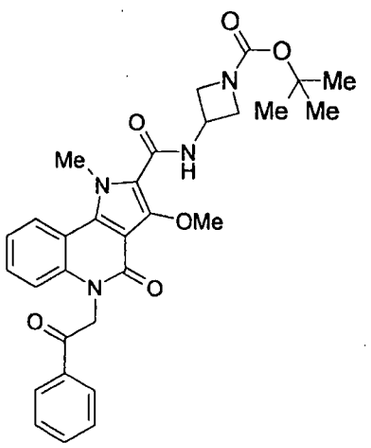
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.55-1.73 (1H, m), 1.90-2.10 (1H, m), 2.55-2.70 (1H, m), 2.85-3.00 (1H, br), 3.10-3.45 (5H, m), 4.05 (3H, s), 6.00 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.49-7.67 (5H, m), 7.77 (1H, t, J = 7.4 Hz), 8.05 (1H, d, J = 7.8, Hz), 8.16-8.19 (2H, m), 8.25 (1H, t, J =5.9 Hz), 9.04 (2H, br s).

[2671]

Example 670

Production of tert-butyl 3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)azetidine-1-carboxylate

[2672]



[2673]

In the same manner as in Example 25, the title compound (610 mg, 88%) was obtained as a white powder from the compound

of Reference Example 28 (500 mg, 1.27 mmol) and 3-amino-1-Boc-azetidine (330 mg, 1.92 mmol).

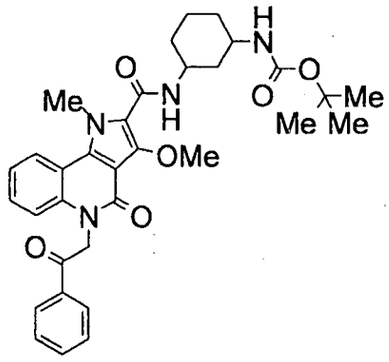
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.40 (9H, m), 3.85-3.95 (2H, m), 3.99 (3H, s), 4.14 (2H, t, J = 7.8 Hz), 4.27 (3H, s), 4.62-4.74 (1H, m), 5.97 (2H, s), 7.31 (1H, t, J = 7.5 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.48 (1H, t, J = 7.5 Hz), 7.64 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.5 Hz), 8.16-8.19 (2H, m), 8.37 (1H, d, J = 8.1 Hz), 8.56 (1H, d, J = 7.2 Hz).

[2674]

Example 671

Production of tert-butyl [3-({[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)cyclohexyl]carbamate

[2675]



[2676]

In the same manner as in Example 25, the title compound (395 mg, 66%) was obtained as a white powder from the compound of Reference Example 7 (400 mg, 1.02 mmol) and tert-butyl (3-aminocyclohexyl)carbamate (285 mg, 1.33 mmol).

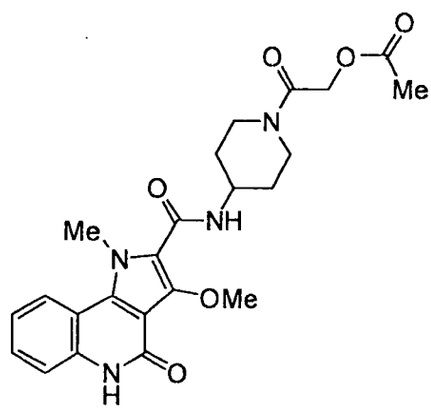
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.98-1.46 (13 H, m), 1.65-1.90 (3 H, m), 2.00-2.12 (1 H, m), 3.23-3.42 (1 H, m), 3.73-3.88 (1 H, m), 3.96 (2 H, s), 4.04 (1 H, s), 4.30 (2 H, s), 4.35 (1 H, s), 5.97 (2 H, s), 6.76-6.94 (1 H, m), 7.24-7.42 (2 H, m), 7.43-7.53 (1 H, m), 7.63 (2 H, t, J = 7.6 Hz), 7.71-7.80 (1 H, m), 7.86 (1 H, d, J = 7.9 Hz), 8.12-8.22 (2 H, m), 8.31-8.42 (1 H, m).

[2677]

Example 672

Production of 2-(4-{[(3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxoethyl acetate

[2678]



[2679]

The compound of Example 558 (500 mg, 0.87 mmol), anisole (376 mg, 3.48 mmol) and trifluoromethanesulfonic acid (2 mL) were dissolved in trifluoroacetic acid (9 mL), and the mixture was stirred at 80°C for 2 hr. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with THF-ethyl acetate. The extract was concentrated to give 3-methoxy-1-methyl-4-oxo-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide (1.10 g) as a beige solid.

To a solution of 3-methoxy-1-methyl-4-oxo-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide (300 mg, 0.87 mmol) and triethylamine (88 mg, 0.87 mmol) in THF (30 mL) was added acetoxyacetyl chloride (119 mg, 0.87 mmol) under ice-cooling, and the mixture was stirred for 2 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated.

The obtained solid was washed with diethyl ether-hexane to give the title compound (221 mg, 56%) as a white solid.

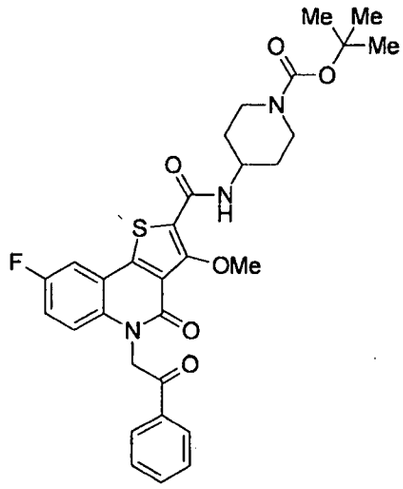
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30-1.65 (2H, m), 1.80-2.00 (2H, m), 2.09 (3H, s), 2.90 (2H, t, J = 11.4 Hz), 3.19 (2H, t, J = 11.4 Hz), 3.70 (2H, d, J = 13.5 Hz), 4.02-4.19 (4H, m), 4.28 (3H, s), 7.22 (1H, t, J = 7.5 Hz), 7.40-7.48 (2H, m), 7.93 (1H, d, J = 7.5 Hz), 8.24 (1H, d, J = 8.4 Hz), 11.34 (1H, s).

[2680]

Example 673

Production of tert-butyl 4-({[8-fluoro-3-methoxy-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydrothieno[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[2681]



[2682]

In the same manner as in Example 25, the title compound (486 mg, 84%) was obtained as a white solid from the compound of Reference Example 116 (400 mg, 0.97 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (234 mg, 1.2 mmol).

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.40-1.53 (11H, m), 1.96-2.11 (2H, m), 2.92-3.10 (2H, m), 3.95-4.08 (2H, m), 4.10-4.24 (4H, m), 5.85 (2H, s), 6.99 (1H, dd, J = 9.3, 4.3 Hz), 7.15-7.25 (1H, m), 7.50-7.62 (4H, m), 7.65-7.74 (1H, m), 8.05-8.16 (2H, m).

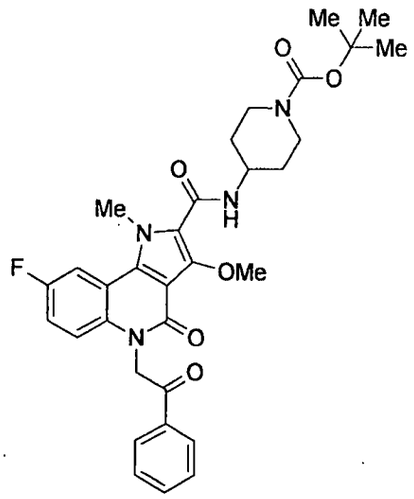
[2683]

Example 674

Production of tert-butyl 4-({[8-fluoro-3-methoxy-1-methyl-4-

oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidine-1-carboxylate

[2684]



[2685]

In the same manner as in Example 25, the title compound (2.5 g, 87%) was obtained as a white solid from the compound of Reference Example 119 (2.0 g, 4.9 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (1.2 g, 5.9 mmol).

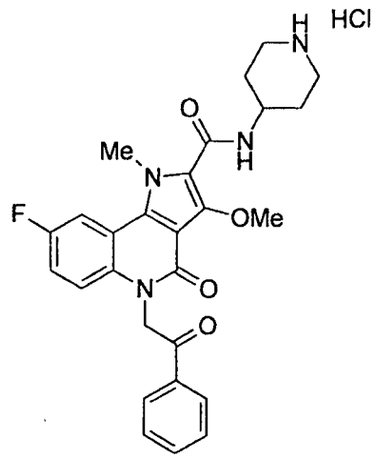
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.34-1.53 (11H, m), 1.89-2.13 (2H, m), 2.94-3.14 (2H, m), 3.89-4.07 (2H, m), 4.08-4.24 (4H, m), 4.46 (3H, s), 5.87 (2H, s), 6.93-7.04 (1H, m), 7.08-7.21 (1H, m), 7.48-7.60 (2H, m), 7.62-7.75 (2H, m), 7.94 (1H, dd, J = 10.0, 2.8 Hz), 8.04-8.20 (2H, m).

[2686]

Example 675

Production of 8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2687]



[2688]

In the same manner as in Example 542, the title compound (1.6 g, 72%) was obtained as a pale-yellow solid from the compound of Example 674 (2.5 g, 4.3 mmol).

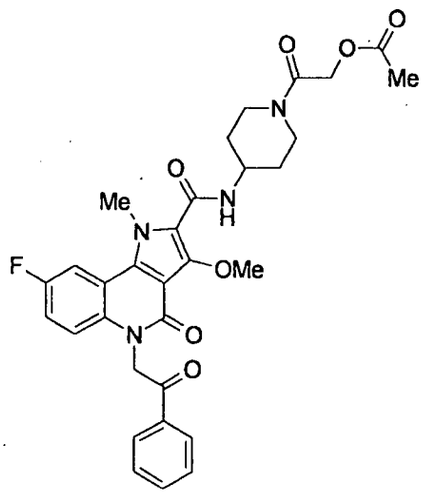
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.62-1.86 (2H, m), 1.96-2.13 (2H, m), 2.95-3.14 (2H, m), 3.21-3.47 (2H, m), 3.95 (3H, s), 4.02-4.18 (1H, m), 4.27 (3H, s), 5.98 (2H, s), 7.23-7.51 (2H, m), 7.57-7.68 (2H, m), 7.71-7.84 (1H, m), 8.04-8.26 (4H, m), 8.64 (2H, br s).

[2689]

Example 676

Production of 2-[4-({[8-fluoro-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}amino)piperidin-1-yl]-2-oxoethyl acetate

[2690]



[2691]

In the same manner as in Example 544, the title compound (293 mg, 87%) was obtained as a white solid from the compound of Example 675 (300 mg, 0.57 mmol).

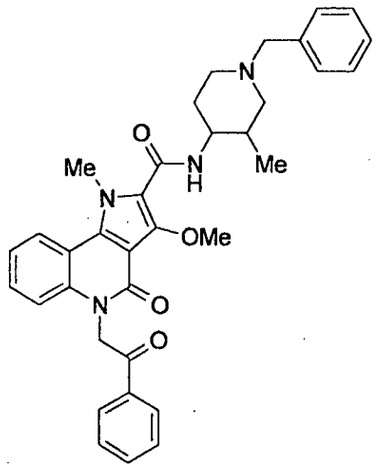
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.30-1.65 (2H, m), 1.82-1.96 (2H, m), 2.08 (3H, s), 2.80-2.96 (1H, m), 3.08-3.26 (1H, m), 3.65-3.78 (1H, m), 3.96 (3H, s), 4.02-4.22 (2H, m), 4.30 (3H, s), 4.74-4.85 (2H, m), 5.97 (2H, s), 7.29-7.50 (2H, m), 7.57-7.68 (2H, m), 7.72-7.81 (1H, m), 7.98-8.06 (1H, m), 8.07-8.21 (3H, m).

[2692]

Example 677

Production of N-(1-benzyl-3-methylpiperidin-4-yl)-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2693]



[2694]

To a solution of 1-benzyl-3-methylpiperidin-4-one (227 mg, 1.1 mmol) and ammonium acetate (861 mg, 11 mmol) in methanol (9.0 mL) was added sodium triacetoxyborohydride (750 mg, 3.5 mol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was diluted with ethyl acetate, washed with 1N sodium hydroxide solution, and the aqueous layer was extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and

concentrated under reduced pressure. To a solution of the residue, the compound of Reference Example 28 (396 mg, 1.0 mmol) and HOBt (151 mg, 1.1 mol) in DMF (7.0 mL) was added WSCD (215 mg, 1.1 mmol) under ice-cooling, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution, and extracted twice with ethyl acetate. The extract was combined, washed with brine, dried over magnesium sulfate, and passed through an aminosilica gel. The filtrate was concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; ethyl acetate/hexane=30/70 - 100/0) and recrystallized from ethyl acetate-hexane to give the title compound (373 mg, 64%) as a white solid.

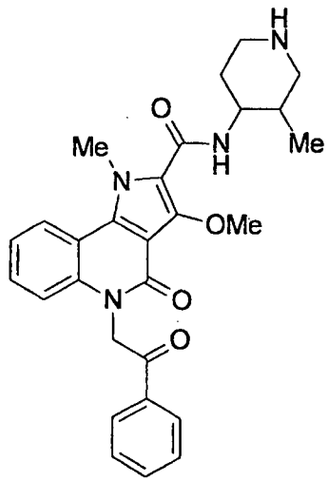
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.83-1.01 (3H, m), 1.49-2.40 (5H, m), 2.56-2.89 (1H, m), 3.22-3.59 (3H, m), 3.94-4.04 (3H, m), 4.07-4.20 (1H, m), 4.25-4.41 (3H, m), 5.98 (2H, s), 7.16-7.42 (7H, m), 7.43-7.54 (1H, m), 7.58-7.69 (2H, m), 7.72-7.81 (1H, m), 7.82-7.94 (1H, m), 8.10-8.23 (2H, m), 8.28-8.45 (1H, m).

[2695]

Example 678

Production of 3-methoxy-1-methyl-N-(3-methylpiperidin-4-yl)-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2696]



[2697]

To a solution of the compound of Example 677 (373 mg, 0.65 mmol) in THF (40 mL) was added 1-chloroethyl chloroformate (0.67 mL, 6.5 mol) under ice-cooling, and the mixture was stirred at room temperature for 3 hr. 1-Chloroethyl chloroformate (0.67 mL, 6.5 mol) and diisopropylethylamine (0.30 mL, 3.2 mmol) were added under ice-cooling, and the mixture was stirred at room temperature for 20 hr. The reaction mixture was concentrated under reduced pressure, and the residue was washed with diethyl ether. The residue was dissolved in methanol (50 mL), and the mixture was stirred at room temperature for 7 hr and concentrated under reduced pressure. The residue was purified by aminosilica gel chromatography (eluate; methanol/ethyl acetate=0/100 - 10/90) and recrystallized from ethyl acetate-hexane to give the title compound (90 mg, 29%) as a pale-brown solid.

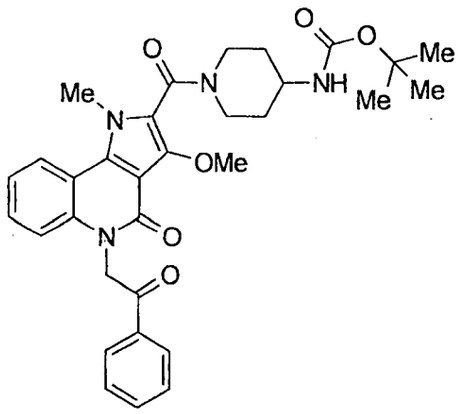
^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.83-0.95 (3H, m), 1.21-2.35 (5H, m), 2.60-3.01 (3H, m), 3.94-4.08 (3H, m), 4.11-4.22 (1H, m), 4.26-4.41 (3H, m), 5.98 (2H, s), 7.22-7.42 (2H, m), 7.43-7.53 (1H, m), 7.59-7.69 (2H, m), 7.71-8.00 (2H, m), 8.12-8.22 (2H, m), 8.32-8.45 (1H, m).

[2698]

Example 679

Production of tert-butyl (1-{[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}piperidin-4-yl)carbamate

[2699]



[2700]

In the same manner as in Example 25, the title compound (440 mg, 86%) was obtained as a white solid from the compound of Reference Example 28 (350 mg, 0.90 mmol) and tert-butyl piperidin-4-ylcarbamate (198 mg, 0.99 mmol).

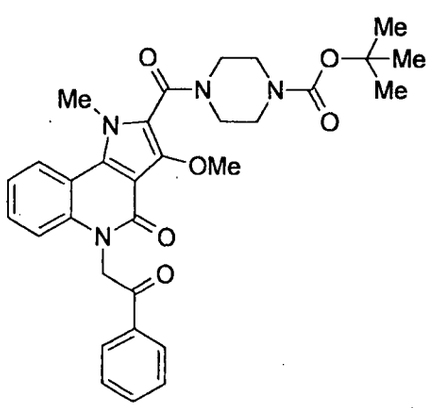
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.25-1.51 (11H, m), 1.68-1.94 (2H, m), 2.91-3.07 (1H, m), 3.10-3.27 (1H, m), 3.47-3.65 (1H, m), 3.67-3.82 (1H, m), 3.88 (3H, s), 3.95-4.06 (3H, m), 4.29-4.48 (1H, m), 5.97 (2H, s), 6.93 (1H, d, J = 6.2 Hz), 7.24-7.51 (3H, m), 7.57-7.69 (2H, m), 7.70-7.83 (1H, m), 8.11-8.23 (2H, m), 8.32 (1H, dd, J = 8.3, 1.1 Hz).

[2701]

Example 680

Production of tert-butyl 4-{[3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinolin-2-yl]carbonyl}piperazine-1-carboxylate

[2702]



[2703]

In the same manner as in Example 25, the title compound (571 mg, quant.) was obtained as a white solid from the compound of Reference Example 28 (400 mg, 1.0 mmol) and tert-butyl piperazine-1-carboxylate (210 mg, 1.1 mmol).

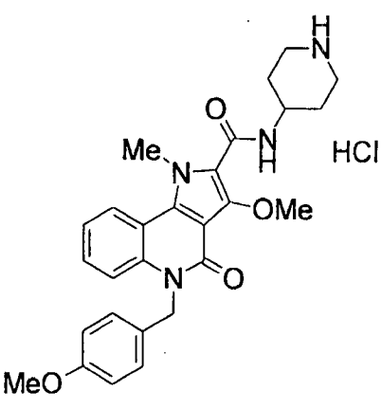
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.49 (9H, s), 3.43-3.88 (8H, m), 4.05 (3H, s), 4.08-4.12 (3H, m), 5.89 (2H, s), 7.01-7.10 (1H, m), 7.20-7.31 (1H, m), 7.35-7.44 (1H, m), 7.50-7.59 (2H, m), 7.62-7.71 (1H, m), 8.07-8.14 (2H, m), 8.20 (1H, dd, J = 8.2, 1.2 Hz).

[2704]

Example 681

Production of 3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-N-piperidin-4-yl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide hydrochloride

[2705]



[2706]

To a solution of the compound of Example 558 (500 mg, 0.87 mmol) in ethyl acetate (15 mL) was added 4N hydrogen chloride ethyl acetate solution (5 mL), and the mixture was stirred at room temperature for 4 hr. The precipitate was collected by filtration, washed with diethyl ether, and dried under reduced pressure to give the title compound (440 mg, 99%) as a pale-pink powder.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.78 (2H, q, J = 10.3 Hz), 2.05 (2H, d, J = 10.8 Hz), 3.06 (2H, t, J = 10.7 Hz), 3.26-3.33 (2H, m), 3.63 (3H, s), 4.02 (3H, s), 4.09-4.13 (1H, m), 4.24 (3H, s),

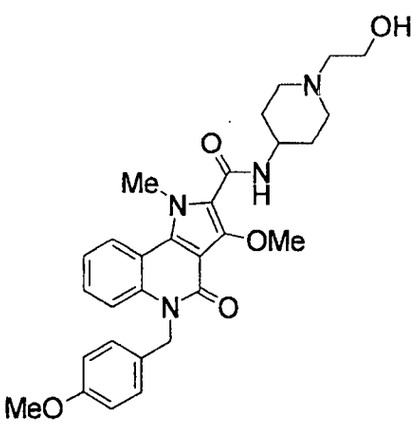
5.40-5.60 (2H, br), 6.86 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz), 7.25-7.30 (1H, m), 7.42-7.49 (2H, m), 8.15 (1H, d, J = 7.5 Hz), 8.33 (1H, d, J = 7.8 Hz), 8.60-8.90 (2H, br).

[2707]

Example 682

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-5-(4-methoxybenzyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2708]



[2709]

In the same manner as in Example 79, the title compound (1.91 g, 75%) was obtained as white crystals from the compound of Example 681 (2.50 g, 4.89 mmol).

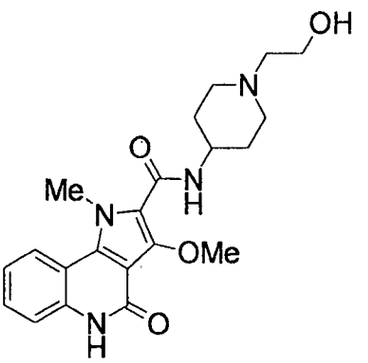
^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.58 (2H, q, J = 9.9 Hz), 1.85 (2H, d, J = 9.6 Hz), 2.18 (2H, t, J = 9.9 Hz), 2.40 (2H, t, J = 6.3 Hz), 2.78 (2H, d, J = 11.4 Hz), 3.50 (2H, q, J = 6.0 Hz), 3.69 (3H, s), 3.70-3.85 (1H, br), 4.04 (3H, s), 4.29 (3H, s), 4.35-4.40 (1H, m), 5.40-5.65 (2H, br), 6.86 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.4 Hz), 7.24-7.30 (1H, m), 7.42-7.49 (2H, m), 7.91 (1H, d, J = 7.8 Hz), 8.33 (1H, d, J = 8.1 Hz).

[2710]

Example 683

Production of N-[1-(2-hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide

[2711]



[2712]

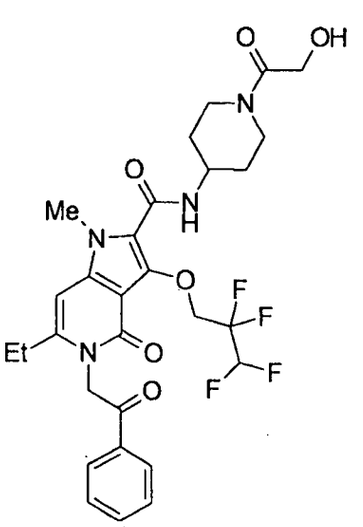
In the same manner as in Example 672, the title compound (457 mg, 33%) was obtained as white crystals from the compound of Example 682 (1.79 g, 3.45 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.50-1.60 (2H, m), 1.83 (2H, d, J = 10.2 Hz), 2.18 (2H, t, J = 10.4 Hz), 2.40 (2H, t, J = 6.3 Hz), 2.65-2.85 (2H, m), 3.50 (2H, q, J = 6.0 Hz), 3.75-3.90 (1H, m), 4.03 (3H, s), 4.29 (3H, s), 4.38 (1H, t, J = 5.4 Hz), 7.22 (1H, t, J = 7.5 Hz), 7.40-7.45 (2H, m), 7.84 (1H, d, J = 7.8 Hz), 8.24 (1H, d, J = 8.1 Hz), 11.33 (1H, s).

Example 684

Production of 6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,3,3-tetrafluoropropoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2713]



[2714]

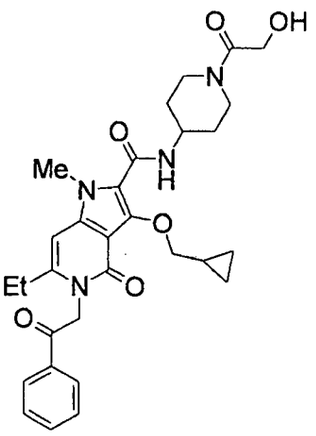
In the same manner as in Example 140, the title compound (224 mg, 74%) was obtained as a white powder from the compound of Reference Example 175 (234 mg, 0.50 mmol).

^{1}H-NMR (300 MHz, DMSO-d_6) δ:1.19 (3H, t, J = 7.4 Hz), 1.24-1.48 (2H, m), 1.82-1.95 (2H, m), 2.58 (2H, q, J = 7.4 Hz), 2.70-2.89 (1H, m), 3.00-3.16 (1H, m), 3.62-3.78 (1H, m), 3.87 (3H, s), 3.96-4.15 (3H, m), 4.23-4.38 (1H, m), 4.53 (1H, t, J = 5.4 Hz), 4.94 (2H, t, J = 14.7 Hz), 5.63 (2H, s), 6.53 (1H, s), 6.66 (1H, tt, J = 52.0, 5.2 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.57-7.66 (2H, m), 7.70-7.78 (1H, m), 8.08-8.16 (2H, m).

Example 685

Production of 3-(cyclopropylmethoxy)-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

[2715]



[2716]

In the same manner as in Example 140, the title compound (100 mg, 76%) was obtained as a colorless powder from the compound of Reference Example 177 (98 mg, 0.24 mmol).

^{1}H-NMR (300MHz, DMSO-d_6) δ:0.19-0.27 (2H, m), 0.46-0.55 (2H, m), 1.06-1.20 (1H, m), 1.18 (3H, t, J = 7.4 Hz), 1.25-1.56 (2H, m), 1.84-2.00 (2H, m), 2.57 (2H, q, J = 7.3 Hz), 2.77-2.94 (1H, m), 3.04-3.20 (1H, m), 3.60-3.75 (1H, m), 3.91 (3H, s), 3.96-4.13 (3H, m), 4.17 (2H, d, J = 7.2 Hz), 4.20-4.32 (1H, m), 4.51 (1H,

t, J = 5.5 Hz), 5.59 (2H, s), 6.48 (1H, s), 7.56-7.66 (2H, m), 7.69-7.81 (2H, m), 8.07-8.15 (2H, m).

[2717]

Formulation Example 1

A pharmaceutical agent containing the compound of the present invention as an active ingredient can be produced, for example, based on the following composition.

1. capsule

(1) compound obtained in Example 25		40 mg
(2) lactose		70 mg
(3) microcrystalline cellulose		9 mg
(4) magnesium stearate		1 mg
	1 capsule	120 mg

(1), (2), (3) and 1/2 of (4) are blended and granulated. Thereto is added the rest of (4) and the total amount is filled in a gelatin capsule.

[2718]

2. tablet

(1) compound obtained in Example 25		40 mg
(2) lactose		58 mg
(3) cornstarch		18 mg
(4) microcrystalline cellulose		3.5 mg
(5) magnesium stearate		0.5 mg
	1 tablet	120 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are blended and granulated. Thereto is added the rest of (4) and (5) and the mixture is compression formed to give a tablet.

[2719]

Formulation Example 2

The compound obtained in Example 25 (50 mg) is dissolved in the Japanese Pharmacopoeia distilled water for injection (50 ml), and the Japanese Pharmacopoeia distilled water for injection is added to 100 ml. The solution is filtered under sterile conditions, and 1 ml of the solution is filled in an injection vial under sterile conditions, and freeze-dried and

sealed.

[2720]

Experimental Example

Genetic operation methods described in Experimental Examples below are based on the methods described in a book (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989), and the appended protocol of the reagent.

Experimental Example 1. Construction of Gli reporter plasmid

Gli reporter plasmid was constructed by inserting 8 x Gli-binding site and chicken δ-crystallin promoter into the upstream of luc+ of pGL3 (Promega).

δ-Crystallin promoter was cloned by PCR method using, as a primer set, synthetic DNAs

5′-GAAGATCTGCCAGCCCAGGCTCCGGGGC-3′ (SEQ ID NO: 1)

5′-CCCAAGCTTCTGCCCGCACAGCCCTGCTC-3′ (SEQ ID NO: 2)

prepared in reference to the base sequence described in GenBank accession No.; X02187, and chicken genome DNA (Clontech) as a template. PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The obtained 108 bp fragment was digested with restriction enzymes BglII and HindIII, and inserted into BglII-HindIII site of pGL3 to give plasmid pGL3/δ-cry promoter.

As 8 x Gli-binding site, a sequence containing eight 9-bp Gli bound consensus sequences (GACCACCCA) described in Yoon et al., J. Biol. Chem., vol. 273, pages 3496-3501 (1998) was prepared from synthetic DNA. That is, two synthetic DNAs,

5′-

GGGGTACCGACCACCCAGACCACCCAGACCACCCACACCACCCAGACCACCCAGACCACCCA

GACCACCCAGACCACCCAAGATCTTC-3′ (SEQ ID NO: 3)

5′-

GAAGATCTTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTGTGGGTGGTC

TGGGTGGTCTGGGTGGTCGGTACCCC-3′ (SEQ ID NO: 4)

were heat treated at 95°C for 2 minutes, and incubated at 37°C for 1 hr for annealing to give a double stranded DNA of the above-mentioned two synthetic DNAs. The obtained double

stranded DNA was digested with restriction enzymes BglII and KpnI, and the obtained DNA fragment was inserted into BglII-KpnI site of pGL3/δ-cry promoter to construct plasmid pGL3/δ-cry promoter, 8 x Gli binding site, i.e., Gli reporter plasmid.

[2721]

Experimental Example 2. Construction of plasmid for expression of mouse Shh-N end fragment

As a material for construction of plasmid for Shh-N end fragment expression, mouse Shh cDNA was cloned at first.

The mouse Shh cDNA was cloned by Nested PCR method using mouse 11-day fetus cDNA (Clontech) as a template. The primer sequence was prepared in reference to the base sequence described in GenBank accession No.; NM_009170.

As the primer set for 1st PCR,

5'-CTGGGTGGGGATCGGAGACA-3' (SEQ ID NO: 5)

5'-GCGCTTTCCCATCAGTTCCTTATT-3' (SEQ ID NO: 6) were used,

and as the primer set for 2nd PCR,

5'-GGGGTACCATGCTGCTGCTGCTGGCCA-3' (SEQ ID NO: 7)

5'-GCTCTAGATCAGCTGGACTTGACCGCCA-3' (SEQ ID NO: 8)

were used. PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The resulting PCR product was cloned by pcDNA3.1 (+) (Invitrogen), and the inserted base sequence was confirmed.

Using the mouse Shh cDNA sequence obtained as mentioned above as a template, a partial cDNA sequence wherein stop codon (TGA) was added to 3'-terminal of cDNA sequence encoding 1st to 198th amino acid sequence of mouse Shh was obtained by PCR method. As the primer set,

5'-ATGCTGCTGCTGCTGGCCAG-3' (SEQ ID NO: 9)

5'-TCAGCCGCCGGATTTGGCCG-3' (SEQ ID NO: 10)

were used.

PCR reaction was performed using Pfu Turbo (Stratagene) and following the attached protocol. The obtained PCR product was cloned by pcDNA3.1 (+) (Invitrogen), and the inserted base sequence was confirmed.

In the manner mentioned above, a plasmid for mouse Shh-N end fragment expression, pcDNA3.1/mShh-N, was constructed.

[2722]

Experimental Example 3. Production of recombinant type mouse Shh-N end fragment

HEK293 cells were grown in D-MEM medium (Invitrogen) containing 10% fetal bovine serum in a 10 cm dish and pcDNA3.1/mShh-N was introduced into the cells using FuGENE6 (Roche Applied Science). Thereafter, the HEK293 cells were cultured in a carbon dioxide gas incubator at 37°C for 24 hours, and the medium was exchanged with D-MEM medium (Invitrogen) containing 2% fetal bovine serum. After culturing for 48 hr, a culture supernatant containing recombinant type mouse Shh-N end fragment was obtained by filtration using a filter (0.22 μM).

[2723]

Experimental Example 4. Introduction of plasmid for Gli-1 expression and reporter plasmid into NIH-3T3 cells and production of expressing cells

Using D-MEM (Invitrogen) containing 10% fetal bovine serum, expression plasmid pcDNA3.1 and Gli reporter plasmid (pGL3/δ-cry promoter, 8 x Gli binding site) produced by the method of Experimental Example 1 were introduced into NIH-3T3 cells grown in a 10 cm dish by the use of FuGENE6 (Roche Applied Science).

After culture for 24 hr, the cells were recovered, suspended in D-MEM medium containing 10% fetal bovine serum and supplemented with Geneticin (Life Technologies Oriental, Inc.) to a final concentration of 500 μg/ml, diluted to 10^4 cells/ml, plated on a 96 well plate, and cultured in a carbon dioxide gas incubator at 37°C to give Geneticin resistant transformed cell line.

The obtained transformed cell line was cultured in a 96 well plate, mouse Shh-N end fragment obtained in Experimental Example 3 was added, and NIH-3T3/Gli reporter cell, which is a

cell line capable of induction of luciferase expression, was selected.

[2724]

Experimental Example 5. Evaluation of compound *

NIH-3T3/Gli reporter cells cultured in D-MEM (Invitrogen) containing 10% fetal bovine serum were plated in a 96 well white plate at $1x10^4$ cells/well, and cultured overnight in a carbon dioxide gas incubator at 37°C. The medium was removed, a compound (50 µl) and culture supernatant of mouse Shh-N end fragment-expressing HEK293 (D-MEM medium containing 2% fetal bovine serum, 50 µl) were added, and the cells were cultured for 48 hr in a carbon dioxide gas incubator at 37°C. Bright-Glo (Promega, 50 µl) was added, and the mixture was stirred, after which luciferase activity was measured by EnVision (PerkinElmer). The inhibition rate was calculated based on the luciferase activity of the control without addition of the compound as 100. The results are shown in Tables below. The concentration of the compound and the inhibition rate were analyzed by PRISM3.00 (software of GraphPad), based on which the IC_{50} value (compound concentration necessary for achieving 50% of the maximum value of inhibition rate) of the compound was calculated.

IC_{50} values of the compounds of Examples 2, 3, 9, 13, 16, 17, 22, 27, 32, 41, 43, 45, 48, 50, 51, 52, 53, 56, 69, 71, 73, 74, 79, 92, 102, 109 and 115 were not more than 1 µM.

[2725]

[Table 3]

Example	inhibition rate (%) at 1 µM
2	100
3	100
9	100
13	100
16	100
17	99
22	91

27	100
32	95
41	100
43	100
45	100
48	10
50	100
51	100
52	95
53	95
56	100
69	100
71	100
73	100
74	100
79	100
92	100
102	80
109	100
115	100
118	100
124	100
131	100
132	100
135	100
136	100
137	100
138	100
139-1)	100
140	100
141	100
142	100
143-1)	100
510	100
517	100
522	100
562	100
563	100
583	100
584	100
643	100

644	100
650	100
654	100
656	100
657	100
658	100
660	100
661	100

[2726]

Experimental Example 6. In vivo anti-tumor test

According to the description in Sasaki, K. et al., (2006) Cancer Res. 66: 4215-4222, an anti-tumor effect of a compound was evaluated using a mouse medulloblastoma allogeneic transplantation model. To be precise, Patched 1 gene mutant mouse (lineage name: Ptch1tm1Mps/J) was purchased from The Jackson Laboratory and p53 gene mutant mouse (lineage name: P53N4-M, Nomenclature: B6.129-Trp53tm/BrdN4) was purchased from Taconic, and a mouse of Patched 1(+/-), p53(-/-) phenotype was prepared by mating. The tumor tissue of medulloblastoma spontaneously occurred in the cerebellum of 7- to 9-week-old Patched 1(+/-), p53(-/-) mouse was taken and subcutaneously transplanted into a nude mouse (lineage name: CAnN.Cg-Foxn1<nu>/CrlCrlj).

An anti-tumor test was performed using a tumor passaged by subcutaneous transplantation. A tumor mass was isolated by a 40 μm cell strainer (BD Biosciences, Cat. No. 352340), a tumor suspension was prepared with Leibovitz's L-15 medium (GIBCO, Cat. No. 11415-114) in a 2-fold amount relative to the tumor mass weight, mixed with an equivalent amount of matrigel (BD Biosciences, Cat. No. 356237), and subcutaneously transplanted to a mouse at 100 μl per transplantation site. The tumor diameter after transplantation was measured and, when the tumor size reached 150 - 250 mm^3, the anti-tumor test was started using 5 mice per group.

The test compound was prepared to achieve a dose of 6.25

mg/kg with a 0.5 % methylcellulose (Shin-Etsu Chemical Co., Ltd., Cat. No. SM-100) suspension, and orally administered twice a day for 2 weeks. The tumor size was calculated based on the longer diameter and shorter diameter of the tumor measured with an electron vernier caliper. After the start of the test, the tumor size was measured every 2 or 3 days and the growth rate of the tumor size was calculated. A tumor growth inhibitory effect of 95% or above was confirmed in each test compound administration group. The growth rate of the tumor size by each test compound at the end of the test is shown in the following Table.

The tumor growth rate and the results of a significant difference test by the administration of each test compound are shown in the Table. The growth rate of the tumor size (T/C) was calculated according to:

growth rate (T/C) = ((tumor size of compound administration group at the end of administration)-(tumor size of compound administration group at the start of administration))/((tumor size of control group at the end of administration)-(tumor size of control group at the start of administration))X100.

[2727]

[Table 4]

Example	T/C (%)	P value (Dunnett's test)
79-1)	0.8	≤0.001
124-1)	2.0	≤0.001
139-1)	0.4	≤0.001
140-1)	5.3	≤0.001
143-1)	0.0	≤0.001

[2728]

The above-mentioned results confirm that the compound of the present invention shows an anti-tumor effect.

Industrially Applicability

[2729]

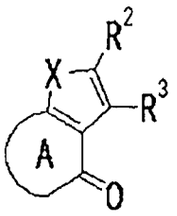
Since the compound of the present invention shows a superior Smo inhibitory action, a clinically useful agent for the prophylaxis or treatment of diseases related to Smo (e.g., cancer etc.) can be provided. In addition, since the compound of the present invention is also superior in the efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability, it is useful as a pharmaceutical agent.

[2730]

This application is based on application Nos. 2008-045134 and 2008-256755 filed in Japan, the contents of which are incorporated hereinto by reference.

CLAIMS

1. A compound represented by the formula



(I)

wherein

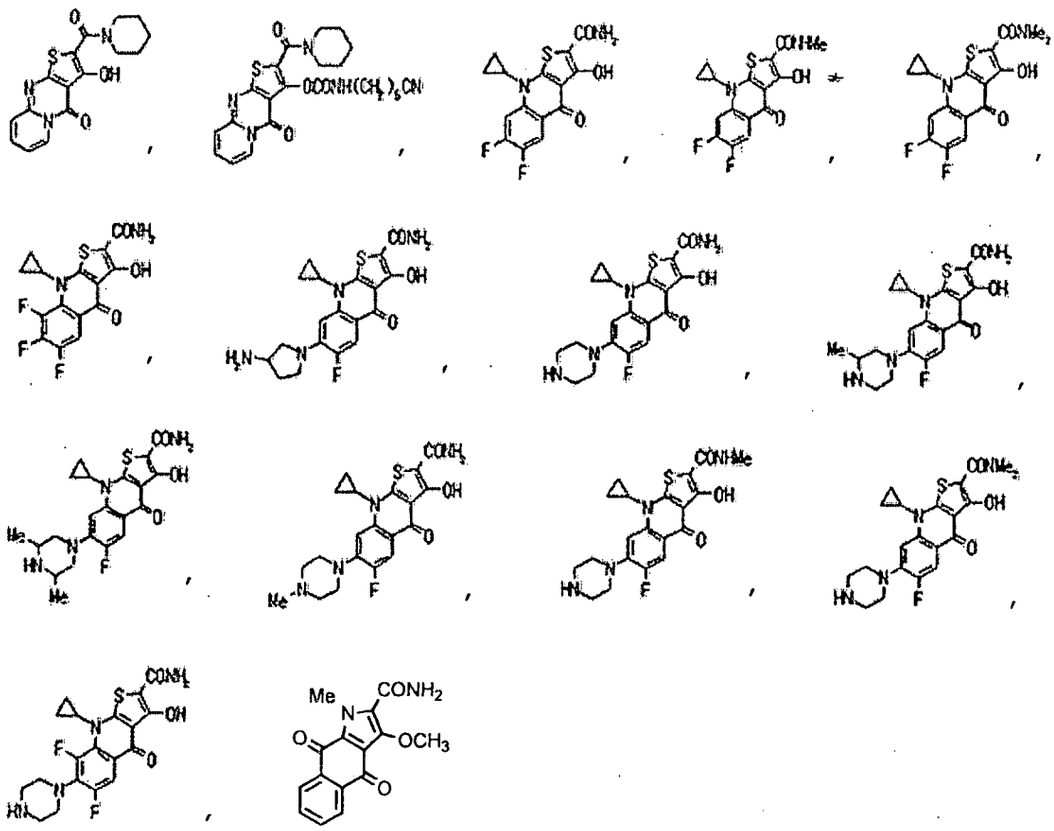
ring A is a 5- to 7-membered ring optionally having substituent(s), where substituents are optionally bonded to each other to form a ring;

X is O, S or NR^1 (R^1 is a hydrogen atom or a hydrocarbon group optionally having substituent(s));

R^2 is carbamoyl optionally having substituent(s); and

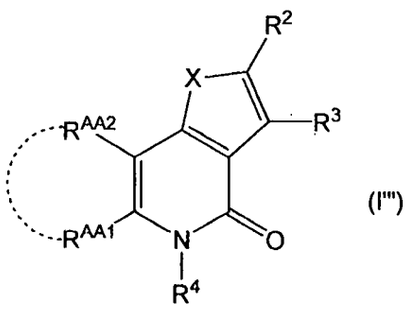
R^3 is hydroxy optionally having substituent(s),

except the following compounds;



or a salt thereof.

2. The compound of claim 1, which is represented by the formula



(I''')

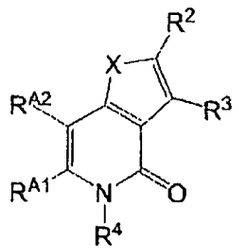
wherein

X, R^2 and R^3 are as defined in claim 1,

R^{AA1} and R^{AA2} are the same or different and each is a hydrogen atom or a substituent, or R^{AA1} and R^{AA2} are optionally bonded to each other to form a 5- to 7-membered ring optionally having substituent(s), and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s).

3. The compound of claim 2, which is represented by the formula



(I")

wherein

X, R^2 and R^3 are as defined in claim 1,

R^{A1} and R^{A2} are the same or different and each is a hydrogen atom or a substituent, and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s).

4. The compound of claim 3, wherein X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

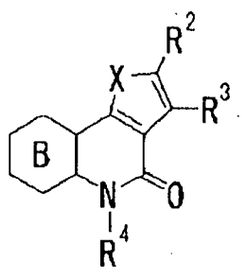
R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s),

R^{A1} is a hydrogen atom or a C_{1-6} alkyl group,

R^{A2} is a hydrogen atom or a C_{1-6} alkyl group, and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s).

5. The compound of claim 1, which is represented by the formula



(I')

wherein

X, R^2 and R^3 are as defined in claim 1,

ring B is a 6-membered ring optionally having substituent(s);

and

R^4 is a hydrogen atom or a hydrocarbon group optionally having substituent(s).

6. The compound of claim 5, wherein ring B is a 6-membered ring optionally having substituent(s),

X is O, S or N(C_{1-6} alkyl),

R^2 is carbamoyl optionally having substituent(s),

R^3 is hydroxy optionally having C_{1-6} alkyl optionally having substituent(s), and

R^4 is a hydrogen atom or C_{1-6} alkyl optionally having substituent(s).

7. N-[1-(2-Hydroxyethyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide or a salt thereof.

8. N-[1-(Hydroxyacetyl)piperidin-4-yl]-3-methoxy-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide or a salt thereof.

9. 3-Ethoxy-6-ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

10. N-[1-(Hydroxyacetyl)piperidin-4-yl]-1,6-dimethyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

11. 6-Ethyl-N-[1-(hydroxyacetyl)piperidin-4-yl]-1-methyl-4-oxo-5-(2-oxo-2-phenylethyl)-3-(2,2,2-trifluoroethoxy)-4,5-dihydro-1H-pyrrolo[3,2-c]pyridine-2-carboxamide or a salt thereof.

12. A prodrug of the compound of claim 1.

13. A pharmaceutical agent comprising the compound of claim 1 or a prodrug thereof.

14. The pharmaceutical agent of claim 13, which is an Smo inhibitor.

15. The pharmaceutical agent of claim 13, which is an agent for the prophylaxis or treatment of cancer.

16. A method of inhibiting Smo in a mammal, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to the mammal.

17. A method for the prophylaxis or treatment of cancer in a mammal, which comprises administering an effective amount of the compound of claim 1 or a prodrug thereof to the mammal.

18. Use of the compound of claim 1 or a prodrug thereof for the production of an Smo inhibitor.

19. Use of the compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

SEQUENCE LISTING

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DERIVADO HETEROCICLICO FUSIONADO Y SU USO

Campo de la Invención

La presente invención se refiere a un derivado heterocíclico fusionado y su uso de lo mismo. Más particularmente, la presente invención se refiere a un compuesto que tiene una fuerte actividad de inhibición de Smo y es útil para la profilaxis o el tratamiento de cáncer y similares, y su uso de lo mismo.

Antecedentes de la Invención

El estudio de la morfogénesis durante la etapa de desarrollo se ha basado en la selección sistemática de variante usando Drosófila. El gen Hedgehog (hh) se encontró como uno de los genes que producen anormalidad morfológica del embrión de Drosófila debido a su mutación de lo mismo. El producto génico Hedgehog (Hh) es una proteína *secretoria*, que se produce como un precursor de aproximadamente 45 kDa y luego se divide, debido a su autolisis, en un dominio lateral N-terminal de 20 kDa, que es un principio activo principal y un dominio lateral C-terminal de 25 kDa. El dominio lateral N-terminal de 20 kDa, que es un principio activo principal, se modifica mediante de ácidos grasos en la N-terminal y el colesterol en la C-terminal de la misma. El sistema de transducción de señal de Hedgehog se forma a través del grupo de proteínas descrito con anterioridad. El receptor Hh tiene Parche (Patched (Ptch)), que es una proteína del tipo de doce transmembranas. Ptch actúa sobre Smoothened (Smo), que es una proteína del tipo de siete transmembranas, y suprime la función de Smo en ausencia de Hh. Cuando Hh se une al receptor Ptch, la supresión de Smo se libera y se activa Smo. La señal producida por la activación de Smo activa el factor de transcripción Ci, que regula la expresión del grupo génico involucrado en la morfogénesis (documento no patente 1).

Una vía correspondiente al sistema de transducción de señal Drosófila Hedgehog se ha confirmado también en mamíferos. En el humano, por ejemplo, se conocen tres tipos de productos génicos, hedgehog sónico (Shh), hedgehog hindú (Ihh) y hedgehog del desierto (Dhh), que corresponden a Drosófila Hh, y sufren modificación post-traducción como en Drosófila Hh (documento no patente 2). En el Shh humano, se divide un principio activo de 19 kDa a partir de una proteína precursora de 45 kDa por autolisis y se añaden ácido graso y colesterol a la N-terminal y C-terminal, respectivamente (documento no patente 3). Tal modificación se considera esencial para el mantenimiento de la actividad de Shh y, por ejemplo, se logró una actividad 40 veces potenciada por la incorporación de ácido palmítico a Shh humano recombinante de Escherichia coli libre de modificación N-terminal con ácido graso, y se logró una actividad potenciada 160 veces a través del agregado de ácido mirístico a este (documento no patente 4). Por otro lado, como un gen humano correspondiente a Drosófila Smo, se conoce el Smo humano, y como un gen humano que corresponde a Drosófila Ptch, se conocen 2 tipos de Ptch1 y Ptch2. Además, se considera que un factor de transcripción correspondiente a Drosófila Ci es Gli en los humanos, y se conocen 3 tipos de Gli1, Gli2 y Gli3 (documento no patente 5). Shh/Ihh/Dhh se unen cada uno a Ptch1 y activan Smo inhibiendo el enlace entre Ptch1 y Smo. Shh/Ihh/Dhh también se unen a Ptch2, Hip1, Gas1 y Cdo/boc, además de Ptch1, y regulan la activación de Smo. Una señal de transducción de Smo induce la localización nuclear de Gli1 y Gli2, y activa la transcripción de Gli1 (documento no patente 6).

La señal de Hedgehog está involucrada en la morfogénesis en las etapas del desarrollo también en los mamíferos. En el humano, por ejemplo, los pacientes con Holoprosencefalia, que es

una anormalidad congénita del desarrollo, mostraron mutación en Shh (documento no patente 7). Más aun, se confirmó que un compuesto natural Ciclopamina derivado del eléboro blanco conocido como un compuesto que induce Cyclopus en las ovejas (documento no patente 8) inhibe Smo como su mecanismo de acción de lo mismo (documento no patente 9). Además, se preparó un ratón con knock-out de Shh, y se encontró que su fenotipo incluye Cyclopus, malformación de extremidades (documento no patente 10), y malformación de la placa neural (documento no patente 11).

La señal de Hedgehog es en forma inherente una señal de desarrollo, que se promueve en tejidos tumorales y funciona como una señal de supervivencia y crecimiento de células cancerosas. Se considera que la señal de Hedgehog funciona para el crecimiento y supervivencia de células cancerosas en un modo autócrino, o funcionan entre las células cancerosas y células intersticiales cancerosas en un modo parácrino, en tejidos tumorales (documento no patente 12). En un modo autócrino, funciona para el crecimiento y mantenimiento de células cancerosas, a través de la activación por Gli-1, por medio de un control del ciclo celular anormal debido al aumento de la expresión de Ciclina D y reducción de la expresión de p21, la promoción de la señal de proliferación por activación de la vía de EGFR y similares. Por otro lado, en un modo parácrino, dado que Shh expresado en células cancerosas actúan sobre Smo en las células intersticiales cancerosas, factores de crecimiento tales como la insulina-como factor de crecimiento factor-1, el crecimiento de fibroblastos, factor de crecimiento derivado de plaquetas y similares se transmiten intersticial de las células cancerosas a las células cancerosas, y la función para el crecimiento y la supervivencia de las células cancerosas.

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También se considera que la promoción de VEGF, la vía de PDGF y similares por Gli-1 promueve la angiogénesis tumoral (documento no patente 13). Respecto del mecanismo de promoción de la señal de Hedgehog, un cáncer en el cual la señal de Hedgehog se promueve debido a la mutación de Ptch1 y un cáncer que se promueve por sobre-expresión de Shh, que es uno de los ligandos, se han informado (documento no patente 14). Como cáncer en el cual la señal de Hedgehog se promueve debido a mutación, se conocen el cáncer de células basales y meduloblastoma, y la mutación de Ptch1 observada en estos cánceres activa la señal de Hedgehog en un modo independiente del ligando (documento no patente 15). Como un cáncer en el cual la señal de Hedgehog se promueve por sobre-expresión de Shh, se han informado el cáncer pancreático (documento no patente 16) y similares. En un ratón transgénico en el cual Shh se expresa en forma forzada en el páncreas, la señal de Hedgehog se sugiere como involucrada no sólo en el crecimiento y mantenimiento del cáncer, sino también en el proceso carcinogénico, dado que se encontró una lesión símilar PanIN en las etapas iniciales del progreso del cáncer en el páncreas (documento no patente 17). Además, la señal de Hedgehog se considera que funciona para el crecimiento y la supervivencia de células madre con cáncer, y cumple una función importante en la metástasis o recurrencia post-operatoria de tumores y similares (documento no patente 18).

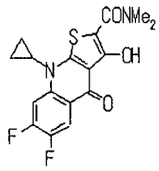
Como inhibidor de la señal de Hedgehog, se conocen los siguientes. Ciclopamina, que es un compuesto inhibidor de Smo natural, se ha informado y muestra un efecto supresor del crecimiento de tumores en glioma (documento no patente 19) y similares. Como compuesto sintético de bajo peso molecular que inhibe Smo, se han informado CUR-61414 (documento no patente

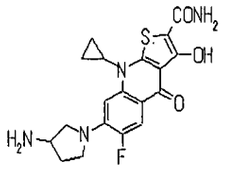
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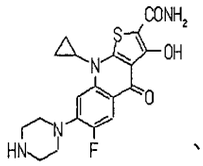
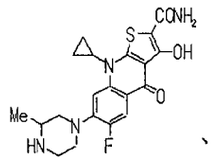
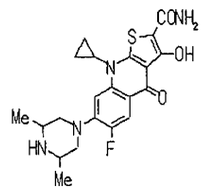
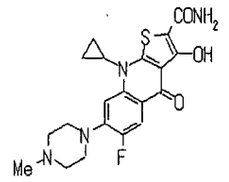
20) y SANT-1, 2, 3, 4 (documento no patente 21). Con respecto al anticuerpo inhibidor de señal de Hedgehog se ha informado que la administración de un anticuerpo anti-Shh para el ratón lampiño con cáncer trasplantado con la línea celular de cáncer colorrectal HT-29 produjo regresión del cáncer (documento de patente 1).

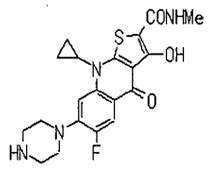
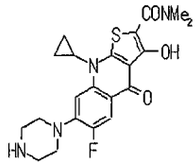
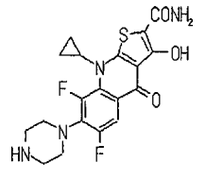
Como compuesto similar al compuesto descrito en la presente especificación, el documento de patente 2 describe los siguientes compuestos que tienen actividad antibacteriana.


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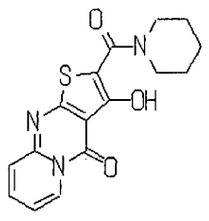
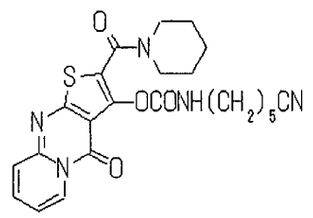
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Como un compuesto que tiene actividad antibacteriana, el documento de patente 3 describe los siguientes compuestos.


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documento de patente 1: WO2004/020599

documento de patente 2: JP-A-3-223289

documento de patente 3: WO93/13664

documento no patente 1: Curr. Opin. Genet. Dev., vol. 12, páginas 503-511 (2002)

documento no patente 2: Cell, vol. 103, páginas 371-374 (2000)

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documento no patente 3: J. Biol. Chem., vol. 273, páginas 14037-14045 (1998)

documento no patente 4: Biochemistry, vol. 40, páginas 4359-4371 (2001)

documento no patente 5: Nature Rev. Cancer, vol. 2, páginas 361-372 (2002)

documento no patente 6: Curr. Opin. Cell Biol., vol. 19, páginas 159-165 (2007)

documento no patente 7: Nat. Genet., vol. 14, páginas 357-360 (1996)

documento no patente 8: Am. J. Vet. Res., vol. 24, páginas 1164-1175 (1963)

documento no patente 9: Development, vol. 125, páginas 3553-3562 (1998)

documento no patente 10: Nature, vol. 383, páginas 407-413 (1996)

documento no patente 11: Cell, vol. 111, páginas 63-75 (2002)

documento no patente 12: Nat. Rev. Drug Discov., vol. 5, páginas 1026-1033 (2006)

documento no patente 13: Clin Cancer Res., vol. 12, páginas 5924-5928 (2006)

documento no patente 14: Nature Rev. Cancer, vol. 3, páginas 903-911 (2003)

documento no patente 15: Am. J. Med. Gen., vol. 123A, páginas 5-28 (2003)

documento no patente 16: Nature, vol. 425, páginas 846-851 (2003)

documento no patente 17: Nature, vol. 425, páginas 851-856 (2003)

documento no patente 18: Trends Cell Biol., vol. 17, páginas

438-227 (2007)

documento no patente 19: Development, vol. 128, páginas 5201-5212 (2001)

documento no patente 20: Proc. Natl. Acad. Sci. U.S.A., vol. 100, páginas 4616-4621 (2003)

documento no patente 21: Proc. Natl. Acad. Sci. U.S.A., vol. 99, páginas 14071-14076 (2002)

Descripción de la invención

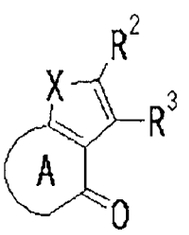
Problemas que se resolverán mediante la invención

Un objetivo de la presente invención es proporcionar un compuesto que tiene una actividad inhibidora de Smo superior, baja toxicidad y es suficientemente satisfactorio como un producto farmacéutico.

Los presentes inventores han conducido estudios intensivos en un intento para resolver los problemas mencionados con anterioridad y encontraron que un compuesto representado por la siguiente fórmula y una sal de lo mismo de lo mismo tiene actividad inhibidora de Smo superior, que produjo la compleción de la presente invención.

En consecuencia, la presente invención proporciona lo siguiente.

[1] Un compuesto representado por la fórmula



(I)

en donde

el anillo A es un anillo que tiene de 5 a 7 miembros opcionalmente sustituidos, donde opcionalmente sustituidos están enlazados entre sí para formar un anillo;

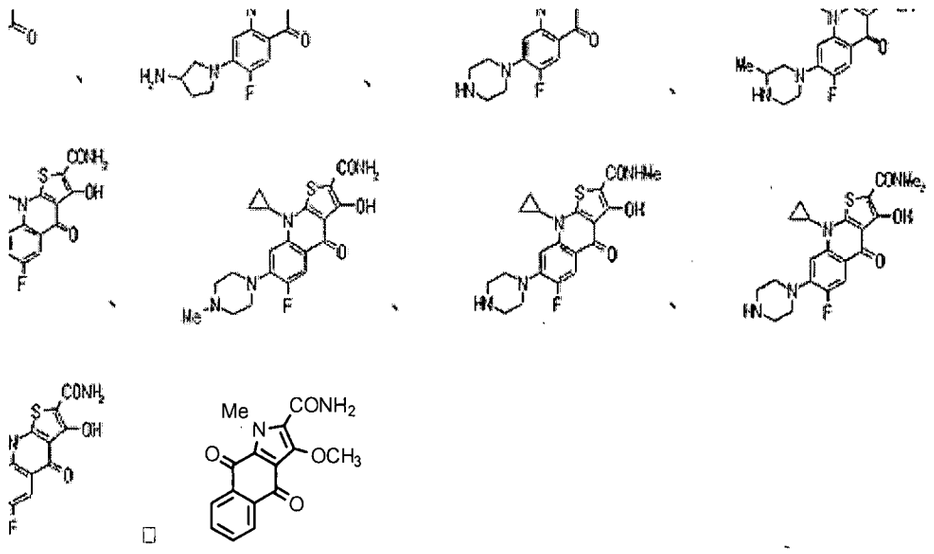
X es O, S o NR^1 (R^1 es un átomo de hidrógeno o un grupo

hidrocarburo que esta opcionalmente sustituido);

R^2 es carbamoilo que esta opcionalmente sustituido; y

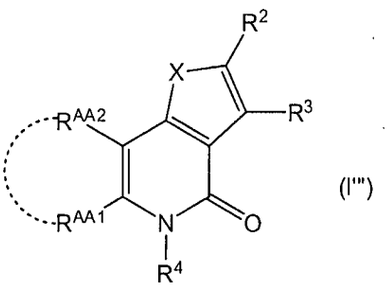
R^3 es hidroxi que esta opcionalmente sustituido,

excepto los siguientes compuestos;



(en ocasiones de aquí en adelante abreviado como compuesto (I)) o una sal de lo mismo de lo mismo.

[2] El compuesto del punto antes mencionado [1], que está representado por la fórmula



(I'")

en donde

X, R^2 y R^3 son como se definen en el punto antes mencionado [1],

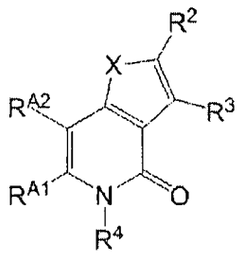
R^{AA1} y R^{AA2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, o R^{AA1} y R^{AA2} están unidos opcionalmente entre sí para formar un anillo de 5 a 7 miembros que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido

(en ocasiones de aquí en adelante abreviado como compuesto (I"')).

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[3] El compuesto del punto antes mencionado [2], el cual es representado por la fórmula



(I")

en donde

X, R^2 y R^3 son como se definen en el punto antes mencionado [1],

R^{A1} y R^{A2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido

(en ocasiones de aquí en adelante abreviado como compuesto (I")).

[4] El compuesto del punto antes mencionado [3], en donde X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

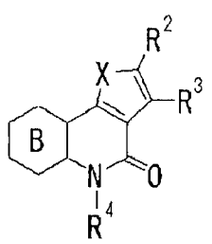
R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido,

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono,

R^{A2} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono, y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido.

[5] El compuesto del punto antes mencionado [1], que está representado por la fórmula



(I')

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en donde

X, R^2 y R^3 son como se definen en el punto antes mencionado [1],

el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido

(en ocasiones de aquí en adelante abreviado como compuesto (I')).

[6] El compuesto del punto antes mencionado [5], en donde el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido,

X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido.

[7] N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida o una sal de lo mismo.

[8] N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida o una sal de lo mismo.

[9] 3-etoxi-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal de lo mismo.

[10] N-[1-(hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal de lo mismo.

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[11] 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal de lo mismo.

[12] Un profármaco del compuesto del punto antes mencionado [1].

[13] Un agente farmacéutico que comprende el compuesto del punto antes mencionado [1] o uno de sus profármacos.

[14] El agente farmacéutico del punto antes mencionado [13], que es un inhibidor de Smo.

[15] El agente farmacéutico del punto antes mencionado [13], que es un agente para la profilaxis o el tratamiento del cáncer.

[16] Un método de inhibición de Smo en un mamífero, que comprende administrar una cantidad efectiva del compuesto del punto antes mencionado [1] o uno de sus profármacos para el mamífero.

[17] Un método para prevenir o tratar el cáncer en un mamífero, que comprende administrar una cantidad efectiva del compuesto del punto antes mencionado [1] o uno de sus profármacos para el mamífero.

[18] El uso del compuesto del punto antes mencionado [1] o uno de sus profármacos para la producción de un inhibidor de Smo.

[19] El uso del compuesto del punto antes mencionado [1] o uno de sus profármacos para la producción de un agente para la profilaxis o el tratamiento del cáncer.

En la presente especificación, el compuesto (I) comprende el compuesto (I'), el compuesto (I") y el compuesto (I"').

(Efecto de la invención)

Dado que el compuesto de la presente invención tiene una fuerte acción inhibidora de Smo, puede proporcionar un agente

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clínicamente útil para la profilaxis o el tratamiento del cáncer, un inhibidor del crecimiento del cáncer y un agente supresor de metástasis del cáncer.

(Descripción detallada de la invención)

La presente invención se explica en detalle con lo siguiente.

En el compuesto (I), X es O, S o NR^1 (R^1 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido).

Ejemplos del "grupo hidrocarburo que esta opcionalmente sustituido" para R^1 incluyen alquilo que esta opcionalmente sustituido, alquenilo que esta opcionalmente sustituido, alquinilo que esta opcionalmente sustituido, cicloalquilo que esta opcionalmente sustituido, arilo que esta opcionalmente sustituido y similares.

Ejemplos de "alquilo" del antes mencionado "alquilo que esta opcionalmente sustituido" incluyen alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*-butilo, *terc*-butilo, pentilo, hexilo) y similares.

Ejemplos del sustituyente que el antes mencionado "alquilo que esta opcionalmente sustituido" pueden incluir siguiente "grupo constituyente A" y similares, y 1 a 5 (preferiblemente 1 a 3) sustituyentes pueden estar presentes en posición(es) sustituibles:

(grupo sustituyente A)

(1) átomo de halógeno (por ejemplo, átomo de flúor, cloro, e bromo, átomo de yodo),

(2) ciano,

(3) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*-butilo, *terc*-butilo, pentilo, hexilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(1') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo, naftilo),

(2') amino,

(3') alcoxi de 1 a 6 átomos de carbono -carbonilamino (por ejemplo, metoxicarbonilamino, etoxicarbonilamino, propoxicarbonilamino),

(4') hidroxi,

(5') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi, propoxi), y

(6') grupo heterocíclico (por ejemplo, pirrolidinilo, benzodioxolilo),

(4) alquenilo de 2 a 6 átomos de carbono (por ejemplo, vinilo, alilo),

(5) alquinilo de 2 a 6 átomos de carbono (por ejemplo, etinilo, propargilo),

(6) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo) que tiene opcionalmente un hidroxi,

(7) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo, naftilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, átomo de flúor, átomo de cloro),

(b) hidroxi,

(c) ciano,

(d) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo), y

(e) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi, propoxi) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor),

(8) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo,

acetilo, etilcarbonilo, propilcarbonilo, butilcarbonilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(1') hidroxi,

(2') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi),

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, metilamino, etilamino, propilamino, isopropilamino),

(5') alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo), y

(6') alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(9) arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo, naftoilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

a) átomo de halógeno (por ejemplo, átomo de cloro), y

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(10) carbamoilo,

(11) alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbamoilo, etilcarbamoilo) que tiene opcionalmente un hidroxi,

(12) di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dimetilcarbamoilo, dietilcarbamoilo),

(13) arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo, naftilcarbamoilo),

(14) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-piperazinilcarbonilo, 4-morfolinilcarbonilo, 4-tiomorfolinilcarbonilo, 1-homopiperazinilcarbonilo),

(15) carboxilo,

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(16) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilo, etoxicarbonilo, butoxicarbonilo),

(17) ariloxicarbonilo de 6 a 10 átomos de carbono (por ejemplo, fenoxicarbonilo),

(18) amino que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(b) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un hidroxi o alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(19) alquilamino de 1 a 6 átomos de carbono (por ejemplo, metilamino, etilamino, propilamino, isopropilamino, butilamino),

(20) di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino, dipropilamino) que tiene opcionalmente un hidroxi,

(21) alquilcarbonilamino de 1 a 6 átomos de carbono (por ejemplo, acetilamino, etilcarbonilamino) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(a) alquilcarbonilo de 1 a 6 átomos de carbono-oxi (por ejemplo, metilcarboniloxi),

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(c) hidroxi,

(22) di-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, di-(acetil)amino, di-(etilcarbonil)amino, di-(propilcarbonil)amino),

(23) alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilamino, etoxicarbonilamino, propoxicarbonilamino, *terc*-butoxicarbonilamino),

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(24) N-alquilo de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-metilamino, N-acetil-N-etilamino),

(25) ureido,

(26) alquilo-ureido de 1 a 6 átomos de carbono (por ejemplo, metilureido, etilureido),

(27) hidroxi,

(28) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, *sec*-butoxi, *terc*-butoxi) que tiene opcionalmente 1 a 3 arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

(29) ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi, naftoxi),

(30) grupo heterocíclico (por ejemplo, grupo heterocíclico aromático de 5 ó 6 miembros tales como 1-pirrolilo, 2-piridilo, 3-piridilo, 4-piridilo, 1-pirazolilo, 1-imidazolilo, 2-imidazolilo, 2-pirazinilo, 2-furilo, 2-thiazolilo, 4-pirimidinilo y similares; grupo heterocíclico no aromático de 3 u 8 miembros tales como 3-azetidinilo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, morfolino, 2-tetrahidrofurilo, tetrahidrotiopiran-4-ilo, tetrahidropiran-4-ilo, 3-azepanilo, 4-azepanilo y similares; un grupo obtenido por fusión de grupo heterocíclico no aromático tales como 1,3-benzodioxol-5-ilo y similares y un anillo de benceno) que tiene opcionalmente 1 a 3 (preferiblemente 1 ó 2) sustituyentes seleccionados de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, átomo de flúor), y

(b) hidroxi,

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(2') hidroxi,

(3') oxo,

(4') ciano,

(5') carbamoilo,

(6') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(7') alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbamoilo),

(8') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(9') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente 1 a 3 sustituyentes seleccionados de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi, propoxi),

(c) amino,

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, metilamino, etilamino, propilamino, isopropilamino),

(e) di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino), y

(f) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(31) oxo,

(32) tioxo,

(33) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo),

(34) heterociclil-carbonil (por ejemplo, pirrolidinilcarbonilo, tetrahidrofurilcarbonilo).

Ejemplos de "alquenilo" del antes mencionado "alquenilo que esta opcionalmente sustituido" incluyen alquenilo de 2 a 6 átomos

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de carbono (por ejemplo, vinilo, alilo) y similares.

Ejemplos del sustituyente del antes mencionado "alquenilo que esta opcionalmente sustituido" incluyen el grupo sustituyente A antes mencionado y similares, y 1 a 5 (preferiblemente 1 a 3) sustituyentes pueden estar presentes en posición(es) sustituibles.

Ejemplos de "alquinilo" del antes mencionado "alquinilo que esta opcionalmente sustituido" incluyen alquinilo de 2 a 6 átomos de carbono (por ejemplo, etinilo, propargilo) y similares.

Ejemplos del sustituyente que el antes mencionado "alquinilo que esta opcionalmente sustituido" pueden incluir el grupo sustituyente A antes mencionado y similares, y 1 a 5 (preferiblemente 1 a 3) sustituyentes pueden estar presentes en posición(es) sustituibles.

Ejemplos de "cicloalquilo" del antes mencionado "cicloalquilo que esta opcionalmente sustituido" incluyen cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo) y similares.

Ejemplos del sustituyente que el antes mencionado "cicloalquilo que esta opcionalmente sustituido" pueden incluir

(1) el grupo sustituyente A antes mencionado,

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados del grupo sustituyente A antes mencionado

y similares, y 1 a 5 (preferiblemente 1 a 3) sustituyentes pueden estar presentes en posición(es) sustituibles.

Más aun, el "cicloalquilo que esta opcionalmente sustituido" puede ser un grupo obtenido por fusión de cicloalquilo de 3 a 6 átomos de carbono y un anillo de benceno (por ejemplo, 1,2,3,4-tetrahidronaftalen-1-ilo).

Ejemplos de "arilo" del antes mencionado "arilo que esta opcionalmente sustituido" incluyen arilo de 6 a 10 átomos de

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carbono (por ejemplo, fenilo, naftilo) y similares.

Ejemplos del sustituyente que el antes mencionado "arilo que esta opcionalmente sustituido" pueden incluir

(1) el grupo sustituyente A antes mencionado (excepto oxo y tioxo),

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados de el grupo sustituyente A antes mencionado

y similares, y 1 a 5 (preferiblemente 1 a 3) sustituyentes pueden estar presentes en posición(es) sustituibles.

X es preferiblemente O, S o $NR^{1'}$ ($R^{1'}$ es alquilo que esta opcionalmente sustituido), y particularmente preferiblemente O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente, N(metilo)).

R^2 es carbamoilo que esta opcionalmente sustituido. Ejemplos de "carbamoilo que esta opcionalmente sustituido" para R^2 incluyen

(1) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de "grupo hidrocarburo que esta opcionalmente sustituido" y "grupo heterocíclico que esta opcionalmente sustituido",

(2) carbamoilo cíclico que esta opcionalmente sustituido

y similares.

Ejemplos del antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" incluyen aquellos similares al antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" para R^1.

Ejemplos del "grupo heterocíclico" del antes mencionado "grupo heterocíclico que esta opcionalmente sustituido", y el "grupo heterocíclico" mencionado como ejemplo del sustituyente que el antes mencionado "alquilo que esta opcionalmente

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sustituido" puede tener y similares incluyen grupo heterocíclico aromático y grupo heterocíclico no aromático saturado o insaturado (grupo heterocíclico alifático), cada uno contiene, como átomo constituyente del sistema anular (átomo del anillo), se usan 1 a 3 clases (preferiblemente 1 ó 2 clases) de por lo menos uno (preferiblemente 1 a 4, con mayor preferencia 1 ó 2) heteroátomos seleccionado de átomo de oxígeno, átomo de azufre (el átomo de azufre puede oxidarse) y átomo de nitrógeno, y un grupo que tiene un enlace en el átomo de carbono y similares.

Ejemplos del "grupo heterocíclico aromático" incluyen

(1) grupo heterocíclico aromático monocíclico de 5 ó 6 miembros tales como furilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, imidazolilo, pirazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, furazanilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,3,4-tiadiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo y similares, y

(2) grupo heterocíclico aromático policíclico condensado de 8 a 12 miembros tales como benzofuranilo, isobenzofuranilo, benzo[b]tienilo, indolilo, isoindolilo, 1H-indazolilo, benzimidazolilo, benzoxazolilo, 1,2-benzoisooxazolilo, benzotiazolilo, benzopiranilo, 1,2-benzoisotiazolilo, 1H-benzotriazolilo, quinolilo, isoquinolilo, cinnolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, naftiridinilo, purinilo, pteridinilo, carbazolilo, α-carbolinilo, β-carbolinilo, γ-carbolinilo, acridinilo, fenoxazinilo, fenotiazinilo, fenazinilo, fenoxatiinilo, tiantrenilo, fenantridinilo, fenantrolinilo, indolizinilo, pirrolo[1,2-b]piridazinilo, pirazolo[1,5-a]piridilo, imidazo[1,2-a]piridilo, imidazo[1,5-a]piridilo, imidazo[1,2-b]piridazinilo, imidazo[1,2-a]pirimidinilo, 1,2,4-triazolo[4,3-a]piridilo, 1,2,4-triazolo[4,3-b]piridazinilo y similares,

y similares.

Ejemplos del "grupo heterocíclico no aromático" incluyen

(1) grupo heterocíclico no aromático de 3 a 8 miembros (preferiblemente 5 ó 6 miembros) saturado o insaturado (preferiblemente saturado) (grupo heterocíclico alifático) tales como oxiranilo, azepanilo, azetidinilo, oxetanilo, tietanilo, pirrolidinilo, tetrahidrofurilo, tioranilo, piperidilo, tetrahidropiranilo, tetrahidrotiopiranilo, morfolinilo, tiomorfolinilo, piperazinilo y similares,

(2) grupo heterocíclico no aromático en donde el enlace doble en el antes mencionado grupo heterocíclico aromático monocíclico o grupo heterocíclico policíclico condensado aromático está parcial o totalmente saturado, tales como 1,2,3,4-tetrahidroquinolilo, 1,2,3,4-tetrahidroisoquinolilo y similares, y

(3) un grupo en donde el grupo heterocíclico no aromático tales como benzodioxolilo y similares y el anillo de benceno están saturados y similares.

Ejemplos del "sustituyente" del antes mencionado "grupo heterocíclico que esta opcionalmente sustituido" incluyen

(1) el grupo sustituyente A antes mencionado,

(2) aquellos similares al antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" (preferiblemente alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados del grupo sustituyente A antes mencionado)

y similares, y sustituyentes en un modo susceptible de sustitución pueden estar presentes en posición(es) sustituibles.

Como carbamoilo cíclico del "carbamoilo cíclico que esta opcionalmente sustituido", se usa carbamoilo cíclico de 5 a 7 miembros, y ejemplos de éstos incluyen pirrolidin-1-ilcarbonilo, piperidin-1-ilcarbonilo, piperazin-1-ilcarbonilo, morfolin-4-

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ilcarbonilo, tiomorfolin-4-ilcarbonilo, homopiperazin-1-ilcarbonil y similares.

Ejemplos del "sustituyente" del "carbamoilo cíclico que esta opcionalmente sustituido" incluyen el grupo sustituyente A antes mencionado y similares, y 1 a 3 sustituyentes pueden estar presentes en posición(es) sustituibles.

Además, los sustituyentes del carbamoilo cíclico que esta opcionalmente sustituido pueden estar unidos entre sí para formar un anillo de 5 a 7 miembros. En otras palabras, el anillo de 5 a 7 miembros y carbamoilo cíclico pueden formar un sistema anular fusionado. El sistema anular fusionado incluye un sistema anular fusionado espiro.

Ejemplos de anillo de 5 a 7 miembros incluyen

(1) anillo homocíclico de 5 a 7 miembros (por ejemplo, ciclohexano, ciclohexeno, ciclohexanodieno, cicloheptano, benceno), y

(2) heterociclo de 5 a 7 miembros (por ejemplo, piperidina, piperazina, morfolina, tiomorfolina, piridina, pirazina, pirimidina, piridazina, triazina, piran, dihidropirano, tetrahidropirano, 1,3-dioxol). Entre estos, se prefieren anillo ciclohexano, anillo de benceno y anillo de 1,3-dioxol.

Como R^2,

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 ó 2 (preferiblemente 1) sustituyentes seleccionados de

(1') átomo de halógeno,

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono,

(5') di-alquilamino de 1 a 6 átomos de carbono que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono,

(7') hidroxi,

(8') di-alquil de 1 a 6 átomos de carbono-carbamoilo,

(9') de 5 a 7 miembros carbamoilo cíclico,

(10') grupo heterocíclico que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) hidroxi,

(b) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un hidroxi,

(c) oxo,

(d) alcoxicarbonilo de 1 a 6 átomos de carbono, y

(e) alquilcarbonilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de alquilcarboniloxi de 1 a 6 átomos de carbono e hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono,

(12') cicloalquilo de 3 a 6 átomos de carbono que tiene opcionalmente un hidroxi,

(13') alcoxi de 1 a 6 átomos de carbono,

(14') alquinilo de 2 a 6 átomos de carbono,

(15') arilo de 6 a 10 átomos de carbono que tiene opcionalmente 1 a 3 (preferiblemente 1 ó 2) alcoxi de 1 a 6 átomos de carbono,

(16') carbamoilo, y

(17') alquilcarbonilo de 1 a 6 átomos de carbono-amino que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono,

(b) alcoxi de 1 a 6 átomos de carbono, y

(c) hidroxi,

(2) cicloalquilo de 3 a 6 átomos de carbono o 1,2,3,4-tetrahidronaftalenilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino que tiene opcionalmente un sustituyente seleccionado de

(a) alcoxicarbonilo de 1 a 6 átomos de carbono, y

(b) alquilcarbonilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de hidroxi y alquilcarboniloxi de 1 a 6 átomos de carbono,

(2') hidroxi,

(3') carboxi,

(4') alcoxicarbonilo de 1 a 6 átomos de carbono,

(5') alquilcarbamoilo de 1 a 6 átomos de carbono que tiene opcionalmente un hidroxi,

(6') alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un hidroxi, y

(7') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(3) arilo de 6 a 10 átomos de carbono, y

(4) grupo heterocíclico que tiene opcionalmente 1 a 4 (preferiblemente 1) sustituyentes seleccionados de

(1') alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 5 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono,

(b) hidroxi, y

(c) átomo de halógeno,

(2') alquilcarbonilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono,

(b) hidroxi,

(c) alcoxi de 1 a 6 átomos de carbono,

(d) alquilsulfonilo de 1 a 6 átomos de carbono, y

(e) amino,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono, y

(4') grupo heterocíclico aromático de 5 ó 6 miembros que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 átomos de halógeno,

(b) ciano,

(c) carbamoilo,

(d) alcoxi de 1 a 6 átomos de carbono, y

(e) alquilcarbamoilo de 1 a 6 átomos de carbono,

(5') oxo,

(6') alquilcarbamoilo de 1 a 6 átomos de carbono,

(7') alquilsulfonilo de 1 a 6 átomos de carbono,

(8') arilo de 6 a 10 átomos de carbono que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) hidroxi,

(b) ciano, y

(c) alquilsulfonilo de 1 a 6 átomos de carbono,

(9') heterociclil-carbonilo, y

(10') ariloxicarbonilo de 6 a 10 átomos de carbono (por ejemplo, fenoxicarbonilo),

(B) carbamoilo cíclico de 5 a 7 miembros que tiene opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono que tiene

opcionalmente 1 a 3 (preferiblemente 1) sustituyentes seleccionados de

(a) grupo heterocíclico,

(b) amino,

(c) alcoxi de 1 a 6 átomos de carbono, y

(d) arilo de 6 a 10 átomos de carbono,

(2) amino que tiene opcionalmente un alquilcarbonilo de 1 a 6 átomos de carbono,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino,

(4) grupo heterocíclico,

(5) alquilcarbonilo de 1 a 6 átomos de carbono que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono,

(c) amino,

(d) alquilamino de 1 a 6 átomos de carbono,

(e) di-alquilamino de 1 a 6 átomos de carbono, y

(f) alquilcarboniloxi de 1 a 6 átomos de carbono,

(6) arilo de 6 a 10 átomos de carbono, y

(7) oxo, o

(C) carbamoilo cíclico de 5 a 7 miembros fusionado con un anillo de 5 a 7 miembros

son los preferidos.

R^3 es hidroxi que esta opcionalmente sustituido. Como el "sustituyente" del "hidroxi que esta opcionalmente sustituido" para R^3, el antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" para R^1, el antes mencionado "grupo heterocíclico que esta opcionalmente sustituido" y similares pueden mencionarse.

Como R^3, hidroxi que tiene opcionalmente alquilo que tiene

sustituyente(s) se prefiere opcionalmente,

hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono,

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 5 (preferiblemente 1 a 3) átomos de halógeno,

(3) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un arilo de 6 a 10 átomos de carbono, o

(4) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un grupo heterocíclico

se prefiere más, e

hidroxi sustituido por

(1) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono,

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 5 (preferiblemente 1 a 3) átomos de halógeno,

(3) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un arilo de 6 a 10 átomos de carbono, o

(4) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un grupo heterocíclico

se prefiere aun más.

El anillo A es un anillo de 5 a 7 miembros que esta opcionalmente sustituido. Como el anillo "de 5 a 7 miembros" del anillo "de 5 a 7 miembros que esta opcionalmente sustituido" para el anillo A,

(1) anillo homocíclico de 5 a 7 miembros (por ejemplo, ciclohexano, ciclohexeno, ciclohexanodieno, cicloheptano, benceno), y

(2) heterociclo de 5 a 7 miembros (por ejemplo, piperidina, piperazina, morfolina, tiomorfolina, piridina, pirazina, pirimidina, piridazina, triazina, piran, dihidropirano, tetrahidropirano, 1,3-

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dioxol)

pueden mencionarse.

Ejemplos del "sustituyente" que el "anillo de 5 a 7 miembros" del "anillo de 5 a 7 miembros que esta opcionalmente sustituido" para el anillo A pueden incluir

(1) el grupo sustituyente A antes mencionado,

(2) aquellos similares al antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" (preferiblemente, alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados del grupo sustituyente A antes mencionado)

y similares, y sustituyentes en un modo susceptible de sustitución pueden estar presentes en posición(es) sustituibles.

Además, respecto del "sustituyente" que el "anillo de 5 a 7 miembros" del "anillo de 5 a 7 miembros que esta opcionalmente sustituido" para el anillo A puede tener, dos sustituyentes están unidos opcionalmente entre sí para formar un anillo. Como el anillo formado por tales "sustituyentes" unidos entre sí,

(1) homocíclico de 5 a 7 miembros anillo (por ejemplo, ciclohexano, ciclohexeno, ciclohexanodieno, cicloheptano, benceno), y

(2) de 5 a 7 miembros heterociclo (por ejemplo, piperidina, piperazina, morfolina, tiomorfolina, piridina, pirazina, pirimidina, piridazina, triazina, pirano, dihidropirano, tetrahidropirano, 1,3-dioxol)

pueden mencionarse.

El anillo formado por los sustituyentes del anillo A, que están unidos entre sí, puede tener sustituyente(s) y algunos ejemplos del sustituyente incluyen

(1) el grupo sustituyente A antes mencionado,

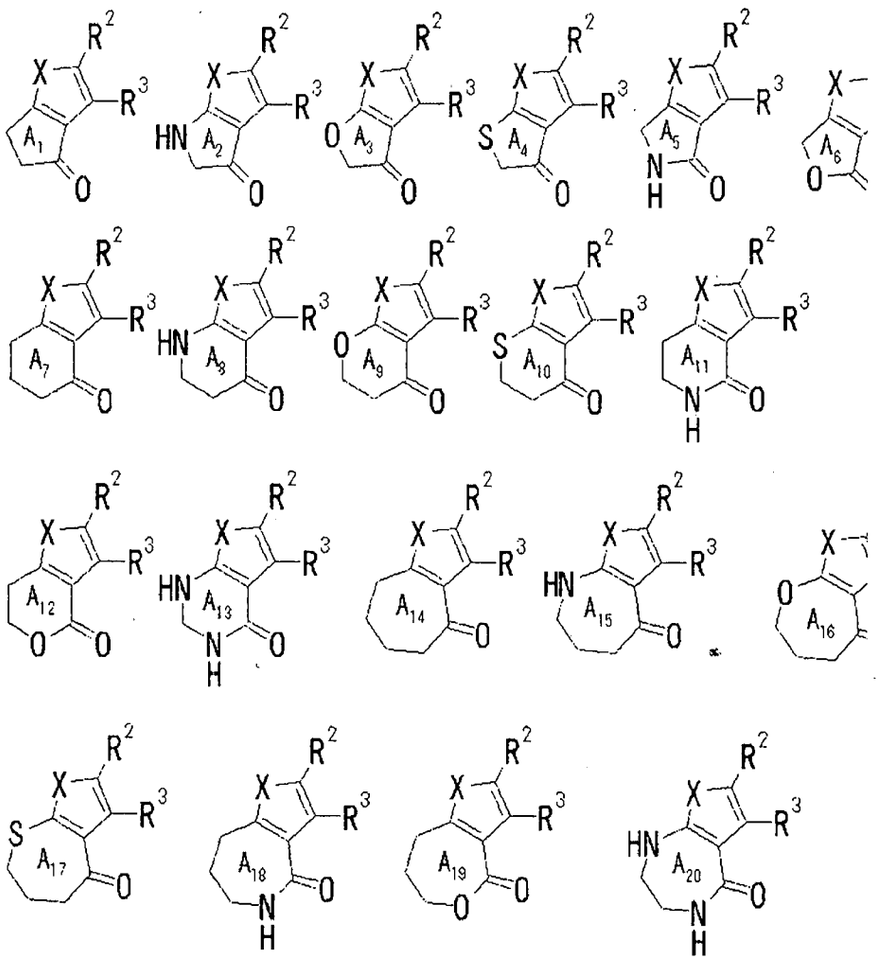
(2) aquellos similares al antes mencionado "grupo

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hidrocarburo que esta opcionalmente sustituido" (preferiblemente alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados del grupo sustituyente A antes mencionado)

y similares, y sustituyentes en un modo susceptible de sustitución pueden estar presentes en posición(es) sustituibles.

El Compuesto (I) en forma específica tiene una estructura representada por la siguiente fórmula.

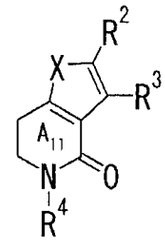


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en donde el anillo A_1 - el anillo A_{20} opcionalmente en forma adicional tienen sustituyente(s), los sustituyentes están unidos opcionalmente entre sí para formar un anillo, $-CH_2-CH_2-$ parte constituyente del anillo en el anillo A_1, el anillo A_7, el anillo A_8, el anillo A_9, el anillo A_{10}, el anillo A_{11}, el anillo A_{12}, el anillo A_{14}, el anillo A_{15}, el anillo A_{16}, el anillo A_{17}, el anillo A_{18}, el anillo A_{19} y el anillo A_{20} se convierte opcionalmente en -CH=CH-, $-NH-CH_2-$ parte constituyente del anillo en el anillo A_2, el anillo A_5, el anillo A_8, el anillo A_{11}, el anillo A_{13}, el anillo A_{15}, el anillo A_{18} y el anillo A_{20} se convierte opcionalmente en -N=CH-, y otros símbolos son como se definió con anterioridad.

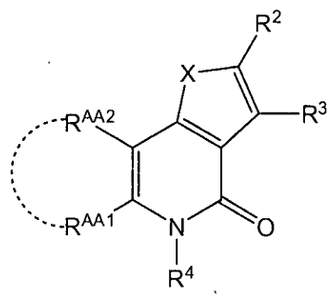
Como el sustituyente que el anillo A_1 - el anillo A_{20} puede tener, aquellos similares al "sustituyente" que el "anillo de 5 a 7 miembros" del "anillo de 5 a 7 miembros que esta opcionalmente sustituido" para el anillo A puede tener pueden mencionarse.

Como compuesto (I), un compuesto representado por la fórmula



en donde cada símbolo es como se definió con anterioridad, es preferible.

De los compuestos antes mencionados, el compuesto (I"') representado por la fórmula



(I"')

en donde X, R^2 y R^3 son como se les definió con

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anterioridad, R^{AA1} y R^{AA2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, o R^{AA1} y R^{AA2} están unidos opcionalmente entre sí para formar un anillo de 5 a 7 miembros que esta opcionalmente sustituido, y R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido, es preferible.

El Compuesto (I"') se explica en detalle a continuación.

X, R^2 y R^3 son como se les definió con anterioridad.

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido. Como el "grupo hidrocarburo que esta opcionalmente sustituido" para R^4, aquellos similares al antes mencionado "grupo hidrocarburo que esta opcionalmente sustituido" para R^1 pueden mencionarse.

Como R^4, un átomo de hidrógeno o alquilo que tiene sustituyente(s) se prefiere opcionalmente. Particularmente,

(1) átomo de hidrógeno,

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono,

(2') arilo de 6 a 10 átomos de carbono que tiene opcionalmente (i) 1 ó 2 alcoxi de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 átomos de halógeno o (ii) 1 a 3 átomos de halógeno,

(3') alquilcarbonilo de 1 a 6 átomos de carbono,

(4') arilcarbonilo de 6 a 10 átomos de carbono que tiene opcionalmente un átomo de halógeno o alcoxi de 1 a 6 átomos de carbono,

(5') alcoxicarbonilo de 1 a 6 átomos de carbono,

(6') arilcarbamoilo de 6 a 10 átomos de carbono,

(7') grupo heterocíclico que tiene opcionalmente 1 ó 2 alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3

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átomos de halógeno,

(8') ariloxi de 1 a 6 átomos de carbono,

(9') carboxi,

(10') ciano, y

(11') alcoxi de 1 a 6 átomos de carbono que tiene opcionalmente un arilo de 6 a 10 átomos de carbono,

(3) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 átomos de halógeno

y similares son preferibles.

(1) R^{AA1} y R^{AA2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente. Como el sustituyente, aquellos similares al antes mencionado sustituyente para el anillo A pueden mencionarse.

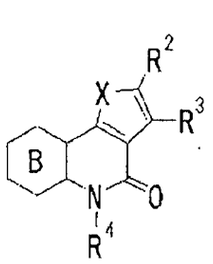
Como R^{AA1}, un átomo de hidrógeno o grupo alquilo de 1 a 6 átomos de carbono es preferible.

Como R^{AA2}, un átomo de hidrógeno o grupo alquilo de 1 a 6 átomos de carbono es preferible.

En forma alternativa,

(2) R^{AA1} y R^{AA2} estan unidos entre sí para formar un anillo de 5 a 7 miembros que esta opcionalmente sustituido. Como el "anillo de 5 a 7 miembros que esta opcionalmente sustituido", aquellos similares al antes mencionado "anillo de 5 a 7 miembros que esta opcionalmente sustituido" para el anillo A pueden mencionarse. El anillo de 5 a 7 miembros opcionalmente tiene un modo susceptible de sustitución de sustituyentes en posiciones que pueden sustituirse.

En una modalidad, el compuesto (I') representado por la fórmula



(I')

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en donde X, R^2 y R^3 son como se les definió con anterioridad, el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido, y R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido, en donde R^{AA1} y R^{AA2} están unidos entre sí para formar un anillo de 6 miembros que esta opcionalmente sustituido, es preferible de entre los compuestos antes mencionados (I"').

El Compuesto (I') se explica en detalle a continuación.

X, R^2, R^3 y R^4 son como se les definió con anterioridad.

En la fórmula (I'), algunos ejemplos preferibles de R^2 incluyen

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, n-butilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo, 1-etilpropilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino, di-i-propilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

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(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, morfolino, 2-piridilo, 3-piridilo, 4-piridilo, 2-pirazinilo, 2-furilo, 2-tetrahidrofurilo, 1,3-benzodioxol-5-ilo) que tiene opcionalmente un

(a) hidroxi,

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(c) oxo,

(d) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), o

(e) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi) y hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo) que tiene opcionalmente un hidroxi,

(13') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, i-propoxi),

(14') alquinilo de 2 a 6 átomos de carbono (por ejemplo, etinilo),

(15') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente 1 ó 2 alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(16') carbamoilo, y

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(17') alquilcarbonilo de 1 a 6 átomos de carbono-amino (por ejemplo, metilo carbonilamino) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarbonilo de 1 a 6 átomos de carbono-oxi (por ejemplo, metilcarboniloxi),

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(c) hidroxi,

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo) o 1,2,3,4-tetrahidronaftalenilo (por ejemplo, 1,2,3,4-tetrahidronaftalen-1-ilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino que tiene opcionalmente un sustituyente seleccionado de

(a) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(b) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un hidroxi o alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(2') hidroxi,

(3') carboxi,

(4') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilo),

(5') alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, etilcarbamoilo) que tiene opcionalmente un hidroxi,

(6') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente un hidroxi, y

(7') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

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y

(4) grupo heterocíclico (por ejemplo, 3-azetidinilo, 3-pirrolidinilo, 4-piperidilo, 2-tetrahidrofurilo, 3-azepanilo, 4-azepanilo, tetrahidrotiopiran-4-ilo, tetrahidropiran-4-ilo) que tiene opcionalmente 1 a 4 sustituyentes seleccionados de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo) que tiene opcionalmente 1 a 5 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

(b) hidroxi, y

(c) átomo de halógeno,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo, etilcarbonilo, i-propilcarbonilo, i-butilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(b) hidroxi,

(c) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(d) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo), y

(e) amino,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo),

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo, 2-tiazolilo, 4-pirimidinilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilo de 1 a 6 átomos de carbono (por ejemplo,

metilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor),

(b) ciano,

(c) carbamoilo,

(d) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(e) alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbamoilo),

(5') oxo,

(6') alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, etilcarbamoilo),

(7') alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo),

(8') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) ciano, y

(c) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo),

(9') heterociclil-carbonil (por ejemplo, 2-pirrolidinilcarbonilo, 2-tetrahidrofurilcarbonilo), y

(10') ariloxicarbonilo de 6 a 10 átomos de carbono (por ejemplo, fenoxicarbonilo),

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-piperazinilcarbonilo, 1-homopiperazinilcarbonilo, morfolinocarbonilo, tiomorfolinocarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo,

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benzodioxol-5-ilo),

(b) amino,

(c) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(d) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

(2) amino que tiene opcionalmente un alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo),

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-piridilo),

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi),

(c) amino,

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(e) di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino), y

(f) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(6) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(7) oxo, y

(C) carbamoilo cíclico de 5 a 7 miembros fusionado con anillo de 5 a 7 miembros (por ejemplo, anillo de ciclohexano,

anillo de benceno, anillo 1,3-dioxol) (por ejemplo, 1-piperidilcarbonilo).

En la fórmula (I'), algunos ejemplos preferibles de R^3 incluyen hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-butilo) que tiene opcionalmente un

(a) alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi),

(b) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), o

(c) grupo heterocíclico (por ejemplo, 4-piridilo, morfolino, 2-tetrahidrofurilo), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxi sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-butilo) que tiene opcionalmente un

(a) alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi),

(b) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), o

(c) grupo heterocíclico (por ejemplo, 4-piridilo, morfolino, 2-tetrahidrofurilo), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)].

En la fórmula (I'), algunos ejemplos preferibles de R^4 incluyen

(1) átomo de hidrógeno,

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo,

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etilo, n-propilo, n-butilo, n-pentilo, i-pentilo, 2-etilbutilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente (i) un alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor) o (ii) 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor, átomo de cloro),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilo, etoxicarbonilo, *terc*-butoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo, 1-pirrolilo, 2-imidazolilo, 2-furilo, 2-tetrahidrofurilo) que tiene opcionalmente 1 ó 2 alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi),

(9') carboxi,

(10') ciano, y

(11') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi) que tiene opcionalmente un arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(3) alquilo de 1 a 6 átomos de carbono (por ejemplo, etilo)

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que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor).

El anillo B es un anillo de 6 miembros que esta opcionalmente sustituido. Como el "anillo de 6 miembros" del "anillo de 6 miembros que esta opcionalmente sustituido",

(1) anillo homocíclico (por ejemplo, ciclohexano, ciclohexeno, ciclohexanodieno, benceno), y

(2) heterociclo (por ejemplo, piperidina, piperazina, morfolina, tiomorfolina, piridina, pirazina, pirimidina, piridazina, triazina, pirano, dihidropirano, tetrahidropirano)

pueden mencionarse.

Ejemplos del sustituyente que el anillo B puede incluir

(1) el grupo sustituyente A antes mencionado,

(2) alquilo de 1 a 6 átomos de carbono que tiene opcionalmente 1 a 3 sustituyentes seleccionados de el grupo sustituyente A antes mencionado

y similares, y sustituyentes en un modo susceptible de sustitución pueden estar presentes en posición(es) sustituibles.

Como el anillo B, ciclohexeno anillo que esta opcionalmente sustituido, anillo de benceno que esta opcionalmente sustituido, o anillo de piridina que tiene sustituyente(s) se prefiere opcionalmente, y el anillo ciclohexeno, anillo de benceno que tiene opcionalmente un átomo de halógeno (por ejemplo, átomo de flúor), o anillo de piridina se prefiere más. Particularmente, anillo de benceno y el anillo de piridina son preferibles.

De los compuestos (I'), un compuesto en donde

el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido,

X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6

átomos de carbono que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido

es preferible.

Ejemplos específicos de compuesto preferible (I') incluyen los siguientes.

[Compuesto (I'-1)]

Compuesto (I') en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente N(metilo));

R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, 2,2-dimetilpropilo, 1-metilbutilo) que tiene opcionalmente un sustituyente seleccionado de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, 2-piridilo, 3-piridilo) que tiene opcionalmente un

(a) hidroxi, o

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi, y

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino, y

(2') hidroxi,

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(4) grupo heterocíclico (por ejemplo, 3-pirrolidinilo, 4-piperidilo) que tiene opcionalmente un alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(b) hidroxi, o

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-homopiperazinilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo), y

(b) amino,

(2) amino,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo), y

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(c) amino, y

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino);

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi);

R^4 es

(1) átomo de hidrógeno, o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por

ejemplo, benzoilo),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi), y

(9') carboxi; y

el anillo B es anillo de benceno.

[Compuesto (I'-2)]

Compuesto (I') en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente N(metilo));

R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

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(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, 2-piridilo, 3-piridilo) que tiene opcionalmente un (a) hidroxi, o (b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo), y

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo),

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino, y

(2') hidroxi,

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(4) grupo heterocíclico (por ejemplo, 3-pirrolidinilo, 4-piperidilo) que tiene opcionalmente un sustituyente seleccionado de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(b) hidroxi,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi), y

(b) hidroxi,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 4-piridilo), o

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-homopiperazinilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo), y

(b) amino,

(2) amino,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo), y

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(c) amino, y

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(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino);

R^3 es hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxilo sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)];

R^4 es

(1) átomo de hidrógeno, o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi), y

(9') carboxi; y

el anillo B es ciclohexeno anillo o anillo de benceno (particularmente, anillo de benceno).

[Compuesto (I'-3)]

Compuesto (I') en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente N(metilo));

R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, n-butilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo, 1-etilpropilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino, di-i-propilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono

(por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, morfolino, 2-piridilo, 3-piridilo, 4-piridilo, 2-pirazinilo, 2-furilo, 2-tetrahidrofurilo, 1,3-benzodioxol-5-ilo) que tiene opcionalmente un

(a) hidroxi,

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(c) oxo,

(d) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), o

(e) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi) y hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo) que tiene opcionalmente un hidroxi,

(13') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, i-propoxi),

(14') alquinilo de 2 a 6 átomos de carbono (por ejemplo, etinilo),

(15') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente 1 ó 2 alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

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(16') carbamoilo, y

(17') alquilcarbonilo de 1 a 6 átomos de carbono-amino (por ejemplo, metilcarbonilamino) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarbonilo de 1 a 6 átomos de carbono-oxi (por ejemplo, metilcarboniloxi),

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(c) hidroxi,

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo) o 1,2,3,4-tetrahidronaftalenilo (por ejemplo, 1,2,3,4-tetrahidronaftalen-1-ilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino que tiene opcionalmente un sustituyente seleccionado de

(a) alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(b) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un hidroxi o alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(2') hidroxi,

(3') carboxi,

(4') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilo),

(5') alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, etilcarbamoilo) que tiene opcionalmente un hidroxi,

(6') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente un hidroxi, y

(7') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(4) grupo heterocíclico (por ejemplo, 3-azetidinilo, 3-pirrolidinilo, 4-piperidilo, 2-tetrahidrofurilo, 3-azepanilo, 4-azepanilo, tetrahidrotiopiran-4-ilo, tetrahidropiran-4-ilo) que tiene opcionalmente 1 a 4 sustituyentes seleccionados de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo) que tiene opcionalmente 1 a 5 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

(b) hidroxi, y

(c) átomo de halógeno,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo, etilcarbonilo, i-propilcarbonilo, i-butilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(b) hidroxi,

(c) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(d) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo), y

(e) amino,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo),

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo, 2-tiazolilo, 4-pirimidinilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor),

(b) ciano,

(c) carbamoilo,

(d) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(e) alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbamoilo),

(5') oxo,

(6') alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, etilcarbamoilo),

(7') alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo),

(8') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) ciano, y

(c) alquilsulfonilo de 1 a 6 átomos de carbono (por ejemplo, metilsulfonilo),

(9') heterociclil-carbonil (por ejemplo, 2-pirrolidinilcarbonilo, 2-tetrahidrofurilcarbonilo), y

(10') ariloxicarbonilo de 6 a 10 átomos de carbono (por ejemplo, fenoxicarbonilo),

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-piperazinilcarbonilo, 1-homopiperazinilcarbonilo, morfolinocarbonilo, tiomorfolinocarbonilo) que tiene opcionalmente un grupo seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo),

(b) amino,

(c) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), y

(d) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo),

(2) amino que tiene opcionalmente un alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo),

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-piridilo),

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi, etoxi),

(c) amino,

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(e) di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino), y

(f) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi),

(6) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(7) oxo, o

(C) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-

piperidilcarbonilo) fusionado con anillo de 5 a 7 miembros (por ejemplo, anillo de ciclohexano, anillo de benceno, 1,3-dioxol anillo);

R^3 es hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-butilo) que tiene opcionalmente un

(a) alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi),

(b) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), o

(c) grupo heterocíclico (por ejemplo, 4-piridilo, morfolino, 2-tetrahidrofurilo), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxi sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-butilo) que tiene opcionalmente un

(a) alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi),

(b) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), o

(c) grupo heterocíclico (por ejemplo, 4-piridilo, morfolino, 2-tetrahidrofurilo), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)];

R^4 es

(1) átomo de hidrógeno,

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo, n-butilo, n-pentilo, i-pentilo, 2-etilbutilo) que tiene

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opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo, ciclohexilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente (i) un alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor) o (ii) 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor, átomo de cloro),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, metoxicarbonilo, etoxicarbonilo, *terc*-butoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo, 1-pirrolilo, 2-imidazolilo, 2-furilo, 2-tetrahidrofurilo) que tiene opcionalmente 1 ó 2 alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi),

(9') carboxi,

(10') ciano, y

(11') alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi) que tiene opcionalmente un arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), o

(3) alquilo de 1 a 6 átomos de carbono (por ejemplo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo,

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átomo de flúor); y

el anillo B es ciclohexeno anillo, anillo de benceno que tiene opcionalmente un átomo de halógeno (por ejemplo, átomo de flúor), o anillo de piridina (particularmente, anillo de benceno y anillo de piridina).

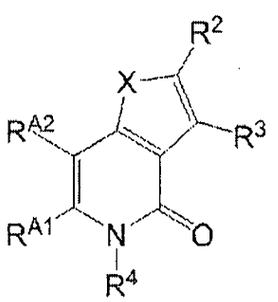
[Compuesto (I'-4)]

N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida;

N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida;

o una sal de lo mismo.

En otra modalidad, del antes mencionado compuestos (I"'), un compuesto (I") representado por la fórmula



(I")

en donde X, R^2, R^3 y R^4 son como se les definió con anterioridad, y R^{A1} y R^{A2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, es preferible.

En el siguiente, compuesto (I") se describe en detalle.

X, R^2, R^3 y R^4 son como se les definió con anterioridad.

En la fórmula (I"), algunos ejemplos preferibles de R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo) que tiene opcionalmente 1 ó 2 sustituyentes

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seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, 2-piridilo, 3-piridilo, 2-tetrahidrofurilo) que tiene opcionalmente un

(a) hidroxi, o

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo), y

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo),

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

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(1') amino, e

(2') hidroxi,

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(4) grupo heterocíclico (por ejemplo, 3-pirrolidinilo, 4-piperidilo, S-oxido-tetrahidrotiopiran-4-ilo) que tiene opcionalmente un sustituyente seleccionado de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(b) hidroxi,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi), y

(b) hidroxi,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 4-piridilo), o

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-homopiperazinilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo), y

(b) amino,

(2) amino,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo), y

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(c) amino, y

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino).

En la fórmula (I"), algunos ejemplos preferibles de R3 es hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo, i-propilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo, i-propilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxilo sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)].

En la fórmula (I"), algunos ejemplos preferibles de R^4 es

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(1) átomo de hidrógeno, o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente (i) 1 ó 2 alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi), o (ii) 1 a 3 átomos de halógeno (por ejemplo, átomo de cloro),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo) que tiene opcionalmente un átomo de halógeno (por ejemplo, átomo de cloro) o alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi), y

(9') carboxi; y

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo).

R^{A1} y R^{A2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente. Como el sustituyente, aquellos similares al sustituyente del antes mencionado el anillo A pueden mencionarse.

Como R^{A1}, un átomo de hidrógeno o grupo alquilo de 1 a 6 átomos de carbono es preferible.

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Como R^{A2}, un átomo de hidrógeno o grupo alquilo de 1 a 6 átomos de carbono es preferible.

De los compuestos (I"), un compuesto en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido,

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo),

R^{A2} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo), y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido

es preferible.

Ejemplos específicos de compuesto (I") preferible incluyen los siguientes.

[Compuesto (I"-1)]

Compuesto (I") en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente N(metilo));

R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por

ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, 2-piridilo, 3-piridilo) que tiene opcionalmente un

(a) hidroxi, o

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo), y

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo),

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino, e

(2') hidroxi,

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(4) grupo heterocíclico (por ejemplo, 3-pirrolidinilo, 4-piperidilo) que tiene opcionalmente un sustituyente seleccionado

de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(b) hidroxi,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi), y

(b) hidroxi,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 4-piridilo), o

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-homopiperazinilcarbonilo) que tiene opcionalmente un grupo seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo), y

(b) amino,

(2) amino,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo), y

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(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(c) amino, y

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino);

R^3 es hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxi sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)];

R^4 es

(1) átomo de hidrógeno, o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de

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carbono (por ejemplo, metoxi),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi), y

(9') carboxi;

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propil); y

R^{A2} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo).

[Compuesto (I"-2)]

Compuesto (I") en donde

X es O, S o N(alquilo de 1 a 6 átomos de carbono) (particularmente N(metilo));

R^2 es

(A) carbamoilo que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, propilo, isopropilo, 2-metilpropilo, 2,2-dimetilpropilo, 1-metilbutilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') átomo de halógeno (por ejemplo, átomo de flúor),

(2') ciano,

(3') amino,

(4') alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino),

(5') di-alquilamino de 1 a 6 átomos de carbono (por ejemplo, dimetilamino, dietilamino) que tiene opcionalmente un hidroxi,

(6') alcoxi-carbonilamino de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilamino),

(7') hidroxi,

(8') di-alquilcarbamoilo de 1 a 6 átomos de carbono (por ejemplo, dietilcarbamoilo),

(9') carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo),

(10') grupo heterocíclico (por ejemplo, 1-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 1-pirazolilo, 1-imidazolilo, 1-piperidilo, 2-piperidilo, 3-piperidilo, 4-piperidilo, 1-piperazinilo, 1-morfolinilo, 2-piridilo, 3-piridilo, 2-tetrahidrofurilo) que tiene opcionalmente un

(a) hidroxi, o

(b) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un hidroxi,

(11') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo), y

(12') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo),

(2) cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclohexilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(1') amino, y

(2') hidroxi,

(3) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

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(4) grupo heterocíclico (por ejemplo, 3-pirrolidinilo, 4-piperidilo, S-oxido-tetrahidrotiopiran-4-ilo) que tiene opcionalmente un sustituyente seleccionado de

(1') alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo) que tiene opcionalmente 1 ó 2 sustituyentes seleccionados de

(a) arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo), y

(b) hidroxi,

(2') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, metilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(a) alquilcarboniloxi de 1 a 6 átomos de carbono (por ejemplo, metilcarboniloxi), y

(b) hidroxi,

(3') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butoxicarbonilo), y

(4') grupo heterocíclico aromático de 5 ó 6 miembros (por ejemplo, 4-piridilo), o

(B) carbamoilo cíclico de 5 a 7 miembros (por ejemplo, 1-pirrolidinilcarbonilo, 1-piperidilcarbonilo, 1-homopiperazinilcarbonilo) que tiene opcionalmente un sustituyente seleccionado de

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(a) grupo heterocíclico (por ejemplo, 1-pirrolidinilo, benzodioxol-5-ilo), y

(b) amino,

(2) amino,

(3) N-alquil de 1 a 6 átomos de carbono-N-(alquilcarbonil de 1 a 6 átomos de carbono)amino (por ejemplo, N-acetil-N-

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etilamino),

(4) grupo heterocíclico (por ejemplo, 1-pirrolidinilo), y

(5) alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, acetilo, propionilo) que tiene opcionalmente un sustituyente seleccionado de

(a) hidroxi,

(b) alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(c) amino, y

(d) alquilamino de 1 a 6 átomos de carbono (por ejemplo, isopropilamino);

R^3 es hidroxi que tiene opcionalmente

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo, i-propilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propilo, i-propilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)

[preferiblemente, hidroxilo sustituido por

(1) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un alcoxi de 1 a 6 átomos de carbono (por ejemplo, etoxi), o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente 1 a 3 átomos de halógeno (por ejemplo, átomo de flúor)];

R^4 es

(1) átomo de hidrógeno, o

(2) alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo) que tiene opcionalmente un sustituyente seleccionado de

(1') cicloalquilo de 3 a 6 átomos de carbono (por ejemplo, ciclopropilo),

(2') arilo de 6 a 10 átomos de carbono (por ejemplo, fenilo) que tiene opcionalmente (i) 1 ó 2 alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi) o (ii) 1 a 3 átomos de halógeno (por ejemplo, átomo de cloro),

(3') alquilcarbonilo de 1 a 6 átomos de carbono (por ejemplo, *terc*-butilcarbonilo),

(4') arilcarbonilo de 6 a 10 átomos de carbono (por ejemplo, benzoilo) que tiene opcionalmente un átomo de halógeno (por ejemplo, átomo de cloro) o alcoxi de 1 a 6 átomos de carbono (por ejemplo, metoxi),

(5') alcoxicarbonilo de 1 a 6 átomos de carbono (por ejemplo, etoxicarbonilo),

(6') arilcarbamoilo de 6 a 10 átomos de carbono (por ejemplo, fenilcarbamoilo),

(7') grupo heterocíclico (por ejemplo, 2-piridilo),

(8') ariloxi de 1 a 6 átomos de carbono (por ejemplo, fenoxi), y

(9') carboxi;

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo, etilo, n-propil); y

R^{A2} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono (por ejemplo, metilo).

[Compuesto (I"-3)]

3-etoxi-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida;

N-[1-(hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida;

6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-

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c]piridin-2-carboxamida;

o una sal de lo mismo.

Cuando el compuesto (I) es una sal, algunos ejemplos de tal sal incluyen sal de metal, amonio, con base orgánica, con ácido inorgánico, con ácido orgánico, con aminoácido alcalino o ácido y similares. Algunos ejemplos preferibles de la sal de metal incluyen sal de metal alcalino tales como sal de sodio, potasio y similares; sal de metal alcalino térreo tales como sal de calcio, magnesio, bario y similares; sal de aluminio y similares. Algunos ejemplos preferibles de la sal con base orgánica incluyen una sal con trimetilamina, trietilamina, piridina, picolina, 2,6-lutidina, etanolamina, dietanolamina, trietanolamina, ciclohexilamina, diciclohexilamina, N,N'-dibenciletilendiamina y similares. Algunos ejemplos preferibles de la sal con ácido inorgánico incluyen una sal con ácido clorhídrico, bromhídrico, nítrico, sulfúrico, fosfórico y similar. Algunos ejemplos preferibles de la sal con ácido orgánico incluyen una sal con ácido fórmico, acético, trifluoroacético, ftálico, fumárico, oxálico, tartárico, maleico, cítrico, succínico, málico, metansulfónico, bencensulfónico, p-toluensulfónico y similares. Algunos ejemplos preferibles de la sal con aminoácido alcalino incluyen una sal con arginina, lisina, onitina y similares, y algunos ejemplos preferibles de la sal con aminoácido ácido incluyen una sal con ácido aspártico, glutámico y similares.

De estos, una sal farmacéuticamente aceptable es preferible. Por ejemplo, cuando un compuesto tiene un grupo funcional ácido, una sal inorgánica tales como sal de metal alcalino (por ejemplo, sal de sodio, potasio etc.), sal de metal alcalino térreo (por ejemplo, sal de calcio, magnesio etc.) y similares, amonio etc., y cuando un compuesto tiene un grupo funcional alcalino, por ejemplo, una sal con ácido inorgánico tales

como ácido clorhídrico, bromhídrico, nítrico, sulfúrico, fosfórico y similares, o una sal con ácido orgánico tales como ácido acético, ftálico, fumárico, oxálico, tartárico, maleico, cítrico, succínico, metansulfónico, bencensulfónico, p-toluensulfónico y similares pueden mencionarse.

El método de producción del compuesto de la presente invención se describe a continuación.

En cada uno de los siguientes métodos de producción, cuando se realiza reacción de alquilación, amidación (reacción de condensación), esterificación, reducción, aminación reductiva, aminación, halogenación, oxidación y similares, estas reacciones se realizan de acuerdo con métodos conocidos. Algunos ejemplos de tales métodos incluyen los métodos descritos en Organic Functional Group Preparations, 2nd edition, Academic Press, Inc. (1989), Comprehensive Organic Transformations, VCH Publishers Inc. (1989) y similares. Las reacciones de protección y desprotección se realizan de acuerdo con métodos conocidos, por ejemplo, los métodos descritos en Protective Groups in Organic Synthesis, 3rd edition, John Wiley y Sons, Inc. (1999) o un método análogo a éste.

Los solventes indicados en términos genéricos, que se usan en las siguientes reacciones se explican a continuación.

Ejemplos de "alcoholes" incluyen metanol, etanol, 1-propanol, 2-propanol, *terc*-butilo alcohol y similares.

Ejemplos de "éteres" incluyen dietil éter, diisopropil éter, difenil éter, tetrahidrofurano, 1,4-dioxane, 1,2-dimetoxietane y similares.

Ejemplos de "ésteres" incluyen acetato de etilo, acetato de metilo, acetato de *terc*-butilo y similares.

Ejemplos de "hidrocarburos" incluyen benceno, tolueno, xileno, ciclohexano, hexano, pentano y similares.

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Ejemplos de "amidas" incluyen N,N-dimetilformamida, N,N-dimetilacetamida, triamida hexametilfosfórica y similares.

Ejemplos de "hidrocarburos halogenados" incluyen diclorometano, cloroformo, tetracloruro de carbono, 1,2-dicloroetano, tetracloroetileno, clorobenceno y similares.

Ejemplos de "nitrilos" incluyen acetonitrile, propionitrilo y similares.

Ejemplos de "cetonas" incluyen acetona, 2-butanona y similares.

Ejemplos de "ácidos orgánicos" incluyen ácido fórmico, acético, propiónico, trifluoroacético, metansulfónico y similares.

Ejemplos de "aminas aromáticas" incluyen piridina, 2,6-lutidina, quinolina y similares.

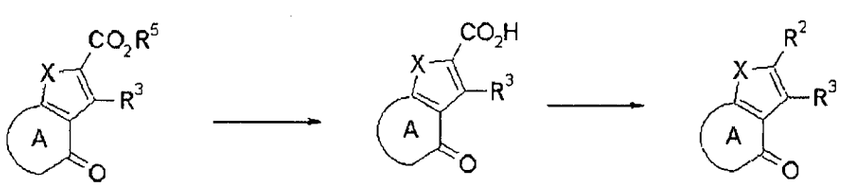
Ejemplos de "sulfóxidos" incluyen dimetil sulfóxido y similares.

En los presentes métodos de producción, los materiales del compuesto de inicio y una producción intermediaria pueden ser sales. Como tales sales, aquellos similares a las sales del compuesto (I) mencionado pueden ser mencionados.

El Compuesto (I) puede producirse, por ejemplo, por [Método A] que se muestra a continuación o un método análogo a éste.

[Método A]

El Compuesto (III) se hidroliza y el compuesto obtenido (II) se condensa con amina, por lo cual puede producirse el compuesto (I).



(III) (II) (I)

en donde R^5 es alquilo de 1 a 6 átomos de carbono o

bencilo, y otros símbolos son como se definió con anterioridad.

Ejemplos de alquilo de 1 a 6 átomos de carbono para R^5 incluyen metilo, etilo y similares, preferiblemente etil.

El Compuesto (III) puede producirse de acuerdo con los métodos de producción del compuesto (IIIa) y compuesto (IIIb) que se muestran a continuación.

El Compuesto (III) puede convertirse en compuesto (II) por hidrólisis en condiciones ácidas o alcalinas en un solvente que no influye en la reacción de manera adversa. Particularmente, cuando R^5 es bencilo, puede usarse una reacción de hidrogenación catalítica en un solvente que no influye en la reacción de manera adversa.

Como el ácido usado para hidrólisis, ácido clorhídrico, ácido sulfúrico y similares pueden mencionarse, y como la base, hidróxido de sodio, hidróxido de potasio, hidróxido de litio y similares pueden mencionarse. La cantidad del mismo es generalmente 1 a 20 equivalentes en moles, preferiblemente 1 a 10 equivalentes en moles, por 1 mol del compuesto (III).

Ejemplos de catalizador usado para la reacción de hidrogenación catalítica incluyen Níquel de Raney, óxido de platino, o paladio, rutenio, rodio, iridio y similares sobre carbón activado, sulfato de bario, carbonato de calcio y similares. La cantidad del mismo es generalmente 0.01 a 1 equivalentes en moles, preferiblemente 0.05 a 0.5 equivalentes en moles, por 1 mol del compuesto (III).

Como la fuente de hidrógeno, se usa hidrógeno, ciclohexeno, hidrazina, formiato de amonio y similares.

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, alcoholes, hidrocarburos, cetonas, nitrilos, amidas, ésteres, agua y similares, preferiblemente administrados para alcoholes, éteres y agua. Dos

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o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 100°C, preferiblemente 20 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

La reacción de condensación del compuesto (II) y amina puede realizarse en un solvente que no influye en la reacción de manera adversa y uso, por ejemplo, un agente de condensación.

La amina que se usará en esta reacción puede condensarse con un grupo carboxi del compuesto (II) para formar un "carbamoilo que esta opcionalmente sustituido" para R^2. Tal amina puede ser una comercial, o puede producirse a partir del correspondiente compuesto como materia prima por un método conocido *per se*.

Ejemplos de agente de condensación incluyen carbodiimida (por ejemplo, diciclohexilcarbodiimida (DCCD), carbodiimida soluble en agua (WSCD) y similares), éster de fosfato (por ejemplo, dietil cianofosfonato, dietil clorofosfonato, difenil fosforoazida y similares), reactivo BOP (hexafluorofosfato de 1H-benzotriazol-1-iloxitripirrolidinofosfonio (PyBOP)), 2-etoxi-1-etoxicarbonil-1,2-dihidroquinolina (EEDQ), carbonildiimidazol y similares, preferiblemente administrados para WSCD.

La cantidad de cada uno de la amina y agente de condensación que se usará es en general 1 a 10 equivalentes en moles, preferiblemente 1 a 2 equivalentes en moles, por 1 mol del compuesto (II).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, cetonas, nitrilos, amidas, ésteres y similares, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados

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con anterioridad pueden usarse en una mezcla en una proporción apropiada.

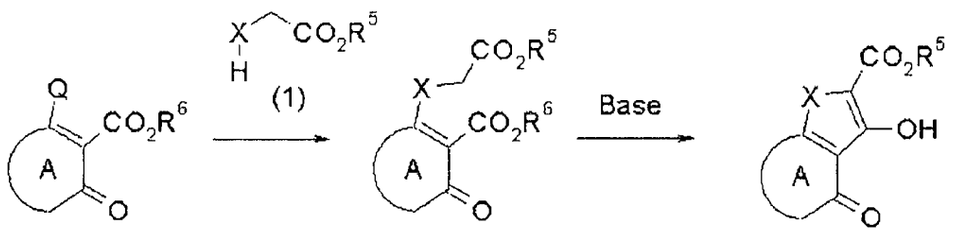
La temperatura de reacción es en general 0 hasta 100°C, preferiblemente 20 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

En compuesto (III), compuesto (IIIa) en donde R^3 es hidroxi puede producirse, por ejemplo, [Método B] que se muestra a continuación o un método análogo a éste.

[Método B]

Compuesto (V) se hace reaccionar con compuesto (1) y el compuesto obtenido (IV) se trata con una base para dar el compuesto (IIIa).



(V) (IV) (IIIa)

en donde Q es un grupo saliente, R^6 es alquilo de 1 a 6 átomos de carbono, y otros símbolos son como se definió con anterioridad.

Ejemplos de grupo saliente para Q incluyen átomo de halógeno (por ejemplo, cloro, bromo, yodo), opcionalmente alquilsulfoniloxi de 1 a 6 átomos de carbono halogenado (por ejemplo, metilsulfoniloxi, etilsulfoniloxi, trifluorometilsulfoniloxi), aril sulfoniloxi de 6 a 10 átomos de carbono que tiene opcionalmente alquilo de 1 a 6 átomos de carbono (por ejemplo, bencensulfoniloxi, 4-toluensulfoniloxi), metil mercapto, metansulfonilo y similares, preferiblemente administrados para átomo de halógeno.

Ejemplos de alquilo de 1 a 6 átomos de carbono para R^6

incluyen metilo, etilo y similares.

Compuesto (V) puede producirse de acuerdo con los métodos de producción del compuesto (Va) y compuesto (Va-2) que se muestra a continuación.

La reacción del compuesto (V) y compuesto (1) puede realizarse en presencia de una base según se necesite y en un solvente que no influye en la reacción de manera adversa.

El Compuesto (1) puede ser uno disponible en el mercado, o puede producirse a partir del correspondiente compuesto como materia prima por un método conocido *per se*.

La cantidad del compuesto (1) que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 1 a 10 equivalentes en moles, por 1 mol del compuesto (V). Algunos ejemplos de la base que se usará según se necesite incluyen hidruro de sodio, metóxido de sodio, etóxido de sodio, carbonato de sodio, hidrógeno carbonato de sodio, hidróxido de sodio, trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina y similares. La cantidad del mismo que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 2 a 10 equivalentes en moles, por 1 mol del compuesto (V).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, amidas, ésteres y similares, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 100°C, preferiblemente 20 hasta 90°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

Compuesto (IV) puede convertirse en compuesto (IIIa) uso

una base en un solvente que no influye en la reacción de manera adversa.

Ejemplos de la base incluyen metóxido de sodio, etóxido de sodio, hidróxido de sodio, trietilamina y similares y la cantidad del mismo que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 2 a 10 equivalentes en moles, por 1 mol del compuesto (IV).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, amidas, ésteres y similares pueden mencionarse, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 100°C, preferiblemente 20 hasta 90°C.

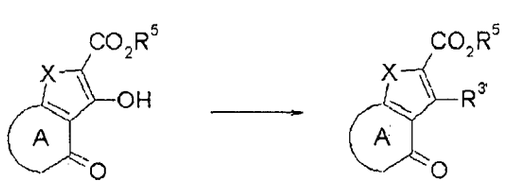
El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

Compuesto (V) puede convertirse directamente en el compuesto (IIIa) sin aislar compuesto (IV).

En el compuesto (III), el compuesto (IIIb) en donde R^3 es alcoxi que esta opcionalmente sustituido puede producirse, por ejemplo, por [Método C] que se muestra a continuación o un método análogo a éste.

[Método C]

El Compuesto (IIIa) se hace reaccionar con alquilo halogenado, éster de sulfato, éster de metansulfonato opcionalmente sustituido por átomo de halógeno(s) y similares para dar el compuesto (IIIb).



(IIIa) (IIIb)

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en donde $R^{3'}$ es alcoxi que esta opcionalmente sustituido, y otros símbolos son como se definió con anterioridad.

El "alcoxi que esta opcionalmente sustituido" para $R^{3'}$ significa "hidroxi sustituido por alquilo que esta opcionalmente sustituido" que comprende en el "hidroxi que esta opcionalmente sustituido" para R^3.

La reacción entre el compuesto (IIIa) y alquilo halogenado, éster de sulfato, éster de metansulfonato opcionalmente sustituido por átomo de halógeno(s) y similares puede realizarse en presencia de una base en un solvente que no influye en la reacción de manera adversa.

El alquilo halogenado, éster de sulfato y éster de metansulfonato opcionalmente sustituido por átomo de halógeno(s) usado en esta reacción puede alquilar el grupo hidroxilo del compuesto (IIIa) para formar "alcoxi que esta opcionalmente sustituido" para $R^{3'}$. Tal alquilo halogenado, éster de sulfato, éster de sulfato y éster de metansulfonato opcionalmente sustituido por átomo de halógeno(s) pueden ser comerciales, o puede producirse a partir del correspondiente compuesto como materia prima por un método conocido *per se*.

La cantidad de alquilo halogenado y similares que se usará es en general 1 a 3 equivalentes en moles, preferiblemente 1 a 2 equivalentes en moles, por 1 mol del compuesto (IIIa). Algunos ejemplos de la base que se usará incluyen metóxido de sodio, etóxido de sodio, carbonato de cesio, carbonato de sodio, hidrógeno carbonato de sodio, hidróxido de sodio, trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina, 1,8-diazabiciclo[5,4,0]undec-7-eno (DBU) y similares, y la cantidad del mismo que se usará es en general 1 a 5 equivalentes en moles, preferiblemente 1 a 3 equivalentes en moles, por 1 mol del

compuesto (IIIa).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, ésteres y similares, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

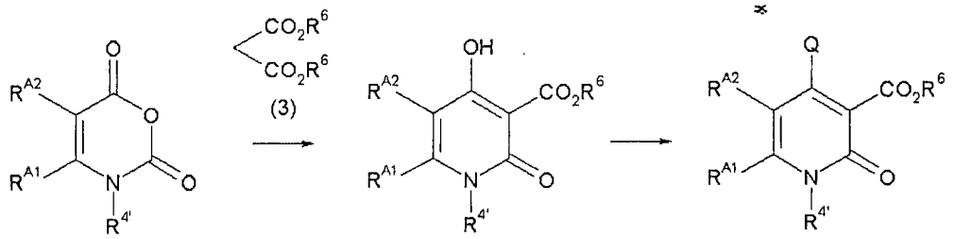
La temperatura de la reacción es en general 0 hasta 100°C, preferiblemente 20 hasta 90°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

De los compuestos (V), 2-oxonicotinate éster (Va) en donde el anillo A es anillo de piridina o anillo de piridina fusionado puede producirse, por ejemplo, por [Método D] que se muestra a continuación o un método análogo a éste.

[Método D]

Compuesto (VII) se hace reaccionar con éster de malonato (3) y hidroxi del compuesto obtenido (VI) se convierte en un grupo saliente Q para dar el compuesto (Va).



(VII) (VI) (Va)

en donde $R^{4'}$ es grupo hidrocarburo que esta opcionalmente sustituido, y otros símbolos son como se definió con anterioridad.

Como el "grupo hidrocarburo que esta opcionalmente sustituido" para $R^{4'}$, aquellos similares al "grupo hidrocarburo que esta opcionalmente sustituido" para R^4 pueden mencionarse.

La reacción del compuesto (VII) y éster de malonato (3) puede realizarse en presencia de una base en un solvente que no

influye en la reacción de manera adversa.

Ester de malonato (3) puede ser uno disponible en el mercado, o puede producirse a partir del correspondiente compuesto como materia prima por un método conocido *per se*.

La cantidad de éster de malonato (3) que se usará es en general 1 a 2 equivalentes en moles, preferiblemente 1 a 1.5 equivalentes en moles, por 1 mol del compuesto (VII). Algunos ejemplos de la base que se usará incluyen hidruro de sodio, metóxido de sodio, etóxido de sodio, carbonato de sodio, hidrógeno carbonato de sodio, hidróxido de sodio, trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina, DBU y similares y la cantidad del mismo que se usará es en general 1 a 10 equivalentes en moles, preferiblemente 1 a 5 equivalentes en moles, por 1 mol del compuesto (VII).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, cetonas, nitrilos, amidas y similares, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 100°C, preferiblemente 0 hasta 80°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

La conversión de hidroxi del compuesto (VI) en el grupo saliente Q puede realizarse, por ejemplo, usando un reactivo de halogenación y un reactivo de sulfonilación en un solvente que no influye en la reacción de manera adversa o sin solvente y en presencia de una base según se necesite.

Ejemplos del reactivo de halogenación incluyen cloruro de tionilo, cloruro de fosforilo, pentacloruro de fósforo, tribromuro de

fósforo y similares.

La cantidad del reactivo de halogenación que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 2 a 10 equivalentes en moles, por 1 mol del compuesto (VI).

La temperatura de la reacción es en general 0 hasta 130°C, preferiblemente 20 hasta 130°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

Ejemplos de reactivo de sulfonilación incluyen anhídrido de ácido trifluoro metansulfónico, haluro de metansulfonilo, haluro de bencensulfonilo y similares y la cantidad del mismo que se usará es en general 1 a 2 equivalentes en moles, preferiblemente 1 a 1.5 equivalentes en moles, por 1 mol del compuesto (VI). Algunos ejemplos de la base que se usará según se necesite incluyen trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina y similares y la cantidad del mismo que se usará es en general 2 a 5 equivalentes en moles, preferiblemente 2 a 3 equivalentes en moles, por 1 mol del compuesto (VI).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, amidas, ésteres y similares pueden mencionarse, preferiblemente administrados para éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de reacción es en general -10 hasta 100°C, preferiblemente 0 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

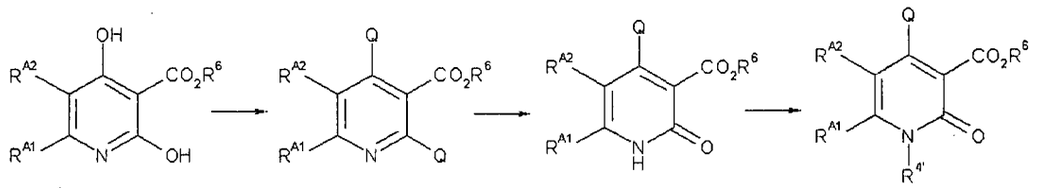
Compuesto (VII) que será material de inicio en [Método D] puede sintetizarse por un método conocido, por ejemplo, el método descrito en Journal of Heterocyclic Chemistry, vol. 12,

páginas 565-572 (1975).

Además, el compuesto (Va) puede producirse, por ejemplo, por [Método E] que se muestra a continuación o un método análogo a éste.

[Método E]

El hidroxi del compuesto (VIII-2) se convierte en el grupo saliente Q, y el compuesto obtenido (VIII) se hidroliza para dar el compuesto (Va-2). Este compuesto (Va-2) se hace reaccionar con hidrocarburo halogenado y similares para dar el compuesto (Va).



(VIII-2) (VIII) (Va-2) (Va)

en donde cada símbolo es como se definió con anterioridad.

El Compuesto (VIII) puede producirse de acuerdo con el método de síntesis del compuesto (Va) en el antes mencionado [Método D]. La cantidad del reactivo de halogenación y el reactivo de sulfonilación que se usará puede aumentarse según se necesite.

La hidrólisis del compuesto (VIII) puede realizarse, por ejemplo, luego de sustituir una vez el grupo saliente Q con acetoxi o alcoxi o directamente en condiciones alcalinas o condiciones ácidas, en un solvente que no influye en la reacción de manera adversa.

Cuando el grupo saliente Q se sustituye una vez con acetoxi o alcoxi, por ejemplo, acetato de sodio, metóxido de sodio, etóxido de sodio y similares pueden usarse y la cantidad del mismo que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 1 a 5 equivalentes en moles, por 1 mol del compuesto (VIII).

Para hidrólisis directa en condiciones ácidas, por ejemplo,

puede usarse ácido acético, clorhídrico, sulfúrico, metansulfónico y similares como ácido.

Para hidrólisis directa en condiciones alcalinas, por ejemplo, solución acuosa de hidróxido de sodio, solución acuosa de hidróxido de potasio, solución acuosa de hidróxido de litio y similares puede usarse como base.

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, agua y similares, preferiblemente administrados para éteres, amidas y agua. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 130°C, preferiblemente 20 hasta 130°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

Compuesto (Va-2) puede convertirse en compuesto (Va) haciendo reaccionar el compuesto (Va-2) con un compuesto representado por la fórmula $R^{4'}$-Q' en donde $R^{4'}$ es como se definió con anterioridad y Q' es un grupo saliente, en un solvente que no influye en la reacción de manera adversa o sin solvente en presencia de una base según se necesite.

Ejemplos de grupo saliente para Q' incluyen átomo de halógeno (por ejemplo, cloro, bromo, yodo), opcionalmente halogenado alquilsulfoniloxi de 1 a 6 átomos de carbono (por ejemplo, metilsulfoniloxi, etilsulfoniloxi, trifluorometilsulfoniloxi), aril sulfoniloxi de 6 a 10 átomos de carbono que tiene opcionalmente alquilo de 1 a 6 átomos de carbono (por ejemplo, bencensulfoniloxi, 4-toluensulfoniloxi), metilmercapto, metanosulfonilo y similares, con la preferencia dada al átomo de halógeno.

La cantidad del compuesto representado por la fórmula $R^{4'}$-Q' que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 2 a 10 equivalentes en moles, por 1 mol del compuesto (Va-2).

Ejemplos de la base que se usará según se necesite incluyen trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina, hidruro de sodio, carbonato de potasio, carbonato de cesio, *terc*-butóxido de potasio, *terc*-butóxido de sodio y similares, preferiblemente administrados para *terc*-butóxido de sodio, y la cantidad del mismo que se usará es en general 2 a 5 equivalentes en moles, preferiblemente 2 a 3 equivalentes en moles, por 1 mol del compuesto (Va-2).

Con preferencia, bromuro de tetrabutilamonio o similares se agregan a la reacción.

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, amidas, ésteres y similares pueden mencionarse, preferiblemente éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general -10 hasta 100°C, preferiblemente 0 hasta 60°C.

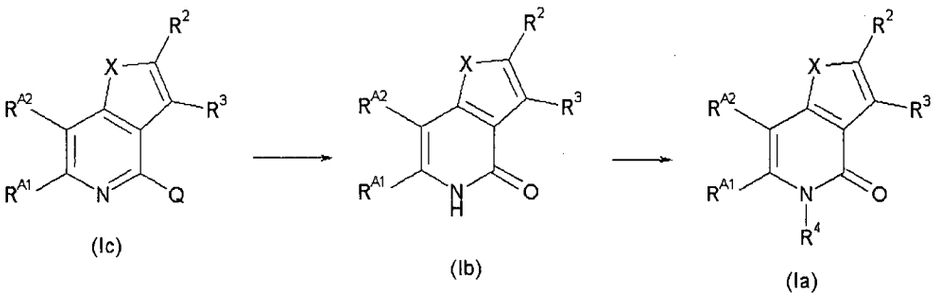
El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 48 hrs.

Compuesto (VIII-2) que será material de inicio en [Método E] puede sintetizarse por un método conocido, por ejemplo, el método descrito en Journal of Organic Chemistry, vol. 46, páginas 3040-3048 (1981).

En compuestos (I), compuesto (Ia) y compuesto (Ib) pueden producirse, por ejemplo, [Método F] que se muestra a continuación o un método análogo a éste.

[Método F]

Compuesto (Ib) y compuesto (Ia) pueden producirse a partir del compuesto (Ic) por reacciones de acuerdo con [Método E].



(Ic) (Ib) (Ia)

en donde cada símbolo es como se definió con anterioridad.

La reacción a partir del compuesto (Ic) al compuesto (Ib) puede realizarse de acuerdo con la reacción a partir del compuesto (VIII) al compuesto (Va-2) en [Método E].

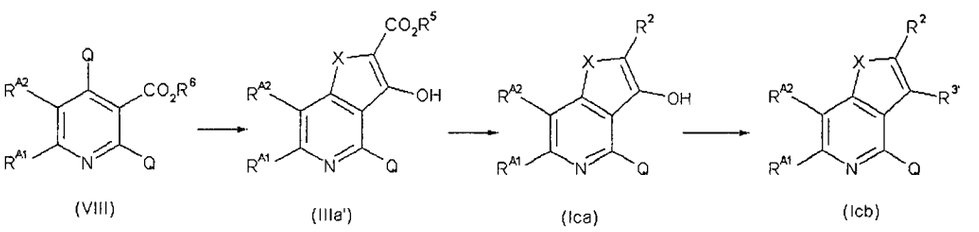
La reacción a partir del compuesto (Ib) al compuesto (Ia) puede realizarse de acuerdo con la reacción a partir del compuesto (Va-2) al compuesto (Va) en [Método E].

El Compuesto (Ic) puede producirse de acuerdo con el método de producción del compuesto (Ica) y compuesto (Icb) que se muestran a continuación.

En compuestos (Ic), compuesto (Ica) en donde R^3 es hidroxi y compuesto (Icb) en donde R^3 es alcoxi que esta opcionalmente sustituido (que se muestra $R^{3'}$ en la siguiente fórmula (Icb)) pueden producirse, por ejemplo, por [Método G] que se muestra a continuación o un método análogo a éste.

[Método G]

Compuesto (Ica) y compuesto (Icb) pueden producirse a partir del compuesto (VIII) por reacciones de acuerdo con [Método A], [Método B] y [Método C].



(VIII) (IIIa') (Ica) (Icb)

en donde cada símbolo es como se definió con anterioridad.

La reacción a partir del compuesto (VIII) al compuesto (IIIa') puede realizarse de acuerdo con [Método B].

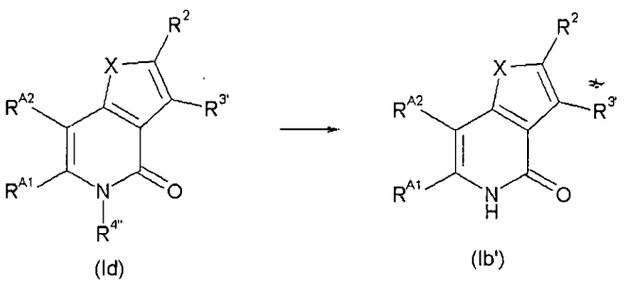
La reacción a partir del compuesto (IIIa') al compuesto (Ica) puede realizarse de acuerdo con [Método A].

La reacción a partir del compuesto (Ica) al compuesto (Icb) puede realizarse de acuerdo con [Método C].

También, el compuesto (Ib) puede producirse, por ejemplo, [Método H] que se muestra a continuación o un método análogo a éste.

[Método H]

De los compuestos (Ib), el compuesto (Ib') en donde R^3 es alcoxi que esta opcionalmente sustituido (que se muestra $R^{3'}$ en la siguiente fórmula (Ib')) pueden producirse por eliminación de $R^{4''}$ a partir del compuesto (Id) en donde R^3 es alcoxi que esta opcionalmente sustituido (que se muestra $R^{3'}$ en la siguiente fórmula (Id)) y R^4 es fenacilo que esta opcionalmente sustituido, metoximetilo, 4-metoxibencilo ó 2,4-dimetoxibencilo (que se muestra R4" en la siguiente fórmula (Id)) de entre los compuestos (Ia).



(Id) (Ib')

en donde $R^{4''}$ es fenacilo que esta opcionalmente sustituido, metoximetilo, 4-metoxibencilo ó 2,4-dimetoxibencilo, y otros símbolos son como se definió con anterioridad.

Cuando $R^{4''}$ es fenacilo que esta opcionalmente sustituido, la conversión del compuesto (Id) en compuesto (Ib') puede realizarse, por ejemplo, en presencia de metal tales como zinc y

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similares en condiciones ácidas en un solvente que no influye en la reacción de manera adversa. La cantidad de zinc que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 1 a 10 equivalentes en moles, por 1 mol del compuesto (Id). Como ácido, se usan ácido clorhídrico, ácido sulfúrico y similares.

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, agua y similares pueden mencionarse, preferiblemente administrados para éteres, amidas y agua. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 20 hasta 120°C, preferiblemente 20 hasta 100°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 24 hrs.

Cuando $R^{4''}$ es metoximetilo, conversión del compuesto (Id) al compuesto (Ib') puede realizarse en condiciones ácidas en un solvente que no influye en la reacción de manera adversa. Como ácido, puede usarse ácido clorhídrico, ácido sulfúrico y similares.

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, agua y similares pueden mencionarse, preferiblemente administrados para éteres, amidas y agua. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 120°C, preferiblemente 20 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 24 hrs.

Cuando $R^{4''}$ es 4-metoxibencilo, conversión del compuesto (Id) al compuesto (Ib') puede realizarse en condiciones ácidas

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fuertes en un solvente que no influye en la reacción de manera adversa. Como ácido, puede usarse ácido trifluoroacético, ácido trifluorometansulfónico y similares. En este caso, puede usarse anisol como depurador de cationes en una cantidad de generalmente 1 a 20 equivalentes en moles, preferiblemente 1 a 5 equivalentes en moles, por 1 mol del compuesto (Id).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, y similares pueden mencionarse, preferiblemente éteres y amidas. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 120°C, preferiblemente 20 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 24 hrs.

Cuando $R^{4''}$ es 2,4-dimetoxibencilo, conversión del compuesto (Id) al compuesto (Ib') puede realizarse en presencia de un oxidante tales como nitrato diamónico de cerio (IV) (CAN), 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) y similares en un solvente que no influye en la reacción de manera adversa.

La cantidad del oxidante que se usará es en general 1 a 20 equivalentes en moles, preferiblemente 1 a 5 equivalentes en moles, por 1 mol del compuesto (Id).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, agua y similares, preferiblemente administrados para éteres, nitrilos, amidas y agua. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 0 hasta 120°C,

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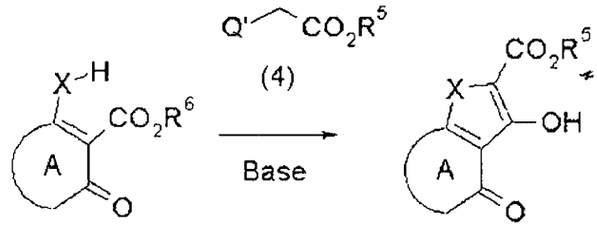
preferiblemente 20 hasta 60°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 24 hrs.

También, el compuesto (IIIa) pueden producirse, por ejemplo, por [Método I] que se muestra a continuación o un método análogo a éste.

[Método I]

El Compuesto (Vb) se hace reaccionar con compuesto (4) para dar el compuesto (IIIa).



(Vb) (IIIa)

en donde Q' es un grupo saliente, y otros símbolos son como se definió con anterioridad.

Ejemplos de grupo saliente para Q' incluyen aquellos similares al grupo saliente para el antes mencionado Q, preferiblemente administrados para átomo de halógeno.

El Compuesto (4) puede ser un reactivo disponible en el mercado, o puede sintetizarse por un método conocido *per se*.

El Compuesto (Vb), por ejemplo, derivado de 6-amino-2,4-dioxo-1,2,3,4-tetrahidropirimidina-5-carboxilato y similares, que será material de inicio en [Método I] puede sintetizarse por un método conocido, por ejemplo, el método descrito en Journal of Chemical Society of Japan, vol. 46, páginas 3849-3853 (1973). Por ejemplo, el derivado de 2-mercapto-4-oxo-1,4-dihidroquinolin-3-carboxilato y similares puede sintetizarse por un método conocido, por ejemplo, el método descrito en Journal of Heterocyclic Chemistry, vol. 27, páginas 839-843 (1990).

La reacción entre el compuesto (Vb) y el compuesto (4)

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puede realizarse en presencia de una base en un solvente que no influye en la reacción de manera adversa.

La cantidad del compuesto (4) que se usará es en general 1 a 3 equivalentes en moles, preferiblemente 1 a 2 equivalentes en moles, por 1 mol del compuesto (Vb). Algunos ejemplos de la base incluyen metóxido de sodio, etóxido de sodio, carbonato de sodio, hidrógeno carbonato de sodio, hidróxido de sodio, trietilamina, diisopropiletilamina, piridina, 4-dimetilaminopiridina y similares y la cantidad del mismo que se usará es en general 2 a 5 equivalentes en moles, preferiblemente 2 a 3 equivalentes en moles, por 1 mol del compuesto (Vb).

Ejemplos de solvente que no influye en la reacción de manera adversa incluyen éteres, hidrocarburos, alcoholes, cetonas, nitrilos, amidas, agua y similares pueden mencionarse, preferiblemente administrados para éteres, amidas y agua. Dos o más clases de los solventes mencionados con anterioridad pueden usarse en una mezcla en una proporción apropiada.

La temperatura de la reacción es en general 20 hasta 120°C, preferiblemente 20 hasta 100°C.

El tiempo de reacción es en general 0.5 hasta 100 hrs, preferiblemente 1 a 24 hrs.

Un compuesto dentro del alcance de la presente invención también puede producirse por aplicación de un medio conocido *per se* al Compuesto (I) para introducción de sustituyentes y la conversión de grupos funcionales. Para la conversión de sustituyentes, puede usarse un método convencional conocido. Por ejemplo, la conversión en carboxi por hidrólisis del éster, la conversión en carbamoilo por amidación de carboxi, la conversión en hidroximetil por reducción de carboxi, la conversión en alcohol compuesto por reducción o alquilación de carbonilo, aminación reductiva de carbonilo, oximación de carbonilo, acilación de

carbonilo, ureación, sulfonilación o alquilación de amino, sustitución y aminación halógeno activo por amina, aminación de nitro por reducción, alquilación de hidroxi, sustitución y aminación de hidroxi y similares pueden mencionarse. Cuando un sustituyente reactivo que produce una reacción no objetiva está presente durante la introducción de sustituyentes y la conversión de grupos funcionales, se introduce un grupo protector por anticipado según se necesite en el sustituyente reactivo por un medio conocido *per se*, y el grupo protector se elimina por un medio conocido *per se* luego de la reacción objetiva, por la cual el compuesto dentro del alcance de la presente invención también puede producirse.

En el método de producción mencionado arriba, cuando el material de inicio o el compuesto de la presente invención tiene un grupo amino, carboxilo, hidroxi o un grupo mercapto como un sustituyente, puede introducirse un grupo protector usado en la química de péptidos y similar. El grupo protector puede ser removido de acuerdo a un método convencional en cualquier etapa de cualquier esquema.

El Compuesto (I) puede aislarse y purificarse por un medio conocido *per se*, tales como transferencia de fases, concentración, extracción con solventes, fraccionamiento, conversión de líquidos, cristalización, recristalización, cromatografía y similares. Cuando el compuesto (I) se obtiene como compuesto libre, puede convertirse en una sal deseada por un método conocido *per se* o un método análogo a éste. Por el contrario, cuando el compuesto se obtiene como una sal, puede convertirse en una forma libre u otra sal deseada por un método conocido *per se* o un método análogo a éste.

El Compuesto (I) puede usarse como un profármaco. Un profármaco del compuesto (I) significa un compuesto convertido

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en el compuesto (I) por una reacción producida por una enzima, un ácido gástrico, etc. en la condición fisiológica en el cuerpo vivo, es decir, un compuesto convertido en Compuesto (I) por oxidación, reducción, hidrólisis, etc. producida por una enzima, un compuesto convertido en Compuesto (I) por hidrólisis etc. debido a ácido gástrico, y similares.

Un profármaco del compuesto (I) puede ser un compuesto obtenido sometiendo un amino en el compuesto (I) a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido sometiendo un amino en el compuesto (I) a eicosanoilación, alanilación, pentilaminocarbonilación, (5-metil-2-oxo-1,3-dioxoln-4-il)metoxicarbonilación, tetrahidrofuranoilación, pirrolidilmetilación, pivaloiloximetilación o ter-butilación); un compuesto obtenido sometiendo hidroxi en el compuesto (I) a acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido sometiendo hidroxi en el compuesto (I) de la presente invención a acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumariloación, alanilación o dimetilaminometilcarbonilación); un compuesto obtenido sometiendo carboxi en el compuesto (I) a esterificación o amidación (por ejemplo, un compuesto obtenido sometiendo carboxi en el compuesto (I) a esterificación con etilo, fenil esterificación, esterificación con carboximetilo, esterificación con dimetilaminometilo, esterificación con pivaloiloximetilo, esterificación con etoxicarboniloxietilo, esterificación con ftalidilo, esterificación con (5-metil-2-oxo-1,3-dioxoln-4-il)metilo, esterificación con ciclohexiloxicarboniletilo o metilamidación) y similares. Cualquiera de estos compuestos puede producirse a partir del compuesto (I) por un método conocido *per se*.

Un profármaco del compuesto (I) también puede ser un compuesto convertido en el compuesto (I) en condiciones

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fisiológicas, tales como las que se describen en IYAKUHIN no KAIHATSU (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p,163-198, Publicado por HIROKAWA SHOTEN (1990).

Cuando el compuesto (I) tiene un isómero tal como isómero óptico, estereoisómero, isómero de posición, isómero de rotación y similares, cualquier isómero y una mezcla de éstos comprenden que en el compuesto (I). Por ejemplo, cuando el compuesto (I) tiene un isómero óptico, un isómero óptico resuelto de un racemato también comprenden que en el compuesto (I). Tales isómeros pueden obtenerse como productos independientes por un medio de síntesis o un medio de separación (concentración, extracción con solvente, cromatografía en columna, recristalización y similares) conocido *per se*.

El Compuesto (I) puede ser un cristal, y ambos, un cristal individual y una mezcla de cristales comprenden que en el compuesto (I). Los cristales pueden producirse por cristalización de acuerdo con métodos de cristalización conocidos *per se*.

Compuesto (I) también puede ser un cocristal.

Compuesto (I) puede ser un hidrato, un no hidrato, un solvato o un no solvato, ambos que comprende en el compuesto (I) y similares.

Un compuesto rotulado con un isótopo (por ejemplo, ^{2}H, ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.) también comprenden que en el compuesto (I).

Compuesto (I) de la presente invención, o una sal de lo mismo, o uno de sus profármacos (en ocasiones abreviado como "el compuesto de la presente invención" en la presente especificación) interactúa, por ejemplo, con la proteína Smo humana y cambia su estructura estérica, por lo cual la formación de un complejo con una proteína involucrada en la transducción de señal en el citoplasma se inhibe y el sistema de transducción de la señal de Hedgehog se inhibe. En forma alternativa, el

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compuesto de la presente invención interactúa con la proteína Smo humana y directamente inhibe la formación de un complejo de proteína Smo humana con una proteína involucrada en el sistema de transducción de la señal de Hedgehog en el citoplasma, por lo cual el sistema de transducción de la señal de Hedgehog se inhibe. En forma alternativa, el compuesto de la presente invención interactúa con un sitio de una proteína Smo, por ejemplo, sitio de fosforilación y similares, que está modificado por una proteína involucrada en el sistema de transducción de la señal de Hedgehog, por el cual la modificación tal como fosforilación de Smo y similares se inhibe y el sistema de transducción de la señal de Hedgehog se inhibe.

La inhibición del sistema de transducción de la señal de Hedgehog puede medirse, por ejemplo, cuantificar una reducción en el nivel de expresión de un gen informante conectado al torrente descendente del sitio de unión a Gli basado en la intensidad de fluorescencia de acuerdo con el Ejemplo Experimental 1. En forma alternativa, puede medirse mediante la cuantificación de la expresión de ARNm de Gli-1 en un extracto celular por un método de PCR cuantitativa y similares. Un compuesto que inhibe la señal de Hedgehog se orienta a Smo, lo cual puede confirmarse, por ejemplo, uniendo Ciclopamina rotulada con fluorescencia y un compuesto experimental a células que expresan Smo, midiendo el nivel de fluorescencia de la célula, y compara el valor con aquel obtenido sin la incorporación de un compuesto experimental para encontrar la reducción.

En consecuencia, el compuesto de la presente invención es útil como un inhibidor de Smo para mamíferos (por ejemplo, ratones, rata, hámster, conejo, gato, perro, bovinos, ovejas, monos, humanos, etc.). El compuesto de la presente invención se usa como un agente farmacéutico tal como un agente para la

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profilaxis o el tratamiento de enfermedades posiblemente influenciadas por Smo, por ejemplo, cáncer [por ejemplo, cáncer colorrectal (por ejemplo, cáncer de colon, rectal, anal, colorrectal familiar, colorrectal sin poliposis hereditario, tumor estromal gastrointestinal, etc.), cáncer de pulmón (por ejemplo, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, mesotelioma maligno, etc.), mesotelioma, cáncer de páncreas (por ejemplo, cáncer del conducto pancreático, tumor pancreático endócrino, etc.), cáncer faríngeo, laríngeo, de esófago, gástrico (por ejemplo, adenocarcinoma papilar, adenocarcinoma mucinoso, cáncer adenoescamoso, etc.), cáncer duodenal, de intestino delgado, de mama (por ejemplo, carcinoma de mama ductal invasivo, cáncer ductal *in situ*, cáncer de mama inflamatorio, etc.), cáncer de ovario (por ejemplo, cáncer epitelial de ovario, tumor de células germinales extragonadales, tumor de células germinales de ovarios, tumor potencial maligno bajo de ovario, etc.), tumor testicular, cáncer de próstata (por ejemplo, cáncer de próstata dependiente de las hormonas, cáncer de próstata no dependiente de las hormonas, etc.), cáncer de hígado (por ejemplo, carcinoma hepatocelular, cáncer de hígado primario, cáncer del conducto extrahepático biliar, etc.), cáncer de tiroides (por ejemplo, cáncer medular de tiroides, etc.), cáncer de riñón (por ejemplo, carcinoma de células renales, cáncer de células transicionales de pelvis renal y uréter, etc.), cáncer de útero (por ejemplo, cáncer cervical, cáncer del cuerpo uterino, sarcoma uterino, etc.), tumor cerebral (por ejemplo, meduloblastoma, glioma, astrocitoma pineal, astrocitoma pilocítico, astrocitoma difuso, astrocitoma anaplásico, adenoma de pituitaria, etc.), retinoblastoma, cáncer de piel (por ejemplo, carcinoma de células basales, melanoma maligno, etc.), sarcoma (por ejemplo, rabdomiosarcoma, leiomiosarcoma, sarcoma de

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tejido suave, etc.), tumor de huesos maligno, cáncer de vejiga urinaria, cáncer de la sangre (por ejemplo, mieloma múltiple, leucemia, linfoma maligno, enfermedad de Hodgkin, trastorno mieloproliferativo crónico, etc.), cáncer desconocido primario etc.], un inhibidor del crecimiento del cáncer, un inhibidor de metástasis del cáncer, un promotor de apoptosis y similares. Entre estos, el compuesto de la presente invención es efectivo, por ejemplo, para el tumor de cerebro, cáncer de piel, pulmón, páncreas, conducto biliar, próstata, esófago, gástrico, colorrectal, sarcoma y mama. Especialmente, el compuesto de la presente invención es efectivo para glioma, meduloblastoma, tumor de células basales, cáncer de pulmón de células pequeñas, cáncer de páncreas, cáncer del conducto biliar, cáncer de próstata, cáncer de esófago, cáncer gástrico, cáncer colorrectal, rabdomiosarcoma y cáncer de mama.

El compuesto de la presente invención puede administrarse por vía oral o parenteral como está o en una mezcla con un vehículo aceptable desde el punto de vista farmacológico.

La forma de dosificación del compuesto de la presente invención para administración oral, por ejemplo, comprimido (incluyendo comprimido con recubrimiento azucarado, comprimido recubierto), píldora, gránulo, polvo, cápsula (incluyendo cápsula suave, microcápsula), jarabe, emulsión, suspensión y similares, y la forma de dosificación para administración parenteral es, por ejemplo, inyección, agente para inyección, instilación, supositorio y similares. Además, es efectivo realizar una preparación de liberación prolongada combinando el compuesto con una base apropiada (por ejemplo, polímero de ácido butírico, polímero de ácido glicólico, copolímero de ácido butírico-ácido glicólico, una mezcla de un polímero de ácido butírico y un polímero de ácido glicólico, éster de ácidos grasos de poliglicerol etc.).

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Como un método para producir el compuesto de la presente invención en la forma de dosificación antes mencionada, puede utilizarse un método de producción conocido generalmente usado en el campo pertinente. Cuando se produce la forma de dosificación mencionada con anterioridad, cantidades apropiadas de aditivos tales como excipiente, aglutinante, desintegrante, lubricante, agente edulcorante, tensioactivo, agente de suspensión, emulsionante y similares, generalmente usados en el campo farmacéutico, se agregan apropiadamente según se necesite para la producción.

Cuando el compuesto de la presente invención se prepara en un comprimido, por ejemplo, puede producirse agregando un excipiente, un aglutinante, un desintegrante, un lubricante y similares, y cuando se debe preparar una píldora o un gránulo, puede producirse agregando un excipiente, un aglutinante, un desintegrante y similares. Cuando debe prepararse un polvo o una cápsula, puede producirse agregando un excipiente y similares, cuando debe prepararse un jarabe, puede producirse agregando un edulcorante y similares, y cuando debe prepararse una emulsión o una suspensión, puede producirse agregarse a agente de suspensión, un tensioactivo, un emulsionante y similares.

Ejemplos de excipientes incluyen lactosa, sacarosa, glucosa, almidón, sacarosa, celulosa microcristalina, glicirriza en polvo, manitol, hidrógeno carbonato de sodio, fosfato de calcio, sulfato de calcio y similares.

Ejemplos de aglutinante incluyen 5 - 10% en peso de pasta líquida de almidón, 10 - 20% en peso de solución de goma arábiga o solución de gelatina, 1 - 5% en peso de solución de tragacanto, solución de carboximetilo celulosa, solución de alginato de sodio, glicerina y similares.

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Ejemplos de desintegrante incluyen almidón, carbonato de calcio y similares.

Ejemplos de lubricante incluyen estearato de magnesio, ácido esteárico, estearato de calcio, talco purificado y similares.

Ejemplos de edulcorante incluyen glucosa, fructosa, azúcar invertida, sorbitol, xilitol, glicerina, jarabe simple y similares.

Ejemplos de tensioactivo incluyen laurilo sulfato de sodio, polisorbato 80, éster de mono ácido graso sorbitano, polioxil 40 estearato y similares.

Ejemplos de agente de suspensión incluyen de goma arábiga, alginato de sodio, carboximetilcelulosa de sodio, metil celulosa, bentonita y similares.

Ejemplos de emulsionante incluyen de goma arábiga, tragacanto, gelatina, polisorbato 80 y similares.

Además, cuando el compuesto de la presente invención se produce en forma de dosificación mencionada con anterioridad, una cantidad apropiada de un colorante, conservante, agente aromático, corrector, estabilizador, agentes aglutinantes y similares normalmente usados en el campo de la preparación pueden agregarse según demanda.

Como la inyección, se menciona inyección intravenosa como también inyección subcutánea, inyección intracutánea, inyección intramuscular, instilación y similares, y como la preparación de liberación prolongada, se mencionan un agente de iontoforesis transdérmica y similares.

Tales inyecciones se preparan por métodos conocidos en sí mismos *per se*, o por disolución, suspensión o emulsión del compuesto de la presente invención en un líquido acuoso u oleoso esterilizado.

Como líquido acuoso para inyección, pueden mencionarse solución salina fisiológica, soluciones isotónicas que contienen

glucosa u otros fármacos auxiliares (por ejemplo, D-sorbitol, D-manitol, cloruro de sodio y similares) y similares, y pueden usarse en combinación con agentes de solubilización apropiados, tales como alcoholes (por ejemplo, etanol), polialcoholes (por ejemplo, propilenglicol, polietilenglicol), tensioactivo no iónicos (por ejemplo, polisorbato 80, HCO-50) y similares. Como líquido oleoso, pueden mencionarse aceite de sésamo, aceite de soja y similares, los cuales pueden usarse en combinación con agentes de solubilización tales como benzoato de bencilo, alcohol bencílico y similares. Además, amortiguadores (por ejemplo, amortiguador de fosfato, amortiguador de acetato de sodio), agentes suavizantes (por ejemplo, cloruro de benzalconio, clorhidrato de procaína y similares), estabilizadores (por ejemplo, albúmina de suero humano, polietilenglicol y similares), conservantes (por ejemplo, alcohol bencílico, fenol y similares) y similares pueden mezclarse. Una inyección preparada en general se envasa en una ampolla.

Mientras que el contenido del compuesto de la presente invención en el agente farmacéutico de la presente invención varía dependiendo de la forma de preparación farmacéutica, es en general aproximadamente 0.01 a 100% en peso, preferiblemente aproximadamente 2 a 85% en peso, con mayor preferencia aproximadamente 5 a 70% en peso, con relación a la preparación completa.

Mientras que el contenido del aditivo en el agente farmacéutico de la presente invención varía dependiendo de la forma de preparación farmacéutica, es en general aproximadamente 1 a 99.9% en peso, preferiblemente aproximadamente 10 hasta 90% en peso, con relación a la preparación completa.

El compuesto de la presente invención es estable y poco

tóxico y puede usarse en forma segura. Mientras que la dosis diaria varía dependiendo de la afección y peso corporal de los pacientes, la clase de compuesto, la vía de administración y similares, en el caso de, por ejemplo, administración oral a pacientes para el tratamiento del cáncer, la dosis diaria a un adulto (peso corporal aproximadamente 60 kg) es de aproximadamente 1 a 1000 mg, preferiblemente aproximadamente 3 hasta 300 mg, con mayor preferencia aproximadamente 10 hasta 200 mg, como ingrediente activo (el compuesto de la presente invención), que puede administrarse en una sola administración o administrado en 2 ó 3 porciones por día.

Cuando el compuesto de la presente invención se administra por vía parenteral, en general se administra en la forma de un líquido (por ejemplo, inyección). Mientras que la dosis varía dependiendo del sujeto de administración, el órgano de destino, síntoma, administración método y similares, es, por ejemplo, aproximadamente 0.01 mg hasta aproximadamente 100 mg, preferiblemente aproximadamente 0.01 a aproximadamente 50 mg, con mayor preferencia aproximadamente 0.01 a aproximadamente 20 mg, en la forma de inyección, con relación a 1 kg peso corporal, que se administra preferiblemente por inyección intravenosa.

El compuesto de la presente invención puede usarse en forma concurrente con otros fármacos. Para ser específicos, el compuesto de la presente invención puede usarse junto con medicamentos tales como agentes terapéuticos hormonales, agentes quimioterapéuticos, agentes inmunoterapéuticos, agentes farmacéuticos que inhiben la acción de factores de crecimiento celular o receptores del factor de crecimiento celular y similares. A continuación, los fármacos que pueden usarse en combinación con el compuesto de la presente invención se abrevian como

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medicamentos concomitantes.

Ejemplos de "agentes terapéuticos hormonales" incluyen fosfestrol, dietilestilbestrol, clorotrianiseno, acetato de medroxiprogesterona, megestrol, clormadinona, aciproterona, danazol, alilestrenol, gestrinona, mepartricina, raloxifeno, omeloxifeno, levormeloxifeno, anti-estrógenos (por ejemplo, citrato de tamoxifeno, toremifeno, y similares), preparaciones de píldoras, mepitiostano, testrolactona, aminoglutetimida, agonistas de LH-RH (por ejemplo, acetato de goserelina, buserelina, leuprorelina, y similares), droloxifeno, epitiostanol, etinilestradiol sulfonato, inhibidores de aromatasa (por ejemplo, clorhidrato de fadrozol, anastrozol, retrozol, exemestane, vorozol, formestano, y similares), anti-yrógenos (por ejemplo, flutamida, bicartamida, nilutamida, y similares), inhibidores de 5α-reductasa (por ejemplo, finasterida, epristerida, y similares), fármacos de hormona de la corteza cerebral (por ejemplo, dexametasona, prednisolona, betametasona, triamcinolona, y similares), inhibidores de la síntesis de andrógenos (por ejemplo, abiraterona, y similares), retinoide y fármacos que retrasan el metabolismo de los retinoides (por ejemplo, liarozol, y similares), hormona tiroides, y DDS (Drug Delivery System) sus preparaciones, y similares.

Ejemplos de "agentes quimioterapéuticos" incluyen agentes de alquilación, antimetabolitos, antibióticos contra el cáncer, agentes contra el cáncer derivado de las plantas, y similares.

Ejemplos de "agentes de alquilación" incluyen mostaza de nitrógeno, clorhidrato de N-óxido de mostaza de nitrógeno, clorambutilo, ciclofosfamida, ifosfamida, tiotepa, carbocuona, tosilato de improsulfan, busulfan, clorhidrato de nimustina, mitobronitol, melfalan, dacarbazina, ranimustina, fosfato sódico de estramustina, trietilenmelamina, carmustina, lomustina,

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estreptozocina, pipobroman, etoglucid, carboplatino, cisplatino, miboplatino, nedaplatino, oxaliplatino, altretamina, ambamustina, clorhidrato de dibrospidio, fotemustina, prednimustina, pumitepa, ribomustina, temozolomida, treosulfan, trofosfamida, estimalámero de zinostatina, adozelesina, cistemustina, bizelesina, DDS (Drug Delivery System), sus preparaciones, y similares.

Ejemplos de "antimetabolitos" incluyen mercaptopurina, 6-mercaptopurina ribosida, tioinosina, metotrexato, pemetrexed, enocitabina, citarabina, citarabina ocfosfato, clorhidrato de ancitabina, fármacos 5-FU (por ejemplo, fluorouracilo, tegafur, UFT, doxifluridina, carmofur, galocitabina, emitefur, capecitabina, y similares), aminopterina, nelzarabina, leucovorina de calcio, tabloide, butocina, folinato de calcio, levofolinato de calcio, cladribina, emitefur, fludarabina, gemcitabina, hidroxicarbamida, pentostatina, piritrexim, idoxuridina, mitoguazona, tiazofrina, ambamustina, bendamustina, DDS sus preparaciones, y similares.

Ejemplos de "antibióticos contra el cáncer" incluyen actinomicina-D, actinomicina-C, mitomicina-C, cromomicina-A3, clorhidrato de bleomicina, sulfato de bleomicina, sulfato de peplomicina, clorhidrato de daoneorubicina, doxorubicina, aclarubicina, pirarubicina, epirubicina, neocarzinostatina, mitramicina, sarcomicina, carzinofilina, mitotano, zorubicina, mitoxantrona, idarubicina, DDS sus preparaciones, y similares.

Ejemplos de "agentes contra el cáncer derivados de las plantas" incluyen etoposida, fosfato de etoposida, sulfato de vinblastina, sulfato de vincristina, sulfato de vindesina, teniposida, paclitaxel, docetaxel, vinorelbina, DDS sus preparaciones, y similares.

Ejemplos de "agentes inmunoterapéuticos (BRM)" incluyen picibanil, krestin, sizofiran, lentinan, ubenimex, interferones,

interleucinas, factor estimulante de la colonia de macrófagos, factor estimulante de la colonia de granulocitos, eritropoyetina, linfotoxina, vacuna BCG, *Corynebacterium parvum,* levamisol, polisacárido K, procodazol, anticuerpo anti-CTLA4, y similares.

Ejemplo de "factores de crecimiento celular" en los "agentes farmacéuticos que inhiben la acción de factores de crecimiento celular o receptores del factor de crecimiento celular" incluyen cualquier sustancia que promueve la proliferación celular, que normalmente son péptidos que tienen no más de 20,000 de peso molecular que son capaces de exhibir su actividad en concentraciones bajas al unirse a un receptor, incluyendo (1) EGF (factor de crecimiento epidérmico) o sustancias que poseen sustancialmente la misma cantidad que EGF [por ejemplo, TGFα, y similares], (2) insulina o sustancias que poseen sustancialmente la misma actividad que la insulina [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 que FGF [por ejemplo, FGF ácido, FGF alcalino, KGF (factor de crecimiento de queratinocitos), FGF-10, y similares], y (4) otros factores de crecimiento celular [por ejemplo, CSF (factor estimulante de colonias), EPO (eritropoyetina), IL-2 (interleucina-2), NGF (factor de crecimiento de nervios), PDGF (factor de crecimiento derivado de plaquetas), TGFβ (factor de crecimiento con transformación β), HGF (factor de crecimiento de hepatocitos), VEGF (factor de crecimiento vascular endotelial), heregulina, angiopoyetina, y similares].

Ejemplos de "receptores del factor de crecimiento celular" incluyen cualquier receptor capaz de unirse a los antes mencionado factores de crecimiento celular, incluyendo EGF receptor, receptor de heregulina (HER3, etc.), receptor de

insulina, receptor-1 de IGF, receptor-2 de IGF, receptor-1 de FGF o receptor-2 de FGF, receptor de VEGF, receptor de angiopoyetina (Tie2 etc.), receptor de PDGF, y similares.

Como el "agentes farmacéuticos que inhiben la acción de factores de crecimiento celular o receptores del factor de crecimiento celular", inhibidor de EGF, TGFα, heregulina, insulina, IGF, FGF, KGF, CSF, EPO, IL-2, NGF, PDGF, TGFβ, HGF, VEGF, angiopoyetina, receptor de EGF, HER2, HER4, inhibidor del receptor de insulina, IGF-1, IGF-2, inhibidor del receptor-1 de FGF, inhibidor del receptor-2 de FGF, inhibidor del receptor-3 de FGF, inhibidor del receptor-4 de FGF, inhibidor del receptor de VEGF, Tie-2, receptor de PDGF, inhibidor de Abl, Raf, FLT3, c-Kit, Src, PKC, Trk, Ret, mTOR, Aurora, PLK, MEK(MEK1/2), MET CDK, Akt, ERK y similares son los que se usan. En forma más específica, anticuerpo anti-VEGF (Bevacizumab etc.), anticuerpo anti-HER2 (Trastuzumab, Pertuzumab etc.), anticuerpo anti-EGFR (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anticuerpo anti-VEGFR, anticuerpo anti-HGF, mesilato de Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-metil-1H-indol-5-iloxi)-6-metoxi-7-[3-(1-pirrolidinil)propoxi]quinazolina (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tyutinib, 3-(4-bromo-2,6-difluorobenciloxi)-5-[3-[4-(1-pirrolidinil)butil]ureido]isotiazol-4-carboxamida (CP-547632), Axitinib, N-(3,3-dimetil-2,3-dihidro-1H-indol-6-il)-2-(piridin-4-ilmetilamino)piridin-3-carboxamida (AMG-706), Nilotinib, 6-[4-(4-etilpiperazin-1-ilmetil)fenil]-N-[1(R)-feniletil]-7H-pirrolo[2,3-d]pirimidin-4-amina (AEE-788), Vyetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-metilpiperazin-1-il)-6-(3-metil-1H-pirazol-5-ilamino)pirimidin-2-ilsulfanil]fenil]ciclopropanocarboxamida (VX-680), 2-[N-[3-[4-[5-

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[N-(3-fluorofenil)carbamoilmetil]-1H-pirazol-3-ilamino]quinazolin-7-iloxi]propil]-N-etilamino]etil éster del ácido fosfórico (AZD-1152), ácido 4-[9-cloro-7-(2,6-difluorofenil)-5H-pirimido[5,4-d][2]benzazepin-2-ilamino]benzoico (MLN-8054), N-[2-metoxi-5-[(E)-2-(2,4.6-trimetoxifenil)vinilsulfonilmetil]fenil]glicina, sal de sodio (ON-1910Na), 4-[8-ciclopentil-7(R)-etil-5-metil-6-oxo-5,6,7.8-tetrahidropteridin-2-ilamino]-3-metoxi-N-(1-metilpiperidin-4-il)benzamida (BI-2536), 2-hidroxietil éster del ácido 5-(4-bromo-2-clorofenilamino)-4-fluoro-1-metil-1H-benzimidazol-6-carbohidroxámico (AZD-6244), N-[2(R),3-dihidroxipropoxi]-3,4-difluoro-2-(2-fluoro-4-yodofenilamino)benzamida (PD-0325901), Everolimus (RAD001) y similares son los que se usan.

Además de los fármacos antes mencionado, L-asparaginasa, aceglatona, clorhidrato de procarbazina, sal de complejo protoporfirina-cobalto, hematoporfirina sódica de mercurio, inhibidores de topoisomerasa I (por ejemplo, irinotecan, topotecan, y similares), inhibidores de topoisomerasa II (por ejemplo, sobuzoxano, y similares), inductores de diferenciación (por ejemplo, retinoide, vitamina D, y similares), otros inhibidores de angiogénesis (por ejemplo, humagilina, extracto de tiburón, inhibidor de COX-2, y similares), α-bloqueadores (por ejemplo, clorhidrato de tamsulosina, y similares), ácidos bisfosfónicos (por ejemplo, pamidronato, zoldronato, y similares), talidomida, 5-azacitidina, decitabina, inhibidor de proteasoma (por ejemplo, bortezomib, y similares), anticuerpo antitumoral tal como anticuerpo anti-CD20 y similares, anticuerpo rotulado con toxina y similares también pueden utilizarse.

Al combinar el compuesto de la presente invención y un medicamento concomitante, puede lograrse un efecto superior tales como

(1) la dosis puede reducirse en comparación con la

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administración simple del compuesto de la presente invención o un medicamento concomitante,

(2) el fármaco que se combinará con el compuesto de la presente invención puede seleccionarse de acuerdo con la afección de los pacientes (caso leve, caso severo y similar),

(3) el período de tratamiento puede ser de mayor duración,

(4) puede diseñarse un efecto de tratamiento prolongado,

(5) puede lograrse un efecto sinergístico con un uso combinado del compuesto de la presente invención y un medicamento concomitante, y similares.

En la presente especificación, el compuesto de la presente invención y un medicamento concomitante usado en combinación se mencionan como el "agente combinado de la presente invención".

Para el uso del agente combinado de la presente invención, el tiempo de administración del compuesto de la presente invención y el fármaco concomitante no está restringido, y el compuesto de la presente invención y el fármaco concomitante puede administrarse a un sujeto de administración en forma simultánea, o pueden administrarse en momentos diferentes. La dosificación del fármaco concomitante puede determinarse de acuerdo con la dosis establecida desde el punto de vista clínico, y puede seleccionarse apropiadamente dependiendo del sujeto de administración, la vía de administración, enfermedad, combinación y similares.

Ejemplos de modo de administración del uso combinado del compuesto de la presente invención y el fármaco concomitante incluyen los siguientes métodos: (1) El compuesto de la presente invención y el fármaco concomitante se producen en forma simultánea para dar una preparación individual, que luego se administra. (2) El compuesto de la presente invención y el

fármaco concomitante se producen en forma separada para dar dos clases de preparaciones que se administran en forma simultánea por la misma vía de administración. (3) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos clases de preparaciones que se administran por la misma vía de administración en momentos diferentes. (4) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos clases de preparaciones que se administran en forma simultánea por vías de administración diferentes. (5) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos clases de preparaciones que se administran por vías de administración diferentes en momentos diferentes (por ejemplo, el compuesto de la presente invención y el fármaco concomitante se administran en este orden, o en el orden inverso). La dosis del fármaco concomitante se determina en forma apropiada de acuerdo con su dosis clínica, y la proporción del compuesto de la presente invención y el fármaco concomitante se determina en forma apropiada dependiendo del sujeto de administración, la vía de administración, la enfermedad de destino, síntoma, combinación, y similares. Por ejemplo, cuando el sujeto de administración es humano, el fármaco concomitante se usa en 0.01 a 100 (partes en peso), con relación a 1 parte en peso del compuesto de la presente invención.

El agente combinado de la presente invención tiene baja toxicidad y, por ejemplo, el compuesto de la presente invención y/o el medicamento concomitante mencionado con anterioridad pueden mezclarse, de acuerdo con un método conocido *per se*, con un vehículo aceptable desde el punto de vista farmacológico para dar composiciones farmacéuticas, tales como comprimidos (incluyendo comprimido con recubrimiento azucarado, comprimido

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recubierto), polvos, gránulos, cápsulas (incluyendo cápsula suave), soluciones, inyecciones, supositorios, agentes de liberación prolongada y similares, que pueden administrarse en forma segura por vía oral o por vía parenteral (por ejemplo, local, recto, venoso, y similares). Una inyección puede administrarse por vía intravenosa, intramuscular, subcutánea o intra-orgánica, o directamente a la lesión.

Como un vehículo aceptable desde el punto de vista farmacológico que puede usarse para preparar el agente combinado de la presente invención, aquellos similares a los vehículos aceptables desde el punto de vista farmacéutico antes mencionados, que pueden usarse para la producción del agente farmacéutico de la presente invención, pueden mencionarse. Donde corresponda, los aditivos el antes mencionados que pueden usarse para la producción del agente farmacéutico de la presente invención, tales como conservantes, antioxidantes, colorantes, agentes edulcorantes, adsorbentes, agentes humectantes y similares también puede usarse en forma apropiada en cantidades apropiadas.

La proporción de formación de compuesto del compuesto de la presente invención al fármaco concomitante en el agente combinado de la presente invención puede determinarse en forma apropiada dependiendo del sujeto de administración, la vía de administración, enfermedades y similares.

Por ejemplo, el contenido del compuesto de la presente invención en el agente combinado de la presente invención varía dependiendo de la forma de dosificación, y es usualmente desde aproximadamente 0.01 a 100% en peso, preferiblemente desde aproximadamente 0.1 a 50% en peso, preferiblemente adicional desde aproximadamente 0.5 a 20% en peso, en base a la preparación completa.

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El contenido del fármaco concomitante en el agente combinado de la presente invención varía dependiendo de la forma de dosificación, y es usualmente desde aproximadamente 0.01 a 90% en peso, preferiblemente desde aproximadamente 0.1 a 50% en peso, preferiblemente adicional desde aproximadamente 0.5 a 20% en peso, en base a la preparación completa.

El contenido de aditivos en el agente combinado de la presente invención varía dependiendo de la forma de dosificación, y es usualmente desde aproximadamente 1 a 99.99% en peso, preferiblemente desde aproximadamente 10 hasta 90% en peso, en base a la preparación completa.

Cuando el compuesto de la presente invención y el fármaco concomitante se preparan por separado, puede adoptarse el mismo contenido.

Estas preparaciones pueden producirse por un método conocido *per se*, que se utiliza en general en el proceso de preparación.

Por ejemplo, el compuesto de la presente invención y el fármaco concomitante pueden producirse en una inyección acuosa junto con un agente de dispersión (por ejemplo, Tween 80 (fabricado por Atlas Polvo, US), HCO 60 (fabricado por Nikko Chemicals), polietilenglicol, carboximetilcelulosa, alginato de sodio, hidroxipropilmetilcelulosa, dextrinas y similares), un estabilizador (por ejemplo, ácido ascórbico, picosulfito de sodio, y similares), un tensioactivo (por ejemplo, Polisorbato 80, macrogol y similares), un solubilizante (por ejemplo, glicerina, etanol y similares), un amortiguador (por ejemplo, ácido fosfórico y su sal de metal alcalino, ácido cítrico y su sal de metal alcalino, y similares), un agente de isotonicidad (por ejemplo, cloruro de sodio, cloruro de potasio, manitol, sorbitol, glucosa y similares), un regulador de pH (por ejemplo, ácido clorhídrico, hidróxido de

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sodio y similares), un conservante (por ejemplo, paraoxibenzoato de etilo, ácido benzoico, metilparabeno, propilparabeno, alcohol bencílico y similares), un agente de disolución (por ejemplo, glicerina concentrado, meglumina y similares), un agente de solubilización (por ejemplo, propilenglicol, sacarosa y similares), un agente suavizante (por ejemplo, glucosa, alcohol bencílico y similares), y similares, o puede disolverse, suspenderse o emulsionarse en un aceite vegetal tales como aceite de oliva, aceite de sésamo, aceite de semilla de algodón, aceite de maíz y similares o un agente de solubilización tales como propilenglicol y similares y se prepara en una inyección oleosa, por la cual se obtiene una inyección.

Además, un excipiente (por ejemplo, lactosa, sacarosa, almidón y similares), un agente de desintegración (por ejemplo, almidón, carbonato de calcio y similares), un aglutinante (por ejemplo, almidón, de goma arábiga, carboximetilcelulosa, polivinilpirrolidona, hidroxipropilcelulosa y similares), un lubricante (por ejemplo, talco, estearato de magnesio, polietilenglicol 6000 y similares) y similares pueden agregarse al compuesto de la presente invención o el fármaco concomitante, y la mezcla puede moldearse por compresión, de acuerdo con un método conocido *per se* luego si se desea, el producto moldeado puede recubrirse por un método conocido *per se* para los fines de enmascarar el sabor, la propiedad entérica o durabilidad, para dar una preparación para administración oral. Como el agente de recubrimiento, por ejemplo, hidroxipropilmetilcelulosa, etilcelulosa, hidroximetilcelulosa, hidroxipropilcelulosa, polioxietilenglicol, Tween 80, Pluronic F68, celulosa acetato ftalato, hidroxipropilmetilcelulosa ftalato, hidroximetilcelulosa acetato succinato, Eudoragit (copolímero de ácido metacrílico□ácido acrílico, fabricado por Rohm, DE), pigmento

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(por ejemplo, óxido de hierro rojo, dióxido de titanio, etc.) y similares puede usarse. La preparación para administración oral puede ser cualquiera de una preparación de liberación inmediata y una preparación de liberación prolongada.

Más aun, el compuesto de la presente invención y el fármaco concomitante puede realizarse en un sólido oleoso o acuoso, supositorio semisólido o líquido de acuerdo con un método conocido *per se*, mezclándolos con un sustrato oleoso, sustrato acuoso o sustrato en gel acuoso. Como el sustrato oleoso mencionado con anterioridad, por ejemplo, se mencionan glicéridos de ácido graso superior [por ejemplo, manteca de cacao, Witepsols (fabricado por Dynamit Nobel, Alemania), etc.], glicéridos de ácido graso de cadena media [por ejemplo, Miglyols (fabricado por Dynamit Nobel, Alemania), etc.], o aceites vegetales (por ejemplo, aceite de sésamo, aceite de soja, aceite de semilla de algodón y similares), y similares. Además, como el sustrato acuoso, por ejemplo, se mencionan polietilenglicol, propilenglicol y similares, y como el sustrato en gel acuoso, por ejemplo, se mencionan gomas naturales, derivados de celulosa, polímeros de vinilo, polímeros de ácido acrílico y similares.

Como la preparación de liberación prolongada mencionada con anterioridad, se mencionan las microcápsulas de liberación prolongada y similares. La microcápsula de liberación prolongada puede producirse por un método conocido *per se*, por ejemplo, un método que se muestra n la siguiente [2].

El compuesto de la presente invención se moldea preferiblemente en una preparación para administración oral tal como una preparación sólida (por ejemplo, polvo, gránulo, comprimido, cápsula) y similares, o se moldea en una preparación para administración rectal tales como un supositorio y similares. Particularmente, a preparación para administración oral es

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preferible.

El fármaco concomitante puede realizarse en la forma farmacológica mencionada con anterioridad dependiendo de la clase de fármaco.

[1] Una inyección del compuesto de la presente invención o el fármaco concomitante, y su preparación, [2] una preparación de liberación prolongada o preparación de liberación inmediata del compuesto de la presente invención o el fármaco concomitante, y su preparación, [3] un agente de integración rápida sublingual, bucal o intraoral del compuesto de la presente invención o el fármaco concomitante, y su preparación, se describirán a continuación en forma específica.

[1] Inyección y su preparación de lo mismo.

Una inyección preparada por disolución el compuesto de la presente invención o el fármaco concomitante en agua es preferible. Esta inyección puede contener un benzoato y/o salicilato.

La inyección se obtiene por disolución el compuesto de la presente invención o el fármaco concomitante, y si se desea, a benzoato y/o salicilato, en agua.

Como las sales mencionadas con anterioridad de ácido benzoico y ácido salicílico, por ejemplo, se enumeran sales de metales alcalinos tales como sodio, potasio y similares, sales de metales alcalino-térreos tales como calcio, magnesio y similares, sal de amonios, sales de meglumina, sales con bases orgánicas tales como trometamol y similares, etc..

La concentración del compuesto de la presente invención o el fármaco concomitante en una inyección es desde 0.5 a 50 w/v%, preferiblemente desde aproximadamente 3 hasta 20 w/v%. La concentración de un benzoato o/y salicilato es desde 0.5 a 50% p/v, preferiblemente desde aproximadamente 3 hasta 20%

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p/v.

La inyección de la presente invención contiene en forma apropiada aditivos usados usualmente en una inyección, por ejemplo, un estabilizador (por ejemplo, ácido ascórbico, picosulfito de sodio y similares), un tensioactivo (por ejemplo, Polisorbato 80, macrogol y similares), un solubilizante (por ejemplo, glicerina, etanol y similares), un amortiguador (por ejemplo, ácido fosfórico y su sal de metal alcalino, ácido cítrico y su sal de metal alcalino, y similares), un agente de isotonicidad (por ejemplo, cloruro de sodio, cloruro de potasio y similares), un agente dispersante (por ejemplo, hidroxipropilmetilcelulosa, dextrina), un regulador de pH (por ejemplo, ácido clorhídrico, hidróxido de sodio y similares), un conservante (por ejemplo, parahidroxibenzoato de etilo, ácido benzoico y similares), un agente de disolución (por ejemplo, glicerina concentrado, meglumina y similares), un agente de solubilización (por ejemplo, propilenglicol, sacarosa y similares), un agente suavizante (por ejemplo, glucosa, alcohol bencílico y similares), y similares. Estos aditivos generalmente se mezclan en una proporción usualmente usada en una inyección.

Resulta ventajoso que el pH de una inyección se controle desde pH 2 a 12, preferiblemente desde pH 2.5 a 8.0, con la incorporación de un regulador de pH.

Una inyección se obtiene por disolución el compuesto de la presente invención o el fármaco concomitante y si se desea, un benzoato y/o un salicilato, y si es necesario, los aditivos antes mencionados en agua. Estos pueden disolverse en cualquier orden y pueden disolverse en forma apropiada del mismo modo que en un método convencional de producir una inyección.

Una solución acuosa para inyección puede calentarse en forma ventajosa, en forma alternativa, por ejemplo, esterilización

por filtrado, esterilización con alta presión y similares pueden conducirse del mismo modo que para una inyección usual, para proporcionar una inyección.

Puede ser ventajoso que una solución acuosa para inyección se someta a esterilización con calor a alta presión a 100 hasta 121°C durante 5 a 30 min.

Además, una preparación provista de una propiedad antibacteriana de una solución también puede producirse para que pueda utilizarse como preparación que se divide y administra múltiples veces.

[2] La preparación de liberación prolongada o preparación de liberación inmediata, y su preparación

Se prefiere una preparación de liberación prolongada que se obtiene, si se desea, por recubrimiento de un núcleo que contiene el compuesto de la presente invención o el fármaco concomitante con un agente de película tales como una sustancia insoluble en agua, polímero expandible y similares. Por ejemplo, una preparación de liberación prolongada para administración oral del tipo de administración una vez por día es preferible.

Como la sustancia insoluble en agua usado en un agente de película, se enumeran, por ejemplo, éteres de celulosa tales como etilcelulosa, butilcelulosa y similares, ésteres de celulosa tales como acetato de celulosa, propionato de celulosa y similares, polivinil ésteres tales como acetato de polivinilo, butirato de polivinilo y similares, copolímeros de ácido acrílico/ ácido metacrílico, copolímeros de metacrilato de metilo, copolímeros de metacrilato de etoxietilo/metacrilato de cinamoetilo /metacrilato de aminoalquilo, ácido poliacrílico, ácido polimetacrílico, copolímeros de alquilamida de ácido metacrílico, poli(metil metacrilato), polimetacrilato, polimetacrilamida, copolímeros de aminoalquilo metacrilato, poli(anhídrido metacrílico), copolímero

de metacrilato de glicidilo, particularmente, polímeros basados en ácido acrílico tales como Eudoragit (fabricado por Rohm Pharma) tales como Eudoragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (copolímero de acrilato de etilo /metacrilato de metilo /metacrilato de trimetilcloruro /etil amonio), Eudoragit NE-30D (copolímero de metacrilato de metilo / acrilato de etilo), y similares, aceites hidrogenados tales como aceite de ricino hidrogenado (por ejemplo, Lubri cera (fabricado por Freund Corporación) y similares), ceras tales como cera carnauba, éster de glicerina de ácidos grasos, parafina y similares, ésteres de ácidos grasos de poliglicerina, y similares.

Como el polímero expandible, se prefieren los polímeros que tienen un grupo de disociación ácida y que muestran una expansión dependiente del pH, y polímeros que tienen un grupo de disociación ácida, que manifiestan una pequeña expansión en regiones ácidas tales como en el estómago y una extensa expansión en regiones neutras tales como en el intestino delgado e intestino grueso, son preferibles.

Como tal polímero que tiene un grupo de disociación ácida y que muestra una expansión dependiente del pH, se enumeran polímeros de ácido poliacrílico de ligación cruzada tales como, por ejemplo, Carbomer 934P, 940, 941, 974P, 980, 1342 y similares, policarbofil, policarbofil de calcio (todos fabricados por BF Goodrich), Hiviswako 103, 104, 105, 304 (todos fabricados por Wako Pure Chemical Industries, Ltd.), y similares.

El agente de recubrimiento usado en una preparación de liberación prolongada puede contener en forma adicional una sustancia hidrofílica.

Como la sustancia hidrofílica, por ejemplo, pueden mencionarse polisacáridos que pueden contener un grupo sulfato tal como pululan, alginato de metal alcalino y similares,

polisacáridos que tienen un hidroxialquilo o carboxialquilo tales como hidroxipropilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa sodio y similares, metilcelulosa, polivinilpirrolidona, polivinilo alcohol, polietilenglicol y similares.

El contenido de una sustancia insoluble en agua en el agente de recubrimiento de una preparación de liberación prolongada es desde aproximadamente 30 hasta aproximadamente 90% (p/p), preferiblemente desde aproximadamente 35 a aproximadamente 80% (p/p), preferiblemente adicional desde aproximadamente 40 hasta aproximadamente 75% (p/p), el contenido de un polímero expandible es desde aproximadamente 3 hasta aproximadamente 30% (p/p), preferiblemente desde aproximadamente 3 hasta aproximadamente 15% (p/p). El agente de recubrimiento puede contener en forma adicional una sustancia hidrofílica, y en cuyo caso, el contenido de una sustancia hidrofílica en el agente de recubrimiento es de aproximadamente 50% (p/p) o menos, preferiblemente aproximadamente 5 a aproximadamente 40% (p/p), preferiblemente adicional desde aproximadamente 5 a aproximadamente 35% (p/p). Este % (p/p) indica % en peso en base a la composición de un agente de película que se obtiene por eliminación un solvente (por ejemplo, agua, alcoholes de tales como metanol, etanol y similares) de la solución de un agente de película.

La preparación de liberación prolongada se produce por preeparación un núcleo que contiene un fármaco como se ejemplifica a continuación, luego recubriendo el núcleo resultante con una solución de un agente de película preparada disolviendo con calor una sustancia insoluble en agua, polímero expandible y similares o por disolución o dispersándola en un solvente.

I. Preparación del núcleo que contiene fármaco.

La forma del núcleo que contiene un fármaco que se recubrirá con un agente de película (de aquí en adelante, denominado en ocasiones simplemente núcleo) no se restringe en forma particular, y preferiblemente, el núcleo se forma en partículas tales como un gránulo o partículas finas.

Cuando el núcleo está compuesto por gránulos o partículas finas, su tamaño de partículas promedio es preferiblemente desde aproximadamente 150 hasta aproximadamente 2000 μm, preferiblemente adicional, desde aproximadamente 500 hasta aproximadamente 1400 μm.

La Preparación del núcleo puede efectuarse por un método de producción usual. Por ejemplo, un excipiente apropiado, agente aglutinante, agente desintegrante, lubricante, estabilizante y similares se mezclan con un fármaco, y la mezcla se somete a un método de granulación por extrusión húmeda, método de granulación en lecho fluidificado o similares, para prepare un núcleo.

El contenido de fármacos presentes en un núcleo es desde aproximadamente 0.5 a aproximadamente 95% (p/p), preferiblemente desde aproximadamente 5.0 hasta aproximadamente 80% (p/p), preferiblemente adicional desde aproximadamente 30 hasta aproximadamente 70% (p/p).

Como el excipiente contenido en el núcleo, por ejemplo, se usan sacáridos tales como sacarosa, lactosa, manitol, glucosa y similares, almidón, celulosa cristalina, fosfato de calcio, almidón de maíz y similares. Entre ellos, son preferibles celulosa cristalina, almidón de maíz.

Como el agente aglutinante, por ejemplo, polivinilo alcohol, hidroxipropilcelulosa, polietilenglicol, polivinilpirrolidona, Pluronic F68, de goma arábiga, gelatina, almidón y similares se usan. Como el agente desintegrante, por ejemplo, se usan

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carboximetilcelulosa calcio (ECG505), croscarmelosa de sodio (Ac-Di-Sol), polivinilpirrolidona entrecruzada (Crospovidona), hidroxipropilcelulosa de baja sustitución (L-HPC) y similares. Entre ellos, hidroxipropilcelulosa, polivinilpirrolidona, hidroxipropilcelulosa de baja sustitución son preferibles. Como el lubricante y el inhibidor de coagulación, por ejemplo, talco, se usan estearato de magnesio y sus sales inorgánicas, y como el lubricante, se usan polietilenglicol y similares. Como el estabilizante, se usan ácidos tales como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico y similares.

Un núcleo pueden prepararse también, además del método de producción antes mencionado, por ejemplo, por un método de granulación con rodillo en donde un fármaco o una mezcla de un fármaco con un excipiente, lubricante y similares se agrega en porciones sobre una partícula vehículo inerte que es el centro del núcleo mientras que se atomiza un aglutinante disuelto en un solvente apropiado tal como agua, alcohol inferior (por ejemplo, metanol, etanol y similares) y similares, un método de recubrimiento en sartén, un método de recubrimiento en lecho fluidificado o un método de granulación por fusión. Como la partícula de vehículo inerte, por ejemplo, pueden usarse aquellas realizadas de sacarosa, lactosa, almidón, celulosa cristalina o ceras, y su tamaño de partículas promedio es preferiblemente desde aproximadamente 100 μm hasta aproximadamente 1500 μm.

Para separar un fármaco contenido en un núcleo y un agente de película, la superficie del núcleo puede recubrirse con un agente protector. Como el agente protector, por ejemplo, se usan las sustancias hidrofílicas mencionadas con anterioridad, sustancias insolubles en agua y similares. Como el agente protector, se usan preferiblemente polietilenglicol, y polisacáridos que tiene un hidroxialquilo o carboxialquilo, con mayor

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preferencia, se usan hidroxipropilmetilcelulosa y hidroxipropilcelulosa. El agente protector puede contener, como estabilizante, ácidos tales como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico y similares, y lubricantes tales como talco y similares. Cuando se usa el agente protector, la cantidad de recubrimiento es desde aproximadamente 1 a aproximadamente 15% (p/p), preferiblemente desde aproximadamente 1 a aproximadamente 10% (p/p), preferiblemente adicional desde aproximadamente 2 a aproximadamente 8% (p/p), en base en el núcleo.

El agente protector puede recubrirse por un método de recubrimiento usual, y en forma específica, el agente protector puede recubrirse por recubrimiento por aspersión del núcleo, por ejemplo, por un método de recubrimiento con lecho fluidificado, método de recubrimiento en sartén y similares.

II. Recubrimiento del núcleo con agente formador de película.

Un núcleo obtenido en el antes mencionado etapa I se recubre con una solución de un agente de película obtenida disolviendo por calor la sustancia insoluble en agua mencionada con anterioridad y polímero expandible dependiente del pH, y una sustancia hidrofílica, o por disolución o su dispersión en un solvente, para dar una preparación de liberación prolongada.

Como el método para recubrir un núcleo con una solución de un agente de película, por ejemplo, se enumeran un método de recubrimiento por aspersión y similares.

La relación de la composición de una sustancia insoluble en agua, polímero expandible o sustancia hidrofílica en una solución de un agente de película se selecciona de manera apropiada de modo tal que los contenidos de estos componentes en la película recubierta son los contenidos mencionados con anterioridad, respectivamente.

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La cantidad de recubrimiento de un agente de película es desde aproximadamente 1 a aproximadamente 90% (p/p), preferiblemente desde aproximadamente 5 a aproximadamente 50% (p/p), preferiblemente adicional desde aproximadamente 5 a aproximadamente 35% (p/p), en base a un núcleo (sin incluir la cantidad de recubrimiento de agente protector).

Como el solvente en una solución de un agente de película, puede usarse agua o un solvente orgánico solo o en una mezcla. En el caso de usarlos mezclados, la proporción de mezclado de agua a un solvente orgánico (agua/solvente orgánico: en peso) puede variar en el intervalo desde 1 a 100%, y preferiblemente desde 1 a aproximadamente 30%. El solvente orgánico no está restringido particularmente siempre que disuelva una sustancia insoluble en agua, y por ejemplo, se usan alcoholes inferiores tales como metil alcohol, etil alcohol, alcohol isopropílico, n-butilo alcohol y similares, alcanona inferior tales como acetona y similares, acetonitrilo, cloroformo, cloruro de metileno y similares. Entre ellos, alcohol inferiores son preferibles, y etil alcohol y alcohol isopropílico se prefieren en particular. Agua, y una mezcla de agua con un solvente orgánico se usan preferiblemente como solvente para un agente de película. En este caso, si es necesario, un ácido tal como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico y similares también pueden agregarse en una solución de un agente de película para estabilizar la solución del agente de película.

Una operación de recubrimiento por recubrimiento por aspersión puede efectuarse por un método de recubrimiento usual, y en forma específica, puede efectuarse por recubrimiento de una solución de un agente de película sobre un núcleo por un método de recubrimiento en lecho fluidificado, método de recubrimiento en sartén y similares. En este caso, si es

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necesario, también pueden agregarse talco, óxido de titanio, estearato de magnesio, estearato de calcio, ácido silícico anhidro liviano como lubricante, y éster de ácido graso de glicerina, aceite de ricino hidrogenado, citrato de trietilo, alcohol cetílico, alcohol estearílico y similares también pueden agregarse como plastificante.

Luego de recubrir con un agente de película, si es necesario, pueden mezclarse un agente anti-estática tales como talco y similares.

La preparación de liberación inmediata puede ser líquida (solución, suspensión, emulsión y similares) o sólida (partícula, píldora, comprimido y similares). Como los agentes de preparación de liberación inmediata, se usan agentes de administración oral y administración parenteral tales como una inyección y similares, y son preferibles los agentes de administración oral.

La preparación de liberación inmediata, usualmente, puede contener, además de un componente activo farmacológico, todos los vehículos, aditivos y excipientes usados convencionalmente en el campo farmacéutico (de aquí en adelante, en ocasiones abreviado como excipiente). El excipiente usado no se restringe particularmente siempre que sea un excipiente usado normalmente como excipiente para preparación. Por ejemplo, como el excipiente para una preparación oral sólida, se enumeran lactosa, almidón, almidón de maíz, celulosa cristalina (Avicel PH101, fabricado por Comoahi Kasei Corporación, y similares), azúcar en polvo, azúcar granulada, manitol, ácido silícico anhidro liviano, carbonato de magnesio, carbonato de calcio, L-cisteína y similares, y preferiblemente, se enumeran almidón de maíz y manitol y similares. Estos excipientes puede usarse solos o en combinación de dos o más. El contenido del excipiente es, por

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ejemplo, desde aproximadamente 4.5 a aproximadamente 99.4 % p/p, preferiblemente desde aproximadamente 20 hasta aproximadamente 98.5 % p/p, preferiblemente adicional desde aproximadamente 30 hasta aproximadamente 97 % p/p, en base a la cantidad total de la preparación de liberación inmediata.

El contenido de un fármaco en la preparación de liberación inmediata puede seleccionarse en forma apropiada en el intervalo desde aproximadamente 0.5 a aproximadamente 95% p/p, preferiblemente desde aproximadamente 1 a aproximadamente 60% p/p en base a la cantidad total de la preparación de liberación inmediata.

Cuando la preparación de liberación inmediata es una preparación sólida oral, usualmente contiene, además de los componentes mencionados con anterioridad, también un agente de integración. Como este agente de integración, por ejemplo, se usan carboximetilcelulosa de calcio (ECG-505, fabricado por Gotoku Yakuhin), croscarmelosa de sodio (por ejemplo, Actisol, fabricado por Comoahi Kasei Corporación), crospovidona (por ejemplo, Kollidon CL, fabricado por BASF), hidroxipropilcelulosa de baja sustitución (fabricado por Shin-Etsu Chemical Co., Ltd.), carboximetil almidón (fabricado por Matsutani Kagaku K.K.), carboximetil almidón de sodio (Exprotab, fabricado por Kimura Sangyo), almidón parcialmente pre-gelatinizado (PCS, fabricado por Comoahi Kasei Corporación), y similares, y por ejemplo, aquellas que desintegran un gránulo absorbiendo agua en contacto con el agua, causan la expansión, o haciendo un canal entre un componente efectivo y un excipiente que constituye el núcleo, puede usarse. Estos agentes desintegrantes pueden usarse solos o en combinación de dos o más. La cantidad del agente desintegrante usado se selecciona apropiadamente dependiendo de la clase y cantidad de mezclado de un fármaco

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usado, el diseño de la propiedad de liberación, y similares, y por ejemplo, desde aproximadamente 0.05 a aproximadamente 30 % p/p, preferiblemente desde aproximadamente 0.5 a aproximadamente 15 % p/p, en base a la cantidad total de la preparación de liberación inmediata.

Cuando la preparación de liberación inmediata es una preparación sólida oral, puede contener en forma adicional, además de la composición mencionada con anterioridad, si se desea, aditivos convencionales en las preparaciones sólidas. Como tal aditivo, se usan, por ejemplo, un aglutinante (por ejemplo, sacarosa, gelatina, de goma arábiga polvo, metilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa, polivinilpirrolidona, pululan, dextrina y similares), un lubricante (por ejemplo, polietilenglicol, estearato de magnesio, talco, ácido silícico anhidro liviano (por ejemplo, Aerosil (fabricado por Nippon Aerosil)), un tensioactivo (por ejemplo, tensioactivos aniónicos tales como alquilsulfonato de sodio y similares, tensioactivos no iónicos tales como éster de ácido graso de polioxietileno y éster de ácido graso sorbitano de polioxietileno, derivados de aceite de ricino de polioxietileno y similares), un colorante (por ejemplo, material colorante de alquitrán, caramel, óxido de hierro rojo, óxido de titanio, riboflavinas), si es necesario, un agente saborizante (por ejemplo, agente edulcorante, agente saborizante y similares), un adsorbente, conservante, agente humectante, agente anti-estática, y similares. Además, como el estabilizante, un ácido orgánico tales como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico y similares también pueden agregarse.

Como el aglutinante mencionado con anterioridad, se usan preferiblemente hidroxipropilcelulosa, polietilenglicol y polivinilpirrolida y similares.

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La preparación de liberación inmediata puede prepararse en base a una tecnología usual de producción de preparaciones, mezcla los componentes antes mencionados, y si es necesario, tejiendo en forma adicional la mezcla, y moldeándola. El mezclado mencionado con anterioridad se conduce por métodos generalmente conocidos, por ejemplo, mezclado, tejido y similar. En forma específica, cuando se forma una preparación de liberación inmediata, por ejemplo, en una partícula, puede prepararse, de acuerdo con el mismo medio que en el antes mencionado método para preparar un núcleo de una preparación de liberación prolongada, mezcla los componentes un granulador vertical, tejedor universal (fabricado por Hata Tekkosho), granulador de lecho fluidificado FD-5S (fabricado por Powrex Corporación), y similares, y luego, granulo la mezcla por un método de granulación con extrusión en húmedo, método de granulación en lecho fluidificado y similares.

La preparación de liberación inmediata obtenida de este modo y la preparación de liberación prolongada puede producirse en productos o en productos apropiadamente unidos con los excipientes de preparación y similares, por separado, por un método normal, luego, pueden administrarse en forma simultánea o pueden administrarse en combinación en cualquier intervalo de administración, o pueden realizarse en una preparación para administración oral (por ejemplo, gránulo, partícula fina, comprimido, cápsula y similares) o en una preparación para administración oral unidos apropiadamente con excipientes de preparación y similares. También puede permitirse que se realicen en gránulos o partículas finas, y se envasen en la misma cápsula que se usará como una preparación para administración oral.

[3] Agente desintegrante sublingual, bucal o intraoral rápido

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y su preparación de lo mismo

Los agentes desintegrantes sublinguales, bucales o intraorales rápidos pueden ser una preparación sólida tales como comprimido y similares, o pueden ser un parche de membrana a la mucosa oral (película).

Como el agente desintegrante sublingual, bucal o intraoral rápido, es preferible una preparación que contiene el compuesto de la presente invención o el fármaco concomitante y un excipiente. También puede contener agentes auxiliares tales como un lubricante, agente de isotonicidad, vehículo hidrofílico, polímero dispersable en agua, estabilizante y similares. Además, para una rápida absorción y amento de eficacia de uso *in vivo*, también pueden incluirse β-ciclodextrina o derivados de β-ciclodextrina (por ejemplo, hidroxipropil-β-ciclodextrina y similares) y similares.

Como el excipiente mencionado con anterioridad, se enumeran lactosa, sacarosa, D-manitol, almidón, celulosa cristalina, ácido silícico anhidro liviano y similares. Como el lubricante, estearato de magnesio, estearato de calcio, talco, sílice coloidal y similares se enumeran, y particularmente, estearato de magnesio y sílice coloidal son preferibles. Como el agente de isotonicidad, cloruro de sodio, glucosa, fructosa, manitol, sorbitol, lactosa, sacarosa, glicerina, urea y similares se enumeran, y particularmente, manitol es preferible. Como el vehículo hidrofílico, se prefieren los vehículos hidrofílicos expandibles tales como celulosa cristalina, etilcelulosa, polivinilpirrolidona entrecruzable, ácido silícico anhidro liviano, ácido silícico, difosfato de calcio, carbonato de calcio y similares se enumeran, y particularmente, celulosa cristalina (por ejemplo, celulosa microcristalina y similares). Como el polímero dispersable en agua, se enumeran gomas (por ejemplo, goma

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tragacanto, goma acacia, goma ciamoposis), alginatos (por ejemplo, alginato de sodio), derivados de celulosa (por ejemplo, metilcelulosa, carboximetilcelulosa, hidroximetilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa), gelatina, soluble en agua almidón, ácidos poliacrílicos (por ejemplo, Carbomer), ácido polimetacílico, polivinilo alcohol, polietilenglicol, polivinilpirrolidona, policarbofil, ácido ascórbico, palmitatos y similares, y hidroxipropilmetilcelulosa, ácido poliacrílico, alginato, gelatina, carboximetilcelulosa, polivinilpirrolidona, polietilenglicol y similares son preferibles. Particularmente, hidroxipropilmetilcelulosa es preferible. Como el estabilizante, cisteína, tiosorbitol, ácido tartárico, ácido cítrico, carbonato de sodio, ácido ascórbico, glicina, sulfito de sodio y similares se enumeran, y particularmente, ácido cítrico y ácido ascórbico son preferibles.

El agente desintegrante sublingual, bucal o intraoral rápido puede producirse por mezcla el compuesto de la presente invención o el fármaco concomitante y un excipiente por un método conocido *per se*. Además, si se desea, los agentes auxiliares mencionados con anterioridad tales como un lubricante, agente de isotonicidad, vehículo hidrofílico, polímero dispersable en agua, estabilizante, colorante, agente edulcorante, conservante y similares pueden mezclarse. El agente desintegrante sublingual, bucal o intraoral rápido se obtiene por mezcla los componentes mencionados con anterioridad en forma simultánea o en un intervalo de tiempo, luego sometiendo la mezcla a moldeado para formar comprimidos bajo presión. Para obtener la dureza apropiada, puede permitirse que los materiales se humedezcan usando un solvente tal como agua, alcohol y similares si se desea antes o después del proceso de modalidad del comprimido, y después de moldear, los materiales se secan,

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para obtener un producto.

En el caso de moldear en un parche para la membrana mucosa (película), el compuesto de la presente invención o el fármaco concomitante y el polímero dispersable en agua mencionado con anterioridad (preferiblemente, hidroxipropilcelulosa, hidroxipropilmetilcelulosa), excipiente y similares se disuelven en un solvente tales como agua y similares, y la solución resultante se lamina para producir una película. Además, los aditivos tales como un plastificante, estabilizante, antioxidante, conservante, colorante, amortiguador, agente edulcorante y similares también pueden agregarse. Para impartir la elasticidad apropiada a la película, glicoles tales como polietilenglicol, propilenglicol y similares pueden incluirse, o para potenciar la adhesión de la película en un recubrimiento de membrana de mucosa intraoral, un polímero bio-adhesivo (por ejemplo, policarbofil, carbopol) también pueden incluirse. En el laminado, se vierte una solución en la superficie que no tiene adhesivo, se asperja hasta obtener un espesor uniforme (preferiblemente, aproximadamente 10 hasta 1000 micrones) con el uso de una herramienta de aplicación tal como un bisturí y similares, luego, la solución se seca para formar una película. Puede ser ventajoso que la película formada de esta manera se seque a temperatura ambiente o bajo calor, y se corta en el área deseada.

Como el agente desintegrante rápido intraoral preferible, se enumeran agentes de dosificación de separación rápida sólidos compuestos de un cuerpo de red que comprende el compuesto de la presente invención o el fármaco concomitante, y se enumeran un vehículo soluble en agua o que se difunde en agua que es inerte para el compuesto de la presente invención o fármaco concomitante. Este cuerpo de red se obtiene por sublimación un

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solvente de la composición sólida formada por una solución preparada por disolución el compuesto de la presente invención o el fármaco concomitante en un solvente apropiado.

Se prefiere que la composición de un agente desintegrante rápido oral contenga un agente formador de matriz y un componente secundario, además del compuesto de la presente invención o el fármaco concomitante.

Ejemplos de agente formador de matriz incluyen gelatinas, dextrinas, proteínas animales o proteínas vegetales tales como soja, trigo, y proteína de semilla de y psilio y similares; sustancias de caucho tales como de goma arábiga, goma guar, agar, goma xántica y similares; polisacáridos; ácidos algínico; carboximetilcelulosas; carrageninas; dextranos; pectinas; polímeros sintéticos tales como polivinilpirrolida y similares; sustancias derivadas de un complejo gelatina - goma arábiga, y similares. Además, sacáridos tales como manitol, dextrosa, lactosa, galactosa, trehalosa y similares; sacáridos cíclicos tales como ciclodextrina y similares; sales inorgánicas tales como sodio fosfato, cloruro de sodio y silicato de aluminio y similares; amino ácidos que tienen 2 a 12 átomos de carbono tales como glicina, L-alanina, ácido L-aspártico, ácido L-glutámico, L-hidroxiprolina, L-isoleucina, L-leucina, L-fenilalanina y similares, están contenidos.

Un o más de los agentes formadores de matriz pueden introducirse en una solución o suspensión antes de la solidificación. Tal agente formador de matriz puede estar presente además de un tensioactivo, o puede estar presente mientras que un tensioactivo que se excluye. Los agentes formadores de matriz ayudan a mantener el compuesto de la presente invención o el fármaco concomitante en la solución o suspensión en condición de difusión, además para la formación

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de la matriz.

La composición puede contener componentes secundarios tales como un conservante, antioxidante, tensioactivo, agente aglutinante, colorante, agente de control del pH, agente saborizante, agente edulcorante, agente enmascarador de sabor y similares. Como el colorante apropiado, se enumeran óxidos de hierro rojo, negro y amarillo, y colorantes de FD & C tales como azul FD & C 2, Rojo FD & C 40 y similares fabricados por Ellis y Everard. Algunos ejemplos del agente saborizante apropiado incluyen menta, arándano, licor, naranja, limón, pomelo, caramelo, vainilla, cereza, sabor a uva y combinaciones de los anteriores. Algunos ejemplos del agente de control de pH apropiado incluyen ácido cítrico, tartárico, fosfórico, clorhídrico y maleico. Algunos ejemplos del agente edulcorante apropiado incluyen aspartamo, acesulfamo K y taumatina y similares. Algunos ejemplos del agente enmascarador de sabor apropiado incluyen sodio bicarbonato, resina de intercambio de iones, compuestos de inclusión de ciclodextrina, sustancias adsorbentes y apomorfina microencapsulada.

La preparación contiene el compuesto de la presente invención o el fármaco concomitante en una cantidad usualmente desde aproximadamente 0.1 a aproximadamente 50% en peso, preferiblemente desde aproximadamente 0.1 a aproximadamente 30% en peso, y se prefieren las preparaciones (tales como el agente bucal, sublingual antes mencionado y similares) que pueden disolverse en un 90% o más del compuesto de la presente invención o el fármaco concomitante (en agua) dentro del intervalo de tiempo de aproximadamente 1 a aproximadamente 60 min, preferiblemente de aproximadamente 1 a aproximadamente 15 min, con mayor preferencia de aproximadamente 2 a aproximadamente 5 min, y preparaciones de desintegración

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intraoral rápida que se desintegran dentro del intervalo de 1 a 60 seg., preferiblemente de 1 a 30 seg., preferiblemente adicional de 1 a 10 seg., luego de colocarse en la cavidad oral.

El contenido del antes mencionado excipiente en la preparación completa es desde aproximadamente 10 hasta aproximadamente 99% en peso, preferiblemente desde aproximadamente 30 hasta aproximadamente 90% en peso. El contenido de β-ciclodextrina o derivado de β-ciclodextrina en la preparación completa es desde 0 hasta aproximadamente 30% en peso. El contenido del lubricante en la preparación completa es desde aproximadamente 0.01 a aproximadamente 10% en peso, preferiblemente desde aproximadamente 1 a aproximadamente 5% en peso. El contenido del agente de isotonicidad en la preparación completa es desde aproximadamente 0.1 a aproximadamente 90% en peso, preferiblemente, desde aproximadamente 10 hasta aproximadamente 70% en peso. El contenido del vehículo hidrofílico en la preparación completa es desde aproximadamente 0.1 a aproximadamente 50% en peso, preferiblemente, desde aproximadamente 10 hasta aproximadamente 30% en peso. El contenido del polímero dispersable en agua en la preparación completa es desde aproximadamente 0.1 a aproximadamente 30% en peso, preferiblemente, desde aproximadamente 10 hasta aproximadamente 25% en peso. El contenido del estabilizante en la preparación completa es desde aproximadamente 0.1 a aproximadamente 10% en peso, preferiblemente, desde aproximadamente 1 a 5% en peso. La preparación mencionada con anterioridad puede contener en forma adicional aditivos tales como un colorante, agente edulcorante, conservante y similares, si es necesario.

La dosificación de un agente combinado de la presente

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invención difiere dependiendo de la clase de un compuesto de la presente invención, edad, peso corporal, condición, forma farmacológico, método de administración, período de administración y similares, y por ejemplo, para un paciente con cáncer (adulto, peso corporal: aproximadamente 60 kg), el agente combinado se administra por vía intravenosa, a una dosis de aproximadamente 0.01 a aproximadamente 1000 mg/kg/día, preferiblemente aproximadamente 0.01 a aproximadamente 100 mg/kg/día, con mayor preferencia aproximadamente 0.1 a aproximadamente 100 mg/kg/día, particularmente aproximadamente 0.1 a aproximadamente 50 mg/kg/día, especialmente aproximadamente 1.5 a aproximadamente 30 mg/kg/día, en términos del compuesto de la presente invención o el fármaco concomitante, respectivamente, una o varias veces divididas durante el día. Por supuesto, dado que la dosis cómo se describió con anterioridad varía dependiendo de varias condiciones, cantidades menores que la dosificación antes mencionada en ocasiones pueden ser suficientes, además, tienen que administrarse a veces cantidades por encima del intervalo.

La cantidad del fármaco concomitante puede determinarse en cualquier valor salvo que los efectos colaterales sean problemáticos. La dosificación diaria en términos del fármaco concomitante difiere dependiendo de la severidad del síntoma, la edad, el sexo, el peso corporal, la diferencia en sensibilidad del sujeto de administración, el período de administración, el intervalo y naturaleza, farmacia, clase de la preparación farmacéutica, la clase de ingrediente efectivo, y similares, y no se restringe en forma particular, y la cantidad de un fármaco es, en el caso de oral administración por ejemplo, usualmente desde aproximadamente 0.001 a 2000 mg, preferiblemente desde aproximadamente 0.01 a 500 mg, preferiblemente adicional desde

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aproximadamente 0.1 a 100 mg, por 1 kg peso corporal de un mamífero, que usualmente se administra de una a 4 veces divididas durante el día.

En la administración de un agente combinado de la presente invención, el compuesto de la presente invención puede administrarse luego de la administración del fármaco concomitante o el fármaco concomitante puede administrarse luego de la administración del compuesto de la presente invención, aunque puedan administrarse en forma simultánea. Cuando se administra en un intervalo de tiempo, el intervalo difiere dependiendo del componente efectivo que se administrará, la forma farmacológica y el método de administración, y por ejemplo, cuando el fármaco concomitante se administra primero, se ejemplifica un método en donde compuesto de la presente invención se administra dentro del intervalo de tiempo de desde 1 min hasta 3 días, preferiblemente desde 10 min hasta 1 día, con mayor preferencia desde 15 min hasta 1 hrs luego de la administración del fármaco concomitante. Cuando el compuesto de la presente invención se administra primero, se ejemplifica un método en donde el fármaco concomitante se administra dentro del intervalo de tiempo desde 1 min hasta 1 día, preferiblemente desde 10 min hasta 6 hrs, con mayor preferencia desde 15 min hasta 1 hrs luego de la administración del compuesto de la presente invención.

En un método de administración preferible, por ejemplo, el fármaco concomitante que se ha moldeado en una preparación de administración oral se administra por vía oral a una dosis diaria de aproximadamente 0.001 a 200 mg/kg, y aproximadamente 15 min más tarde, el compuesto de la presente invención que se ha moldeado en una preparación de administración oral se administra por vía oral a una dosis diaria de aproximadamente

0.005 hasta 100 mg/kg.

Además, el compuesto de la presente invención o el agente combinado de la presente invención puede usarse en forma concurrente con un tratamiento no farmacológico. Para ser precisos, el compuesto de la presente invención o el agente combinado de la presente invención puede combinarse con un tratamiento no farmacológico tal como (1) cirugía, (2) quimioterapia hipertensiva usando angiotensina II etc., (3) terapia génica, (4) termoterapia, (5) crioterapia, (6) cauterización con láser, (7) radioterapia, y similares.

Por ejemplo, mediante el uso del compuesto de la presente invención o el agente combinado de la presente invención antes o después de una cirugía y similares, o antes o después de un tratamiento combinado de dos o tres clases de éstos, pueden lograrse efectos tales como prevención de la emergencia de resistencia, prolongación de la Sobrevida Sin Enfermedad, supresión de metástasis o recurrencia del cáncer, prolongación de la vida y similares.

Además, es posible combinar un tratamiento con el compuesto de la presente invención o el agente combinado de la presente invención con una terapia de soporte [(i) administración de antibiótico (por ejemplo, tipo β-lactama tales como pansporina y similares, tipo macrólida tales como claritromicina y similares etc.) para la complicación con varias enfermedades infecciosas, (ii) administración de transfusión de alto contenido calórico, preparación de aminoácidos o preparación general de vitaminas para la mejora de deficiencias de nutrición, (iii) administración de morfina para mitigación del dolor, (iv) administración de un agente farmacéutico para aliviar los efectos colaterales tales como náuseas, vómitos, anorexia, diarrea, leucopenia, trombocitopenia, reducción de la concentración de hemoglobina,

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pérdida de cabello, hepatopatía, renopatía, DIC, fiebre y similares y (v) administración de un agente farmacéutico para suprimir la resistencia del cáncer a fármacos múltiples y similares].

Con preferencia, el compuesto de la presente invención o el agente combinado de la presente invención se administra por vía oral (incluyendo preparaciones de liberación prolongada), por vía intravenosa (incluyendo bolos, infusiones y clatratos), por vía subcutánea e intramuscular (incluyendo bolos, infusiones y preparaciones de liberación prolongada), por vía transdérmica, por vía intraoral o proximal antes o después de conducir el tratamiento descrito con anterioridad.

Como un período para administrar el compuesto de la presente invención o el agente combinado de la presente invención antes de la cirugía, etc., por ejemplo, puede administrarse 1 vez aproximadamente 30 min hasta 24 hrs antes de la cirugía, etc., ó en 1 a 3 ciclos aproximadamente 3 meses a 6 meses antes de la cirugía, etc. De este modo, la cirugía, etc. puede conducirse fácilmente porque, por ejemplo, un tejido con cáncer se reduciría por la administración del compuesto de la presente invención o el agente combinado de la presente invención antes de la cirugía, y similares.

Como período para administrar el compuesto de la presente invención o el agente combinado de la presente invención luego de la cirugía, etc., por ejemplo, puede administrarse reiteradamente durante algunas semanas hasta 3 meses, aproximadamente 30 min hasta 24 hrs luego de la cirugía, y similares. De este modo, potencia el efecto de la cirugía, etc. mediante administración el compuesto de la presente invención o el agente combinado de la presente invención luego de la cirugía, y similares.

Ejemplos

La presente invención se explica en detalle a continuación con referencia a Ejemplos de Referencia, Ejemplos, Ejemplos de Formulación y Ejemplos Experimentales, que no se construyen como limitativos.

En los Ejemplos de Referencia y Ejemplos, la pureza de los compuestos se midió en las siguientes condiciones de HPLC.

dispositivo de medición: sistema SHIMADZU Corporación LC-10 Avp

columna: CAPSEL PAK C18UG120 S-3 μm, 2.0 X 50 mm

solvente: Solución A; 0.1% ácido trifluoroacético que contiene agua,

Solución B; 0.1% ácido trifluoroacético que contiene acetonitrilo

ciclo gradiente: 0.00 min (Solución A/Solución B=90/10), 4.00 min (Solución A/Solución B=5/95), 5.50 min (Solución A/Solución B=5/95), 5.51 min (Solución A/Solución B=90/10), 8.00 min (Solución A/Solución B=90/10)

Volumen de inyección: 2 ml

caudal de flujo: 0.5 ml/min

Método de detección: UV 220 nm

En los Ejemplos de Referencia y Ejemplos, la purificación de los compuestos por HPLC preparativa se realizó en las siguientes condiciones.

1) dispositivo de medición: Gilson Company Inc., High Thrsoughput Purification System

columna: YMC CombiPrep ODS-A, S-5 μm, 50 X 20 mm

método de detección: UV 220 nm

solvente: Solución A; 0.1% ácido trifluoroacético-que contiene agua,

Solución B; 0.1% ácido trifluoroacético que contiene acetonitrilo

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ciclo gradiente: ejemplo representativo 0.00 min (Solución A/Solución B=98/2), 1,00 min (Solución A/Solución B=98/2), 5.20 min (Solución A/Solución B=0/100), 6.40 min (Solución A/Solución B=0/100), 6.50 min (Solución A/Solución B=98/2), 6.60 min (Solución A/Solución B=98/2), caudal de flujo: 25 ml/min, ó 0.00 min (Solución A/Solución B= 90/10), 1,00 min (Solución A/Solución B= 90/10), 4.00 min (Solución A/Solución B= 10/95), 8.50 min (Solución A/Solución B= 10/95), 8.60 min (Solución A/Solución B= 90/10), 8.70 min (Solución A/Solución B= 90/10)

caudal de flujo: 20 ml/min

2) dispositivo de medición: Gilson Company Inc., High Thrsoughput Purification System

columna: YMC CombiPrep, ProC18 RS, S-5 μm, 20 X 50 mm (YMC)

solvente: SOLUCIÓN A; 10 mM carbonato de amonio que contiene agua,

SOLUCIÓN B; acetonitrilo

ciclo gradiente: 0.00 min (SOLUCIÓN A/SOLUCIÓN B=95/5), 2.00 min (SOLUCIÓN A/SOLUCIÓN B=95/5), 4.02 min (SOLUCIÓN A/SOLUCIÓN B=5/95), 6.40 min (SOLUCIÓN A/SOLUCIÓN B=5/95), 6.50 min (SOLUCIÓN A/SOLUCIÓN B=95/5), 8.00 min (SOLUCIÓN A/SOLUCIÓN B=95/5)

3) dispositivo de medición: Gilson Company Inc., High Thrsoughput Purification System

columna: YMC CombiPrep, ProC18 RS, S-5 μm, 20 X 50 mm (YMC)

solvente: SOLUCIÓN A; 0.1% ácido trifluoroacético que contiene agua,

SOLUCIÓN B; 0.1% ácido trifluoroacético-que contiene acetonitrilo

ciclo gradiente: 0.00 min (SOLUCIÓN A/SOLUCIÓN B=98/2),

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1.00 min (SOLUCIÓN A/SOLUCIÓN B=98/2), 5.20 min (SOLUCIÓN A/SOLUCIÓN B=60/40), 5.40 min (SOLUCIÓN A/SOLUCIÓN B=5/95), 6.40 min (SOLUCIÓN A/SOLUCIÓN B=5/95), 6.50 min (SOLUCIÓN A/SOLUCIÓN B=98/2), 6.60 min (SOLUCIÓN A/SOLUCIÓN B=98/2)

volumen de inyección: 500 ml, caudal de flujo: 20 ml/min, método de detección: UV 220 nm, 254 nm

En los Ejemplos de Referencia y Ejemplos, el espectro de masa (EM) se midió en las siguientes condiciones.

dispositivo de medición: Micromass platform II o Aguas ZMD

método de ionización: Atmospheric Pressure Chemical Ionization: APCI o método de ionización por impacto de electrones (Ionización por Electroaspersión: Electron Spray Ionization: ESI)

En los Ejemplos de Referencia y Ejemplos, el espectro de masa por HPLC (LC-EM) se midió en las siguientes condiciones.

1) dispositivo de medición: Micromass ZMD, Agilent Technologies HP1100 y 1200 LC/EMD

columna: CAPCELL PAK C18UG120, S-3 µm, 1.5 X 35 mm

solvente: SOLUCIÓN A; 0.05% ácido trifluoroacético que contiene agua,

SOLUCIÓN B; 0.04% ácido trifluoroacético que contiene acetonitrilo

ciclo gradiente: 0.00 min (Solución A/Solución B=90/10), 2.00 min (Solución A/Solución B=5/95), 2.75 min (Solución A/Solución B=5/95), 2.76 min (Solución A/Solución B=90/10), 3.45 min (Solución A/Solución B=90/10)

volumen de inyección: 2 ml

caudal de flujo: 0.5 ml/min

método de detección: UV 220 nm

método de ionización: método de ionización por impacto de

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electrones (Ionización por Electro Comopersión: ESI)

2) dispositivo de medición: Sistema Waters, 4-ch LC/EM con MUX

columna: CAPCELL PAK C18 UG-120, S-3 μm, 1.5 X 35 mm (Shiseido Co., Ltd.)

solvente: SOLUCIÓN A; 5 mM acetato de amonio que contiene agua,

SOLUCIÓN B; 5 mM acetato de amonio-que contiene acetonitrilo

ciclo gradiente: gradiente: 0.00 min (SOLUCIÓN A/SOLUCIÓN B=100/0), 2.00 min (SOLUCIÓN A/SOLUCIÓN B=0/100), 3.00 min (SOLUCIÓN A/SOLUCIÓN B=0/100), 3.01 min (SOLUCIÓN A/SOLUCIÓN B=100/0), 3.30 min (SOLUCIÓN A/SOLUCIÓN B=100/0)

volumen de inyección: 2 ml, caudal de flujo: 0.5 ml/min, método de detección: UV 220 nm

método de ionización: método de Ionización por Electro Comopersión (ESI)

modo de administración: barrido completo (iones positivos + negativos)

intervalo del valor de masa medida: m/z=150-750

El espectro ^{1}H-RMN se midió usando tetrametilsilano como el estándar interno, usando BRUKER AVANCE DPX-300 (300 MHz), AV300 (300 MHz), AV400 (400 MHz) y VARIAN Mercury-300 (300 MHz), y todos los valores de δ se expresan en ppm.

Como el aparato de reacción con microondas, se usó Emrys Optimizer, Biotage Japan Ltd.

Salvo que se especifique de otro modo, el valor numérico de solvente mixto muestra una relación de mezclado en volumen de cada solvente. Salvo que se especifique de otro modo, % significa % en peso. Mientras que la temperatura ambiente (temperatura

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ambiente) en la presente especificación significa una temperatura de desde aproximadamente 10°C hasta aproximadamente 35°C, esta no es particularmente limitada en forma estricta.

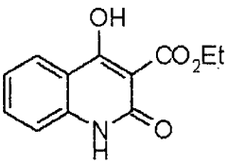
Otras abreviaturas usadas en la especificación significan lo siguiente:

s:	singulete
d:	duplete
t:	triplete
q:	cuarteto
m:	multiplete
sext:	sexteto
br:	amplio
J:	Constante de acoplamiento
Hz:	Hertz
$CDCl_3$:	cloroformo deuterado
DEMO-d_6:	dimetil sulfóxido-d6
CD_3OD:	metanol deuterado
^{1}H-RMN:	resonancia nuclear magnética protónica
LC/EM:	espectro de cromatografía líquida-espectrometría de masa
DMF:	N,N-dimetilformamida
DEMO:	dimetil sulfóxido
THF:	tetrahidrofurano
WSCD:	soluble en agua carbodiimida (1-etil-3-(3-dimetilaminopropil)carbodiimida) clorhidrato
HOBt:	1-hidroxibenzotriazol
boc:	*terc*-butoxicarbonilo
K_2CO_3:	carbonato de potasio
M:	concentración molar

Ejemplo de Referencia 1.

Producción de etil 4-hidroxi-2-oxo-1,2-dihidroquinolin-3-

carboxilato.

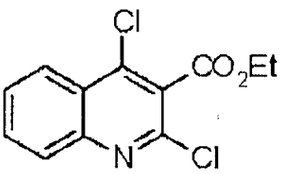


A una solución de antranilato de metilo (121 g, 0.8 mol) y malonato de dietilo (128 g, 0.8 mol) en etanol (900 ml) se agregó una solución al 20% (274 g) de etóxido de sodio en etanol, y la mezcla se agitó a temperatura ambiente durante 30 min. Se evaporó el etanol, y la mezcla se agitó a 14°C durante 12 hrs. Luego de enfriar, el sólido obtenido se lavó con dietil éter, y disolvió en agua. Los materiales insolubles se eliminaron por filtración, el filtrado se acidificó con ácido clorhídrico 5 N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (161 g, 86%) como un polvo amarillo pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.31 (3H, t, J = 7.1 Hz), 4.34 (2H, q, J = 7.1 Hz), 7.19 - 7.29 (2H, m), 7.63 (1H, td, J = 7.8, 1,2 Hz), 7.94 (1H, d, J = 8.1 Hz), 11.51 (1H, s amplio), 13.40 (1H, s amplio).

Ejemplo de Referencia 2.

Producción de etil 2,4-dicloroquinolin-3-carboxilato.



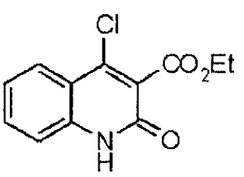
Una mezcla del compuesto del Ejemplo de Referencia 1 (75 g, 0.32 mol) y oxicloruro de fósforo (200 ml) se agitó a 11°C durante 6 hrs. Luego de enfriar, la mezcla de reacción se concentró bajo presión reducida, el residuo se disolvió en una pequeña cantidad de acetato de etilo y la mezcla se vertió en agua helada. La mezcla resultante se extrajo con acetato de etilo,

y el extracto se lavó en forma consecutiva con solución acuosa 1 N de hidróxido de sodio, agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=1/5) para dar el compuesto del título (68 g, 79%) como un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.47 (3H, t, J = 7.2 Hz), 4.54 (2H, q, J = 7.2 Hz), 7.71 (1H, t, J = 7.5 Hz), 7.85 (1H, t, J = 7.5 Hz), 8.06 (1H, d, J = 8.2 Hz), 8.24 (1H, d, J = 8.2Hz).

Ejemplo de Referencia 3

Producción de etil 4-cloro-2-oxo-1,2-dihidroquinolin-3-carboxilato

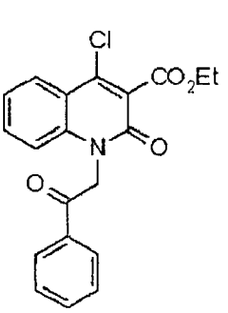


Una mezcla del compuesto del Ejemplo de Referencia 2 (68.0 g, 0.25 mol) y acetato de sodio (21.7 g, 0.26 mol) en ácido acético (200 ml) se agitó a 12°C durante 20 hrs. Luego de enfriar, la mezcla de reacción se agregó a agua, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y secó bajo presión reducida para dar el compuesto del título (58.8 g, 94%) como un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.46 (3H, t, J = 7.2 Hz), 4.53 (2H, q, J = 7.2 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.33 (1H, d, J = 8.1 Hz), 7.63 (1H, t, J = 7.8 Hz), 8.00 (1H, d, J = 8.1Hz), 12.41 (1H, s amplio).

Ejemplo de Referencia 4.

Producción de etil 4-cloro-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidroquinolin-3-carboxilato.

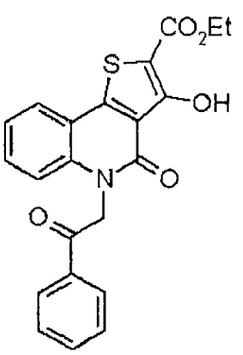


A una solución del compuesto del Ejemplo de Referencia 3 (10.0 g, 39.7 mmol) en DMF (160 ml) se agregó hidruro de sodio (60% en aceite, 1.7 g, 41.7 mmol) enfrió con hielo, y la mezcla se agitó durante 15 min. Se agregó bromuro de fenacilo (8.7 g, 43.7 mmol) a la mezcla resultante enfrió con hielo, y la mezcla se agitó durante 1 hrs. La mezcla de reacción se agregó a agua (1.5 l), y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=1/2 - 1/1) para dar el compuesto del título (10.5 g, 71%) como un sólido amarillo pálido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz), 4.47 (2H, q, *J* = 7.2 Hz), 5.80 (2H, s), 7.02 (1H, d, *J* = 8.1 Hz), 7.34 (1H, t, *J* = 7.8 Hz), 7.53 - 7.60 (3H, m), 7.65 - 7.70 (1H, m), 8.06 - 8.13 (3H, m).

Ejemplo de Referencia 5.

Producción de etil 3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



Una solución al 20% (17.2 g, 50.5 mmol) de etóxido de sodio en etanol se diluyó con etanol (50 ml), tioglicolato de etilo (6.1 g, 50.5 mmol) se agregó a la solución obtenida, y la mezcla se agitó a temperatura ambiente durante 5 min. El compuesto del Ejemplo

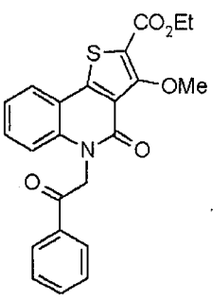
907

de Referencia 4 (9.3 g, 25.3 mmol) se agregó a la mezcla, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con agua helada (50 ml), se agregó ácido clorhídrico 2 N (30 ml) y la mezcla se agitó durante 30 min. El sólido precipitado se recolectó por filtración, se lavó con agua y dietil éter, y se secó bajo presión reducida para dar el compuesto del título (10.0 g, 96%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 (3H, t, *J* = 7.0 Hz), 4.25 - 4.35 (2H, m), 6.01 (2H, s), 7.30 (1H, t, *J* = 7.2 Hz), 7.55 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.00 - 8.07 (1H, m), 8.07 - 8.19 (2H, m), 10.40 - 10.65 (1H, amplio).

Ejemplo de Referencia 6.

Producción de etil 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 5 (7.0 g, 17.1 mmol) y DBU (4.3 g, 18.3 mmol) en DMF (150 ml) se agitó a temperatura ambiente durante 10 min, y se agregó yodometano (4.0 g, 28.0 mmol). La mezcla se agitó a temperatura ambiente durante 4 hrs, y concentró bajo presión reducida. El residuo se diluyó con agua, y se extrajo dos veces con solución mixta de acetato de etilo-THF. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se lavó con solución mixta de acetato de etilo-dietil éter, y secó bajo presión reducida para dar el compuesto del título (5.7 g, 79%) como un polvo verde

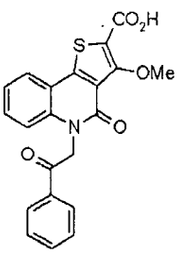
408

pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 (3H, t, *J* = 7.1 Hz), 3.95 (3H, s), 4.34 (2H, q, *J* = 7.1 Hz), 5.98 (2H, s), 7.37 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.7 Hz), 7.57 - 7.67 (3H, m), 7.76 (1H, t, *J* = 7.5 Hz), 8.06 (1H, d, *J* = 7.8 Hz), 8.16 - 8.19 (2H, m).

Ejemplo de Referencia 7.

Producción de ácido 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

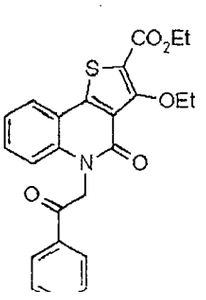


Una solución mixta del compuesto del Ejemplo de Referencia 6 (5.7 g, 13.5 mmol) y solución acuosa 2N de hidróxido de sodio (60 ml) en THF (200 ml)-etanol (100 ml) se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se neutralizó con ácido clorhídrico 2 N (60 ml), y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó en forma consecutiva con agua y dietil éter, y se secó bajo presión reducida para dar el compuesto del título (4.2 g, 79%) como un polvo rosa pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.93 (3H, s), 5.98 (2H, s), 7.35 (1H, t, *J* = 7.8 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.2 Hz), 8.04 (1H, dd, *J* = 8.1, 1.2 Hz), 8.16 - 8.19 (2H, m).

Ejemplo de Referencia 8.

Producción de etil 3-etoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

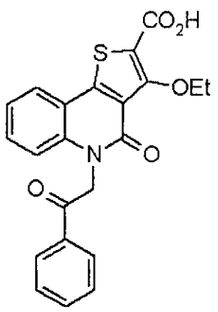


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (461 mg, 87%) se obtuvo como un polvo blanco a partir del compuesto (500 mg, 1.22 mmol) del Ejemplo de Referencia 5, DBU (280 mg, 1.84 mmol) y yodoetano (302 mg, 1.84 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 (6H, t, *J* = 7.0 Hz), 4.21 (2H, q, *J* = 7.0 Hz), 4.34 (2H, q, *J* = 7.0 Hz), 5.98 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.76 (1H, t, *J* = 7.2 Hz), 8.06 (1H, dd, *J* = 7.8, 1,2 Hz), 8.16 - 8.19 (2H, m).

Ejemplo de Referencia 9.

Producción de ácido 3-etoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

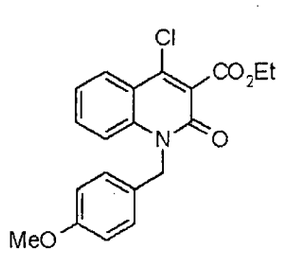


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (392 mg, 95%) se obtuvo como un polvo rosa pálido a partir del compuesto (440 mg, 1.01 mmol) del Ejemplo de Referencia 8.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.33 (3H, t, *J* = 7.0 Hz), 4.20 (2H, q, *J* = 7.0 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.04 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.19 (2H, m).

Ejemplo de Referencia 10.

Producción de etil 4-cloro-1-(4-metoxibencil)-2-oxo-1,2-dihidroquinolin-3-carboxilato.

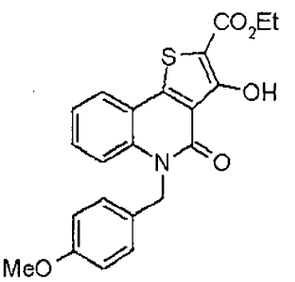


Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (10.8 g, 79%) se obtuvo como un polvo blanco a partir del compuesto (10.0 g, 39.8 mmol) del Ejemplo de Referencia 3 y cloruro de 4-metoxibencilo (7.38 ml, 47.8 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 (3H, t, *J* = 7.1 Hz), 3.70 (3H, s), 4.40 (2H, q, *J* = 7.1 Hz), 5.48 (2H, s), 6.89 (2H, d, *J* = 8.7 Hz), 7.19 (2H, d, *J* = 8.7 Hz), 7.32 (1H, t, *J* = 7.8 Hz), 7.61 (1H, d, *J* = 8.7 Hz), 7.69 - 7.75 (1H, m), 8.04 (1H, dd, *J* = 7.8, 1.2 Hz).

Ejemplo de Referencia 11.

Producción de etil 3-hidroxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



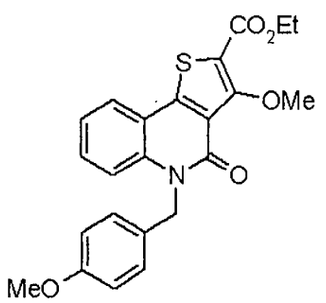
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Del mismo modo que en el Ejemplo de Referencia 5, el compuesto del título (10.4 g, 88%) se obtuvo como un polvo blanco a partir del compuesto (10.6 g, 31.0 mmol) del Ejemplo de Referencia 10.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 (3H, t, *J* = 7.0 Hz), 3.70 (3H, s), 4.32 (2H, q, *J* = 7.0 Hz), 5.53 (2H, s), 6.87 (2H, d, *J* = 8.9 Hz), 7.23 (2H, d, *J* = 8.9 Hz), 7.34 - 7.39 (1H, m), 7.58 - 7.66 (2H, m), 8.00 - 8.03 (1H, m), 10.77 (1H, s).

Ejemplo de Referencia 12.

Producción de etil 3-metoxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

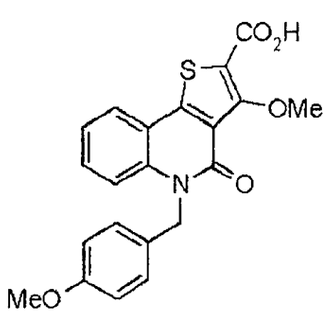


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (5.2 g, 64%) se obtuvo como un polvo blanco a partir del compuesto (7.5 g, 19.8 mmol) del Ejemplo de Referencia 11.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 (3H, t, *J* = 7.1 Hz), 3.70 (3H, s), 4.01 (3H, s), 4.34 (2H, q, *J* = 7.1 Hz), 5.50 (2H, s), 6.87 (2H, d, *J* = 8.7 Hz), 7.20 (2H, d, *J* = 8.7 Hz), 7.27 - 7.32 (1H, m), 7.38 - 7.60 (2H, m), 8.01 (1H, dd, *J* = 7.7, 1.4 Hz).

Ejemplo de Referencia 13.

Producción de ácido 3-metoxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

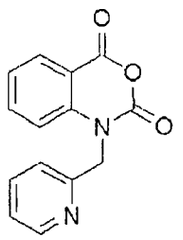


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (4.75 g, 98%) se obtuvo como un polvo blanco a partir del compuesto (5.0 g, 12.3 mmol) del Ejemplo de Referencia 12.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.70 (3H, s), 3.93 (3H, s), 5.51 (2H, s), 6.87 (2H, d, *J* = 8.7 Hz), 7.20 (2H, d, *J* = 8.7 Hz), 7.27 - 7.32 (1H, m), 7.38 - 7.59 (2H, m), 7.99 (1H, dd, *J* = 7.8, 1.2 Hz), 13.40 (1H, s).

Ejemplo de Referencia 14.

Producción de 1-(piridin-2-ilmetil)-2H-3,1-benzooxazin-2,4(1H)-diona.



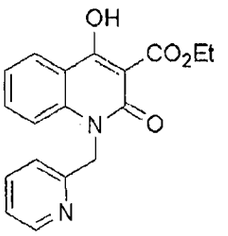
A una solución de anhídrido isatoico (25.4 g, 0.156 mol) en DMF (300 ml) se agregaron 2-(clorometil)piridina clorhidrato (28.1 g, 0.171 mol) y hidruro de sodio (66% en aceite, 12.5 g, 0.34 mol) enfrió con hielo. La mezcla resultante se agitó a temperatura ambiente durante 42 hrs. Se agregó agua (750 ml) a la mezcla de reacción y la mezcla se enfrió con hielo. El sólido precipitado se recolectó por filtración, y se recristalizó a partir de acetona-diisopropil éter para dar el compuesto del título (13.4 g, 34%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 5.36 (2H, s), 7.24 - 7.34 (3H, m), 7.39 (1H, d, *J* = 8.1 Hz), 7.73 (1H, ddd, *J* = 8.6, 7.2, 1.5 Hz), 7.77 (1H, td, *J* = 7.7, 1.6 Hz), 8.03 (1H, dd, *J* = 7.8, 1.8 Hz), 8.50 (1H, ddd, *J* = 4.9, 1.7, 1.0 Hz).

Ejemplo de Referencia 15.

Producción de etil 4-hidroxi-2-oxo-1-(piridin-2-ilmetil)-1,2-dihidroquinolin-3-carboxilato.

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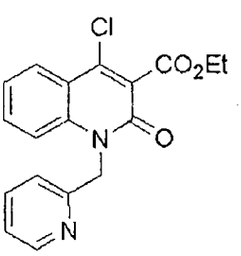


A una solución de malonato de dietilo (15.6 g, 97.3 mmol) en DMF (90 ml) se agregó hidruro de sodio (66% en aceite, 2.60 g, 72 mmol) enfrió con hielo, y la mezcla se agitó a la misma temperatura durante 10 min. El compuesto del Ejemplo de Referencia 14 (16.5 g, 64.9 mmol) se agregó a la mezcla resultante en pequeñas porciones, y la mezcla se agitó a 12°C durante 6 hrs. La mezcla de reacción se concentró bajo presión reducida, agua helada se agregó al residuo y la mezcla se lavó con dietil éter. La fase acuosa se alcalinizó débilmente con ácido clorhídrico 5N (8 ml) enfrió con hielo. Los cristales precipitados se recolectaron por filtración por filtración, se lavó con agua, y se recristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (12,8 g, 60%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.50 (3H, t, *J* = 7.1 Hz), 4.53 (2H, q, *J* = 7.1 Hz), 5.61 (2H, s amplio), 7.12 - 7.18 (2H, m), 7.18 - 7.25 (1H, m), 7.36 (1H, d, *J* = 8.7 Hz), 7.51 - 7.59 (2H, m), 8.18 (1H, dd, *J* = 8.3, 1.7 Hz), 8.56 (1H, dd, *J* = 5.3, 2.0 Hz), 14.53 (1H, s).

Ejemplo de Referencia 16.

Producción de etil 4-cloro-2-oxo-1-(piridin-2-ilmetil)-1,2-dihidroquinolin-3-carboxilato.



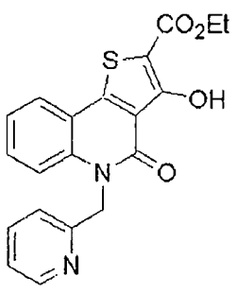
A una mezcla del compuesto del Ejemplo de Referencia 15 (16.1 g, 49.6 mmol) y tolueno (50 ml) se agregó oxicloruro de

fósforo (12 ml, 0.13 mol), y la mezcla se agitó a 11°C durante 1 hrs. La mezcla de reacción se dejó enfriar, y el solvente se eliminó por decantación. Se agregó agua al residuo y la mezcla se lavó con dietil éter. La fase acuosa se neutralizó con carbonato de sodio y se extrajo dos veces con cloroformo. La fase orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio, filtró, y concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/1 - 3/1) y se cristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (2.54 g, 15%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.44 (3H, t, *J* = 7.2 Hz), 4.50 (2H, q, *J* = 7.2 Hz), 5.64 (2H, s amplio), 7.15 - 7.26 (2H, m), 7.31 (1H, ddd, *J* = 8.2, 5.9, 2.3 Hz), 7.52 - 7.63 (3H, m), 8.06 (1H, dt, *J* = 7.8, 0.8 Hz), 8.56 (1H, ddd, *J* = 4.7, 1.9, 0.8 Hz).

Ejemplo de Referencia 17.

Producción de etil 3-hidroxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



Una solución al 20% (4.51 g, 13 mmol) de etóxido de sodio en etanol se diluyó con etanol (15 ml), y tioglicolato de etilo (1.74 ml, 15.9 mmol) se agregó a la solución obtenida. La mezcla se agitó a temperatura ambiente durante 10 min. El compuesto del Ejemplo de Referencia 16 (2.27 g, 6.62 mmol) se agregó a la mezcla, y la mezcla se agitó a temperatura ambiente durante 5.5 hrs. La mezcla de reacción se neutralizó con agua helada y ácido clorhídrico 2N (3.2 ml) enfrió con hielo, y se extrajo dos veces

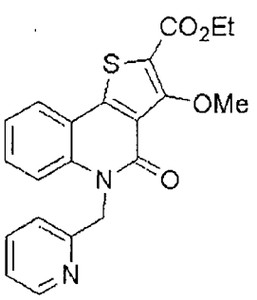
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con cloroformo. La fase orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio, se filtró, y concentró bajo presión reducida. El sólido obtenido se lavó con etanol para dar el compuesto del título (2.50 g, 99%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J* = 7.1 Hz), 4.43 (2H, q, *J* = 7.1 Hz), 5.69 (2H, s amplio), 7.16 - 7.24 (2H, m), 7.25 - 7.32 (1H, m), 7.39 (1H, ddd, *J* = 8.6, 7.1, 1.5 Hz), 7.57 (1H, d, *J* = 8.1 Hz), 7.60 (1H, td, *J* = 7.7, 1.8 Hz), 7.82 (1H, dd, *J* = 8.1, 1.5 Hz), 8.57 (1H, ddd, *J* = 4.9, 1.6, 0.8 Hz), 10.68 (1H, s).

Ejemplo de Referencia 18.

Producción de etil 3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



A una suspensión del compuesto del Ejemplo de Referencia 17 (2.26 g, 5.94 mmol) en DMF (20 ml) se agregó DBU (1.06 ml, 7.09 mmol), y se agregó yodometano (0.74 ml, 12 mmol) a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs, se agregó agua, y la mezcla se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua, 0.5 N solución de hidróxido de sodio y agua, se segó paso a través de gel de sílice alcalino (eluido con acetato de etilo), y se concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (1.16 g, 50%).

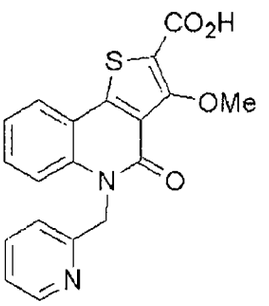
^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J* = 7.1 Hz), 4.17 (3H, s), 4.41 (2H, q, *J* = 7.1 Hz), 5.70 (2H, s amplio), 7.14 - 7.26 (3H, m), 7.35 (1H, ddd, *J* = 8.6, 7.0, 1.6 Hz), 7.51 (1H, dd, *J* =

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8.6, 0.8 Hz), 7.57 (1H, td, *J* = 7.7, 1.8 Hz), 7.83 (1H, ddd, *J* = 7.7, 1.5, 0.3 Hz), 8.57 (1H, ddd, *J* = 5.0, 2.0, 0.9 Hz).

Ejemplo de Referencia 19.

Producción de ácido 3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

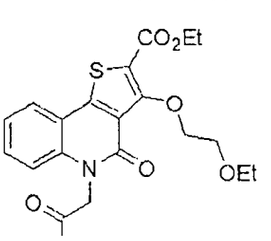


A una suspensión del compuesto del Ejemplo de Referencia 18 (1.21 g, 3.07 mmol) en THF (10 ml) y etanol (10 ml) se agregó solución acuosa 5N de hidróxido de sodio (1.2 ml, 6.0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 45 min, etanol (5 ml) se agregó y la mezcla se agitó adicionalmente durante 135 min. La mezcla de reacción se enfrió con hielo, se neutralizó con ácido clorhídrico 1N (6.0 ml), y cloroformo y agua se agregaron. La fase orgánica se separó, y la fase acuosa se extrajo dos veces con cloroformo. La fase orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio, filtró, y concentró bajo presión reducida. El residuo se recristalizó a partir de cloroformo-diisopropil éter para dar el compuesto del título (1.11g, 99%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.96 (3H, s), 5.65 (2H, s), 7.23 - 7.33 (3H, m), 7.33 (1H, d, *J* = 8.7 Hz), 7.54 (1H, ddd, *J* = 8.6, 7.3, 1.4 Hz), 7.73 (1H, td, *J* = 7.7, 1.9 Hz), 7.97 - 8.02 (1H, m), 8.45 - 8.48 (1H, m), 13.38 (1H, s amplio).

Ejemplo de Referencia 20.

Producción de etil 3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



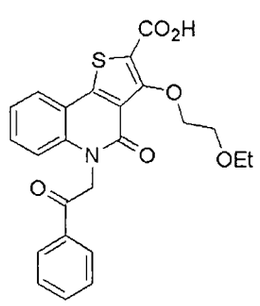
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A una suspensión del compuesto del Ejemplo de Referencia 5 (1.35 g, 3.31 mmol) en DMF (20 ml) se agregaron DBU (1.48 ml, 9.90 mmol) y 2-bromoetiletil éter (1.12 ml, 9.93 mmol), y la mezcla se agitó a 6°C durante 30 hrs. Cloroformo y agua se agregaron a la mezcla de reacción, la fase orgánica se separó y la fase acuosa se extrajo con cloroformo. La fase orgánica combinada se lavó con solución 0.5 N de hidróxido de sodio y agua, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/3 - 2/3) y se recristalizó a partir de diclorometan-diisopropil éter para dar el compuesto del título (1.36 g, 86%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1,17 (3H, t, *J* = 7.1 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 3.56 (2H, q, *J* = 7.1 Hz), 3.89 (2H, dd, *J* = 5.5, 4.6 Hz), 4.40 (2H, q. *J* = 7.1 Hz), 4.45 (2H, dd, *J* = 5.5, 4.6 Hz), 5.85 (2H, s), 6.97 (1H, d, *J* = 8.1 Hz), 7.21 - 7.28 (1H, m), 7.35 (1H, ddd, *J* = 8.7, 7.2, 1.4 Hz), 7.51 - 7.58 (2H, m), 7.63 - 7.69 (1H, m), 7.86 (1H, dd, *J* = 7.8, 1.5 Hz), 8.07 - 8.12 (2H, m).

Ejemplo de Referencia 21.

Producción de ácido 3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



A una suspensión del compuesto del Ejemplo de Referencia

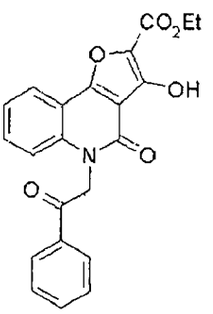
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20 (1.20 g, 2.50 mmol) en THF (16 ml) y etanol (16 ml) se agregó solución acuosa 5N de hidróxido de sodio (1.0 ml, 5.0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se acidificó con ácido clorhídrico 1N, y se agregó agua. Los cristales precipitados se recolectaron por filtración y se lavó con agua para dar el compuesto del título (1.09 g, 97%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.01 (3H, t, *J* = 6.9 Hz), 3.40 (2H, q, *J* = 6.9 Hz), 3.71 (2H, t, *J* = 5.0 Hz), 4.30 (2H, t, *J* = 5.0 Hz), 5.97 (2H, s), 7.33 (1H, t, *J* = 7.7 Hz), 7.36 (1H, d, *J* = 8.7 Hz), 7.54 - 7.66 (3H, m), 7.76 (1H, t, *J* = 7.2 Hz), 8.02 (1H, d, *J* = 7.8 Hz), 8.16 (2H, d, *J* = 7.5 Hz), 13.27 (1H, s amplio).

Ejemplo de Referencia 22.

Producción de etil 3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrofuro[3,2-c]quinolin-2-carboxilato.



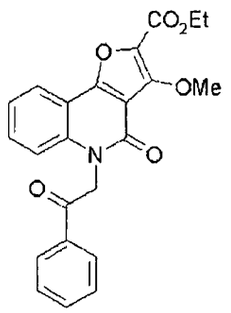
Del mismo modo que en el Ejemplo de Referencia 5, el compuesto del título (1.10 g, 69%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 4 (1.50 g, 4.06 mmol), una solución al 20% (2.76 g, 8.11 mmol) de etóxido de sodio en etanol y glicolato de etilo (1.01 g, 9.73 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 (3H, t, *J* = 7.1 Hz), 4.35 (2H, q, *J* = 7.1 Hz), 5.96 (2H, s), 7.39 (1H, t, *J* = 7.7 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.60 - 7.67 (3H, m), 7.74 - 7.79 (1H, m), 8.05 (1H, dd, *J* = 7.7, 1.4 Hz), 8.15 - 8.18 (2H, m), 9.80 – 11.10 (1H, amplio).

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Ejemplo de Referencia 23.

Producción de etil 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrofuro[3,2-c]quinolin-2-carboxilato.

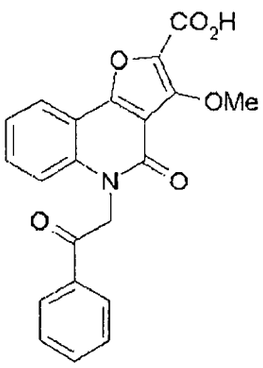


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (250 mg, 23%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 22 (1.05 g, 2.68 mmol), DBU (612 mg, 4.02 mmol) y yodometano (250 µl, 4.02 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, *J* = 7.1 Hz), 4.14 (3H, s), 4.37 (2H, q, *J* = 7.1 Hz), 5.99 (2H, s), 7.39 - 7.35 (1H, m), 7.55 (1H, d, *J* = 8.7 Hz), 7.62 - 7.68 (3H, m), 7.74 - 7.80 (1H, m), 8.09 (1H, dd, *J* = 7.8, 1.5 Hz), 8.16 - 8.18 (2H, m).

Ejemplo de Referencia 24.

Producción de ácido 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrofuro[3,2-c]quinolin-2-carboxílico.



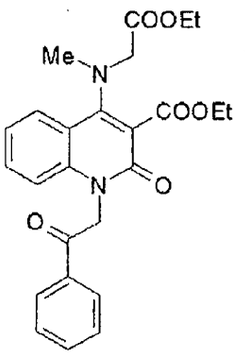
Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (160 mg, 72%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 23 (240 mg, 0.592 mmol), solución acuosa 8 N de hidróxido de sodio (1.0 ml) y etanol (14 ml).

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^{1}H-RMN (300 MHz, DEMO-d_6) δ: 4.12 (3H, s), 5.99 (2H, s), 7.32 (1H, t, *J* = 7.6 Hz), 7.54 (1H, d, *J* = 7.8 Hz), 7.62 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.8 Hz), 8.07 (1H, dd, *J* = 7.6, 1.5 Hz), 8.16 - 8.18 (2H, m), 12.60 - 14.10 (1H, amplio).

Ejemplo de Referencia 25.

Producción de etil 4-[(2-etoxi-2-oxoetil)(metil)amino]-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidroquinolin-3-carboxilato.

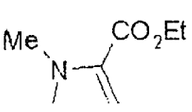


Una mezcla del compuesto del Ejemplo de Referencia 4 (24.1 g, 65.2 mmol), etil éster de sarcosina, clorhidrato (12.0 g, 78.2 mmol), trietilamina (18.1 ml, 130 mmol) y etanol (200 ml) se agitó a 85°C durante 15 hrs, etil éster de sarcosina, clorhidrato (3.00 g, 19.6 mmol) y trietilamina (18.1 ml, 130 mmol) se agregaron en forma adicional, y la mezcla se agitó a 85°C durante 7 hrs. Luego de enfriar, se agregó agua a la mezcla de reacción, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (24.6 g, 84%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.21 - 1.31 (6H, m), 2.93 (3H, s), 3.95 (2H, s), 4.15 - 4.31 (4H, m), 5.87 (2H, s), 7.31 (1H, t, *J* = 7.8 Hz), 7.30 (1H, d, *J* = 8.4 Hz), 7.55 - 7.65 (3H, m), 7.72 - 7.78 (1H, m), 8.05 (1H, dd, *J* = 7.8, 1.5 Hz), 8.12 - 8.15 (2H, m).

Ejemplo de Referencia 26.

Producción de etil 3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-



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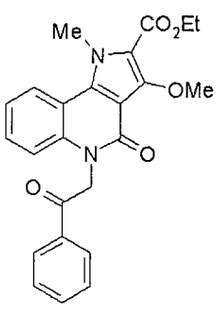
4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.

Una mezcla del compuesto del Ejemplo de Referencia 25 (1.25 g, 2.77 mmol), una solución al 20% (1.23 g, 3.33 mmol) de etóxido de sodio en etanol y etanol (25 ml) se agitó a 55°C durante 15 hrs. La mezcla de reacción se diluyó con agua, ácido clorhídrico 1N (5 ml) se agregó y la mezcla se agitó durante 30 min. El sólido precipitado se recolectó por filtración, se lavó con agua, etanol y acetato de etilo, y se recristalizó a partir de dimetilformamida-etanol para dar el compuesto del título (760 mg, 68%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.33 (3H, t, J = 7.2 Hz), 4.30 - 4.38 (5H, m), 5.93 (2H, s), 7.30 - 7.30 (2H, m), 7.38 - 7.53 (1H, m), 7.61 - 7.66 (2H, m), 7.73 - 7.79 (1H, m), 8.15 - 8.18 (2H, m), 8.34 - 8.37 (1H, m), 9.00 (1H, s).

Ejemplo de Referencia 27.

Producción de etil 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (420 mg, 55%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 26 (740

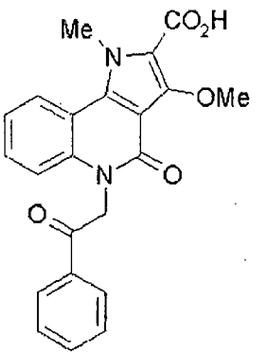
923

mg, 1.83 mmol), DBU (410 µl, 2.74 mmol) y yodometano (171 µl, 2.74 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, *J* = 7.1 Hz), 3.89 (3H, s), 4.29 - 4.37 (5H, m), 5.96 (2H, s), 7.30 - 7.30 (2H, m), 7.38 - 7.53 (1H, m), 7.61 - 7.66 (2H, m), 7.73 - 7.78 (1H, m), 8.15 - 8.18 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.4 Hz).

Ejemplo de Referencia 28.

Producción de ácido 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxílico.

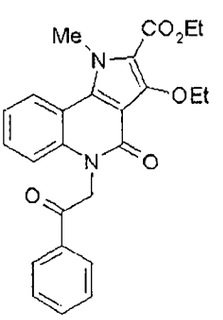


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (345 mg, 91%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 27 (405 mg, 0.968 mmol), solución acuosa 8N de hidróxido de sodio (1.5 ml) y etanol (15 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.88 (3H, s), 4.31 (3H, s), 5.95 (2H, s), 7.29 - 7.39 (2H, m), 7.36 - 7.52 (1H, m), 7.61 - 7.66 (2H, m), 7.73 - 7.78 (1H, m), 8.16 - 8.18 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1,1 Hz), 12.92 (1H, s).

Ejemplo de Referencia 29.

Producción de etil 3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.



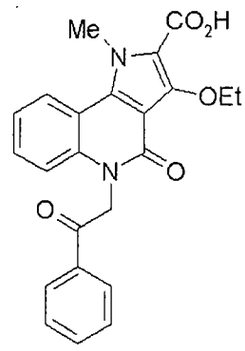
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Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (2,10 g, cuant.) se obtuvo como un polvo blanco a partir del compuesto (1.90 g, 4.70 mmol) del Ejemplo de Referencia 26, DBU (1.05 ml, 7.05 mmol) y yodoetano (564 µl, 7.05 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.27 - 1.37 (6H, m), 4.16 (2H, q, *J* = 6.9 Hz), 4.29 - 4.36 (5H, m), 5.95 (2H, s), 7.27 - 7.39 (2H, m), 7.50 (1H, t, *J* = 8.0 Hz), 7.63 (2H, t, *J* = 7.3 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.17 (2H, d, *J* = 7.3 Hz), 8.38 (1H, d, *J* = 8.1 Hz).

Ejemplo de Referencia 30.

Producción de ácido 3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxílico.



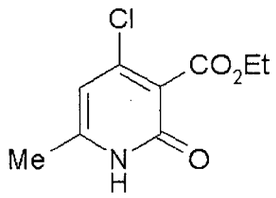
Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (1.62 g, 89%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 29 (1.95 g, 4.51 mmol), solución acuosa 8N de hidróxido de sodio (2.0 ml) y etanol (14 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.27 (3H, t, *J* = 7.0 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 4.31 (3H, s), 5.95 (2H, s), 7.27 - 7.39 (2H, m), 7.39 (1H, t, *J* = 7.3 Hz), 7.63 (2H, t, *J* = 7.3 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.15 - 8.18 (2H, m), 8.38 (1H, d, *J* = 7.2 Hz), 12.83 (1H, s).

925

Ejemplo de Referencia 31.

Producción de etil 4-cloro-6-metil-2-oxo-1,2-dihidropiridin-3-carboxilato.

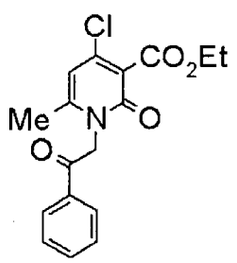


Una mezcla de etil 4-hidroxi-6-metil-2-oxo-1,2-dihidropiridin-3-carboxilato (3.00 g, 15.2 mmol), oxicloruro de fósforo (7.75 ml), cloruro de n-butiltrietilamonio (1 3.8 g, 60.8 mmol) y acetonitrilo (60 ml) se agitó a 4°C durante 30 min y en condiciones de reflujo durante 30 min. Luego de enfriar, la mezcla de reacción se concentró bajo presión reducida, se agregó agua al residuo y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se lavó con solución mixta de acetato de etilo-hexano, y se secó bajo presión reducida para dar el compuesto del título (1.45 g, 44%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.26 (3H, t, J = 7.0 Hz), 2.20 (3H, s), 4.25 (2H, q, J = 7.0 Hz), 6.26 (1H, s), 12.29 (1H, s).

Ejemplo de Referencia 32.

Producción de etil 4-cloro-6-metil-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidropiridin-3-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 31

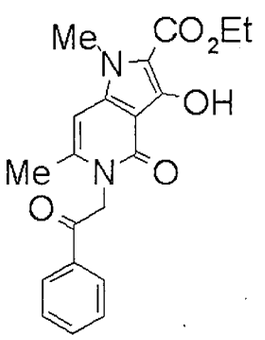
926

(9.00 g, 41.7 mmol), carbonato de potasio (17.3 g, 125 mmol), bromuro de fenacilo (16.6 g, 83.5 mmol) y DMF (100 ml) se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se vertió en agua (100 ml), y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=1/9 - 7/3) para dar el compuesto del título (3.18 g, 23%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.25 (3H, t, J = 7.0 Hz), 2.30 (3H, s), 4.25 (2H, q, J = 7.0 Hz), 5.63 (2H, s), 6.54 (1H, d, J = 0.6 Hz), 7.61 (2H, t, J = 7.5 Hz), 7.72 - 7.78 (1H, m), 8.07 - 8.10 (2H, m).

Ejemplo de Referencia 33.

Producción de etil 3-hidroxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 32 (2.00 g, 5.99 mmol), etil éster de sarcosina, clorhidrato (1.84 g, 12.0 mmol), trietilamina (4.98 ml, 36.0 mmol) y etanol (20 ml) se agitó a 8°C durante 15 hrs, se agregó una solución al 20% (3.5 ml) de etóxido de sodio en etanol, y la mezcla se agitó a 10°C durante 24 hrs. Luego de enfriar, la mezcla de reacción se diluyó con agua (50 ml), se agregó ácido clorhídrico 6 N para ajustar el pH 3 - 4, y la mezcla se agitó durante 30 min. El sólido precipitado se recolectó

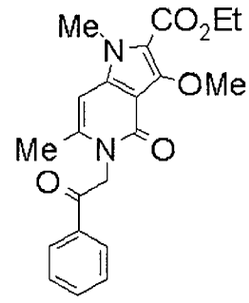
927

por filtración, y se lavó con agua y acetato de etilo/THF para dar el compuesto del título (1.50 g, 68%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.31 (3 H, t, *J* = 7.1 Hz), 2.26 (3 H, s), 3.77 (3 H, s), 4.30 (2 H, q, *J* = 7.0 Hz), 5.57 (2 H, s), 6.52 (1 H, s), 7.54 - 7.67 (2 H, m), 7.69 - 7.79 (1 H, m), 8.03 - 8.18 (2 H, m), 8.90 (1 H, s).

Ejemplo de Referencia 34.

Producción de etil 3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

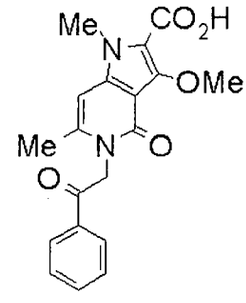


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (390 mg, 26%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 33 (1.45 g, 3.94 mmol), DBU (882 µl, 5.90 mmol) y yodometano (367 µl, 5.90 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.30 (3 H, t, *J* = 7.1 Hz), 2.28 (3 H, s), 3.81 (3 H, s), 3.86 (3 H, s), 4.27 (2 H, q, *J* = 7.0 Hz), 5.60 (2 H, s), 6.59 (1 H, s), 7.54 - 7.66 (2 H, m), 7.69 - 7.79 (1 H, m), 8.05 - 8.16 (2 H, m).

Ejemplo de Referencia 35.

Producción de ácido 3-metoxi-1.6-dimetil-4-oxo-5-(2-bxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



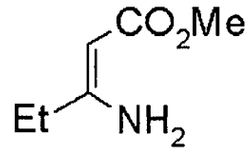
428

Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (305 mg, 89%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 34 (370 mg, 0.968 mmol), solución acuosa 8N de hidróxido de sodio (1 ml) y etanol (7 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.28 (3 H, s), 3.81 (3 H, s), 3.86 (3 H, s), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, *J* = 7.3 Hz), 7.74 (1 H, t, *J* = 7.3 Hz), 8.11 (2 H, d, *J* = 7.7 Hz), 12.50 (1 H, s amplio).

Ejemplo de Referencia 36.

Producción de metil (2Z)-3-aminopenta-2-noato.

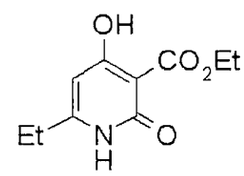


Una mezcla de 3-oxovalerato de metilo (75.0 g, 576 mmol), acetato de amonio (222g, 2.88 mmol) y metanol (750 ml) se agitó a temperatura ambiente durante 3 días. La mezcla se concentró bajo presión reducida, se agregó agua (500 ml) al residuo y la mezcla se extrajo con acetato de etilo (200 ml). El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, se concentró bajo presión reducida, y se secó para dar el compuesto del título (68.5 g, 92%) como un aceite amarillo pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.06 (3 H, t, *J* = 7.6 Hz), 2.09 (2 H, q, *J* = 7.6 Hz), 3.49 (3 H, s), 4.34 (1 H, s), 6.94 (1 H, s), 7.72 (1 H, s amplio).

Ejemplo de Referencia 37.

Producción de etil 6-etil-4-hidroxi-2-oxo-1,2-dihidropiridin-3-carboxilato.

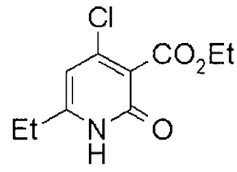


A una solución del compuesto del Ejemplo de Referencia 36 (50.0 g, 387 mmol) y malonato de dietilo (58.8 ml, 387 mmol) en etanol (400 ml) se agregó una solución al 20% (133 g) de etóxido de sodio en etanol, y la mezcla se agitó a 15°C durante 15 hrs mientras que se evaporó el etanol. Luego de enfriar, el sólido obtenido se recolectó por filtración, se lavó con acetato de etilo, y se disolvió en agua. Se eliminó por filtración el material insoluble, el filtrado se acidificó con ácido clorhídrico 5N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua y acetato de etilo-hexano para dar el compuesto del título (36.4 g, 45%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.12 (3 H, t, *J* = 7.6 Hz), 1.26 (3 H, t, *J* = 7.1 Hz), 2.42 (2 H, q, *J* = 7.6 Hz), 4.25 (2 H, q, *J* = 7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, s amplio), 12.57 (1 H, s).

Ejemplo de Referencia 38.

Producción de etil 4-cloro-6-etil-2-oxo-1,2-dihidropiridin-3-carboxilato.



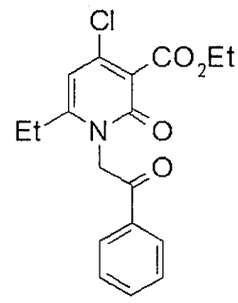
Una mezcla del compuesto del Ejemplo de Referencia 37 (15.0 g, 71.0 mmol) y oxicloruro de fósforo (19.9 ml, 213 mmol) se agitó a 8°C durante 30 min. La mezcla se concentró bajo presión reducida, se agregó agua helada al residuo, y el sólido precipitado se recolectó por filtración, y se lavó con agua y acetato de etilo para dar el compuesto del título (9.80 g, 60%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 (3 H, t, *J* = 7.5 Hz), 1.26 (3 H, t, *J* = 7.0 Hz), 2.44 - 2.55 (2 H, m), 4.25 (2 H, q, *J* = 7.1 Hz), 6.26 (1 H, s), 12.28 (1 H, s).

430

Ejemplo de Referencia 39.

Producción de etil 4-cloro-6-etil-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidropiridin-3-carboxilato.

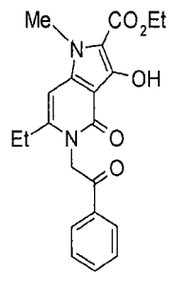


Del mismo modo que en el Ejemplo de Referencia 32, el compuesto del título (1.00 g, 7%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 38 (9.50 g, 41.4 mmol), carbonato de potasio (13.7 g, 99.2 mmol), bromuro de fenacilo (9.88 g, 49.6 mmol) y DMF (100 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.14 (3 H, t, J = 7.3 Hz), 1.24 (3 H, t, J = 7.1 Hz), 2.62 (2 H, q, J = 7.3 Hz), 4.25 (2 H, q, J = 7.1 Hz), 5.61 (2 H, s), 6.44 (1 H, s), 7.54 - 7.66 (2 H, m), 7.70 - 7.79 (1 H, m), 8.05 - 8.13 (2 H, m).

Ejemplo de Referencia 40.

Producción de etil 6-etil-3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 39 (950 mg, 2.73 mmol), etil éster de sarcosina, clorhidrato (839 mg, 5.46 mmol), trietilamina (2.27 ml, 16.4 mmol) y etanol (10 ml) se agitó a 8°C durante 10 hrs, se agregó trietilamina (2.27 ml, 16.4 mmol) en forma adicional, y la mezcla se agitó a 10°C durante 15 hrs. Luego de enfriar, se agregó agua a la mezcla de reacción, y

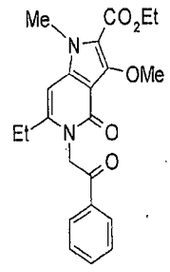
93)

la mezcla se acidificó con ácido clorhídrico 1N y se extrajo con acetato de etilo. El extracto se lavó en forma consecutiva con agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/metanol=10/1) para dar el compuesto del título (698 mg, 67%) como un sólido marrón.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.31 (3 H, t, *J* = 7.1 Hz), 2.56 (2 H, q, *J* = 7.6 Hz), 3.80 (3 H, s), 4.30 (2 H, q, *J* = 7.2 Hz), 5.55 (2 H, s), 6.43 (1 H, s), 7.60 (2 H, t, *J* = 7.6 Hz), 7.68 - 7.79 (1 H, m), 8.00 - 8.21 (2 H, m), 8.90 (1 H, s).

Ejemplo de Referencia 41.

Producción de etil 6-etil-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

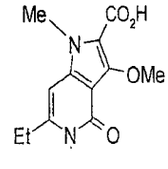


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (156 mg, 23%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 40 (650 mg, 1.70 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 3.85 (3 H, s), 4.27 (2 H, q, *J* = 7.0 Hz), 5.58 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.67 - 7.82 (1 H, m), 8.03 - 8.19 (2 H, m).

Ejemplo de Referencia 42

Producción de ácido 6-etil-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



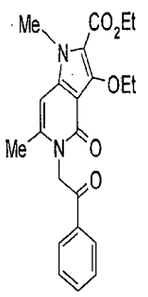
932

Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (110 mg, 79%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 41 (150 mg, 0.378 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 2.57 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 3.85 (3 H, s), 5.58 (2 H, s), 6.48 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.67 - 7.86 (1 H, m), 7.97 - 8.31 (2 H, m), 12.51 (1 H, s amplio).

Ejemplo de Referencia 43.

Producción de etil 3-etoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

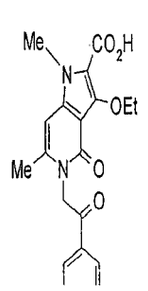


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (560 mg, 52%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 33 (1.00 g, 2.71 mmol) y yodoetano (326 µl, 4.07 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.24 (3 H, t, *J* = 7.0 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 2.28 (3 H, s), 3.81 (3 H, s), 4.15 (2 H, q, *J* = 7.0 Hz), 4.26 (2 H, q, *J* = 7.1 Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.78 (1 H, m), 8.06 - 8.14 (2 H, m).

Ejemplo de Referencia 44.

Producción de ácido 3-etoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



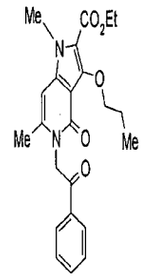
933

Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (380 mg, 74%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 43 (550 mg, 1.39 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.22 (3 H, t, *J* = 7.0 Hz), 2.28 (3 H, s), 3.81 (3 H, s), 4.16 (2 H, q, *J* = 7.0 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.79 (1 H, m), 8.03 - 8.16 (2 H, m), 12.38 (1 H, s amplio).

Ejemplo de Referencia 45.

Producción de etil 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (152 mg, 18%) se obtuvo como un polvo blanco a partir del compuesto (750 mg, 2.04 mmol) del Ejemplo de Referencia 33, y 1-bromopropano (277 µl, 3.05 mmol).

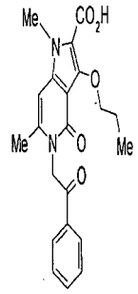
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.94 (3 H, t, *J* = 7.5 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 1.57 - 1.73 (2 H, m), 2.28 (3 H, s), 3.80 (3 H, s), 4.08 (2 H, t, *J* = 6.5 Hz), 4.26 (2 H, q, *J* = 7.1 Hz), 5.60 (2 H, s), 6.58 (1 H, s), 7.56 - 7.66 (2 H, m), 7.69 - 7.78 (1 H, m), 8.06 - 8.15 (2 H, m).

Ejemplo de Referencia 46.

Producción de ácido 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-

934

propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

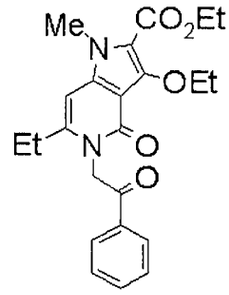


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (105 mg, 81%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 45 (140 mg, 0.341 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.88 - 0.94 (3 H, m), 1.58 - 1.67 (2 H, m), 2.27 (3 H, s), 3.81 (3 H, s), 4.08 (2 H, t, *J* = 6.6 Hz), 5.60 (2 H, s), 6.57 (1 H, s), 7.55 - 7.65 (2 H, m), 7.69 - 7.77 (1 H, m), 8.06 - 8.14 (2 H, m).

Ejemplo de Referencia 47.

Producción de etil 6-etil-3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



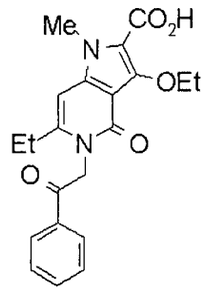
Una mezcla del compuesto del Ejemplo de Referencia 40 (330 mg, 0.863 mmol), carbonato de potasio (715 mg, 5.18 mmol), yodoetano (138 µl, 1.73 mmol) y DMF (5 ml) se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se recolectó por filtración, y secó para dar el compuesto del título (189 mg, 46%) como un polvo blanco.

435

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.35 (9 H, m), 2.57 (2 H, q, *J* = 7.2 Hz), 3.84 (3 H, s), 4.10 - 4.19 (2 H, m), 4.26 (2 H, q, *J* = 7.2 Hz), 5.58 (2 H, s), 6.49 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.77 (1 H, m), 8.07 - 8.14 (2 H, m).

Ejemplo de Referencia 48.

Producción de ácido 3-etoxi-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

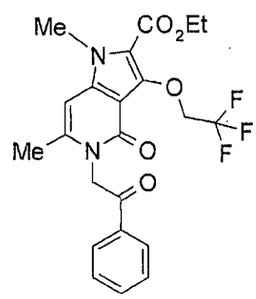


A solución del compuesto del Ejemplo de Referencia 47 (160 mg, 0.390 mmol) y solución acuosa 8N de hidróxido de sodio (1 ml) en etanol (7 ml) se agitó a 6°C durante 1 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 6N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y secó bajo presión reducida para dar el compuesto del título (74.0 mg, 50%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.25 (6 H, m), 2.57 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 4.15 (2 H, q, *J* = 7.0 Hz), 5.57 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, *J* = 7.5 Hz), 7.69 - 7.78 (1 H, m), 8.08 - 8.15 (2 H, m), 12.35 (1 H, s amplio).

Ejemplo de Referencia 49.

Producción de etil 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

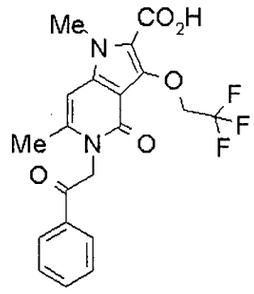


Una mezcla del compuesto del Ejemplo de Referencia 33 (750 mg, 2.04 mmol), 1,1,1-trifluoro-2-yodoetano (603 µl, 6.12 mmol), fluoruro de potasio (119 mg, 2.04 mmol) y dimetil sulfóxido (10 ml) se agitó a 10°C durante 15 hrs. La mezcla de reacción se diluyó con agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo) para dar el compuesto del título (125 mg, 14%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.28 (3 H, t, *J* = 7.2 Hz), 2.30 (3 H, s), 3.83 (3 H, s), 4.19 - 4.31 (2 H, m), 4.84 (2 H, q, *J* = 9.3 Hz), 5.64 (2 H, s), 6.66 (1 H, s), 7.57 - 7.66 (2 H, m), 7.69 - 7.79 (1 H, m), 8.07 - 8.15 (2 H, m).

Ejemplo de Referencia 50.

Producción de ácido 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



A solución del compuesto del Ejemplo de Referencia 49 (110 mg, 0.244 mmol) y solución acuosa 8N de hidróxido de sodio (1 ml) en etanol (7 ml) se agitó a 6°C durante 1 hrs. La mezcla de reacción se diluyó con agua y se acidificó con ácido clorhídrico 6N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (78.0 mg, 76%) como un polvo blanco.

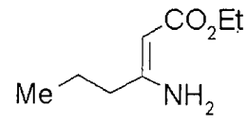
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.29 (3 H, s), 3.83 (3 H, s),

938

4.82 (2 H, q, *J* = 9.3 Hz), 5.63 (2 H, s), 6.64 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.78 (1 H, m), 8.07 - 8.15 (2 H, m), 12.57 (1 H, s amplio).

Ejemplo de Referencia 51.

Producción de etil (2Z)-3-aminohex-2-enoato.

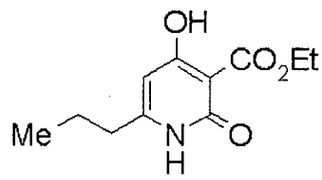


Del mismo modo que en el Ejemplo de Referencia 36, el compuesto del título (109 g, cuant.) se obtuvo como un aceite amarillo pálido a partir de 3-oxohexanoato de etilo (100 g, 632 mmol), acetato de amonio (244 g, 3.16 mmol) y metanol (750 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.87 (3 H, t, *J* = 7.3 Hz), 1.11 - 1.17 (3 H, m), 1.42 - 1.58 (2 H, m), 2.00 - 2.07 (2 H, m), 3.96 (2 H, q, *J* = 7.2 Hz), 4.30 (1 H, s), 6.90 (1 H, s amplio), 7.73 (1 H, s amplio).

Ejemplo de Referencia 52.

Producción de etil 4-hidroxi-2-oxo-6-n-propil-1,2-dihidropiridin-3-carboxilato.



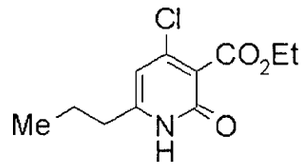
Del mismo modo que en el Ejemplo de Referencia 37, el compuesto del título (27.5 g, 34%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 51 (50.0 g, 0.387 mmol), malonato de dietilo (58.8 ml, 387 mmol) y etanol (400 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.87 (3 H, t, *J* = 7.3 Hz), 1.26 (3 H, t, *J* = 7.2 Hz), 1.49 - 1.65 (2 H, m), 2.38 (2 H, t), 4.25 (2 H, q, *J* = 7.0 Hz), 5.79 (1 H, s), 11.37 (1 H, s), 12.56 (1 H, s).

939

Ejemplo de Referencia 53.

Producción de etil 4-cloro-2-oxo-6-propil-1,2-dihidropiridin-3-carboxilato.

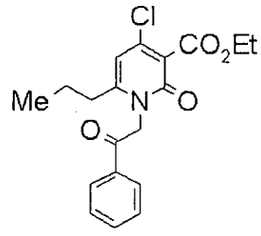


Una mezcla del compuesto del Ejemplo de Referencia 52 (37.0 g, 164 mmol) y oxicloruro de fósforo (45.9 ml, 493 mmol) se agitó a 8°C durante 30 min. La mezcla se concentró bajo presión reducida, y agua helada se agregó al residuo. El sólido precipitado se recolectó por filtración, y se lavó con agua y acetato de etilo para dar el compuesto del título (17.6 g, 44%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.87 (3 H, t, J = 7.3 Hz), 1.26 (3 H, t, J = 7.1 Hz), 1.52 - 1.65 (2 H, m), 2.40 - 2.48 (2 H, m), 4.25 (2 H, q, J = 7.1 Hz), 6.27 (1 H, s), 12.17 (1 H, s amplio).

Ejemplo de Referencia 54.

Producción de etil 4-cloro-2-oxo-1-(2-oxo-2-feniletil)-6-propil-1,2-dihidropiridin-3-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (7.15 g, 28%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 53 (17.0 g, 69.8 mmol), hidruro de sodio (60% en aceite, 3.07 g, 76.7 mmol), bromuro de fenacilo (16.7 g, 8 3.8 mmol) y DMF (150 ml).

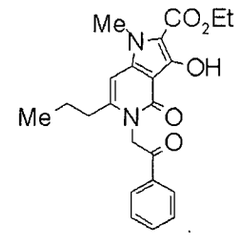
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.91 (3 H, t, J = 7.3 Hz),

940

1.24 (3 H, t, *J* = 7.1 Hz), 1.47 - 1.64 (2 H, m), 2.55 - 2.66 (2 H, m), 4.24 (2 H, q, *J* = 7.1 Hz), 5.59 (2 H, s), 6.47 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.80 (1 H, m), 8.06 - 8.17 (2 H, m).

Ejemplo de Referencia 55.

Producción de etil 3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-6-propil-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

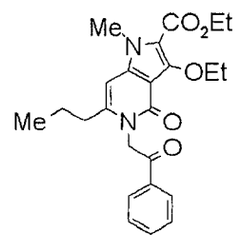


Una mezcla del compuesto del Ejemplo de Referencia 54 (7.00 g, 19.3 mmol), etil éster de sarcosina, clorhidrato (5.94 g, 38.7 mmol), trietilamina (29.7 ml, 193 mmol) y etanol (100 ml) se agitó durante 2 días en condiciones de reflujo. La mezcla se concentró bajo presión reducida, se agregó agua (200 ml) al residuo, y la mezcla se acidificó con ácido clorhídrico 5N (3 ml). El sólido precipitado se recolectó por filtración, y se lavó con agua y hexano-acetato de etilo para dar el compuesto del título (5.70 g, 74%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.92 (3 H, t, *J* = 7.3 Hz), 1.31 (3 H, t, *J* = 7.1 Hz), 1.50 - 1.65 (2 H, m), 2.49 - 2.57 (2 H, m), 3.78 (3 H, s), 4.30 (2 H, q, *J* = 7.1 Hz), 5.52 (2 H, s), 6.45 (1 H, s), 7.60 (2 H, t, *J* = 7.5 Hz), 7.68 - 7.78 (1 H, m), 8.07 - 8.15 (2 H, m), 8.90 (1 H, s amplio).

Ejemplo de Referencia 56.

Producción de etil 3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-6-propil-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



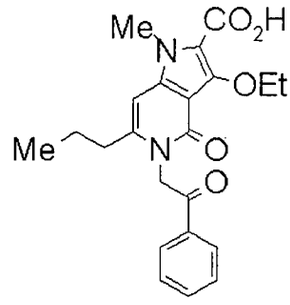
942

Una mezcla del compuesto del Ejemplo de Referencia 55 (1.00 g, 8.08 mmol), sulfato de dietilo (397 µl, 3.03 mmol), carbonato de potasio (1.05 g, 7.57 mmol) y acetona (20 ml) se agitó durante 15 hrs en condiciones de reflujo. Agua (30 ml) se agregó a la mezcla, y el sólido precipitado se recolectó por filtración, y se lavó con agua y acetato de etilo-hexano para dar el compuesto del título (876 mg, 82%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.93 (3 H, t, *J* = 7.3 Hz), 1.23 (3 H, t, *J* = 7.0 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 1.52 - 1.66 (2 H, m), 2.51 - 2.58 (2 H, m), 3.83 (3 H, s), 4.14 (2 H, q, *J* = 7.1 Hz), 4.26 (2 H, q, *J* = 7.1 Hz), 5.54 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.77 (1 H, m), 8.08 - 8.15 (2 H, m).

Ejemplo de Referencia 57.

Producción de ácido 3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-6-propil-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



A solución del compuesto del Ejemplo de Referencia 56 (850 mg, 2.00 mmol) y solución acuosa 8N de hidróxido de sodio (2 ml) en etanol (14 ml) se agitó a 6°C durante 30 min. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 5N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (705 mg, 89%) como un polvo blanco.

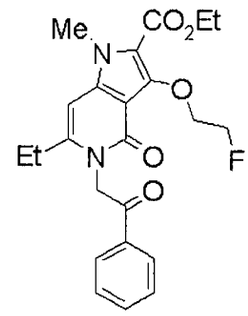
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.93 (3 H, t, *J* = 7.3 Hz), 1,21 (3 H, t, *J* = 7.0 Hz), 1.50 - 1.66 (2 H, m), 2.50 - 2.58 (2 H, m), 3.83 (3 H, s), 4.15 (2 H, q, *J* = 7.1 Hz), 5.54 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.78 (1 H, m), 8.08 - 8.16 (2

943

H, m), 12.42 (1 H, s amplio).

Ejemplo de Referencia 58.

Producción de etil 6-etil-3-(2-fluoroetoxi)-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

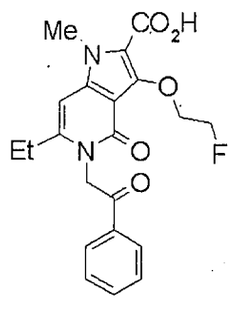


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (649 mg, 77%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 40 (750 mg, 1.96 mmol), DBU (440 µl, 2.94 mmol) y 1-fluoro-2-yodoetano (512 mg, 2.94 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1,19 (3 H, t, *J* = 7.3 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 4.32 - 4.36 (1 H, m), 4.42 - 4.47 (1 H, m), 4.53 - 4.59 (1 H, m), 4.69 - 4.75 (1 H, m), 5.58 (2 H, s), 6.51 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.77 (1 H, m), 8.08 - 8.14 (2 H, m).

Ejemplo de Referencia 59.

Producción de ácido 6-etil-3-(2-fluoroetoxi)-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



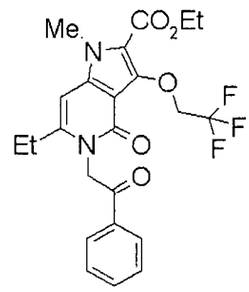
A solución del compuesto del Ejemplo de Referencia 58 (620 mg, 1.45 mmol) y solución acuosa 8N de hidróxido de sodio (1 ml) en etanol (7 ml) se agitó a 6°C durante 30 min. La mezcla de

reacción se diluyó con agua, se acidificó con ácido clorhídrico 5N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (470 mg, 56%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.32 - 4.36 (1 H, m), 4.42 - 4.47 (1 H, m), 4.54 - 4.59 (1 H, m), 4.70 - 4.74 (1 H, m), 5.58 (2 H, s), 6.50 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.77 (1 H, m), 8.09 - 8.15 (2 H, m), 12.48 (1 H, s amplio).

Ejemplo de Referencia 60.

Producción de etil 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



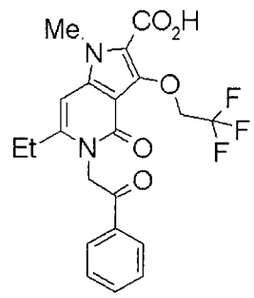
Una mezcla del compuesto del Ejemplo de Referencia 40 (1.00 g, 2.61 mmol), 1,1,1-trifluoro-2-yodoetano (1.29 ml, 13.1 mmol), carbonato de cesio (4.27 g, 13.1 mmol) y dimetil sulfóxido (10 ml) se agitó a 10°C durante 5 hrs. La mezcla de reacción se filtró, el filtrado se diluyó con ácido clorhídrico 1N (30 ml), y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; hexano/acetato de etilo=9/1 - 0/10) para dar el compuesto del título (278 mg, 23%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz),

1.28 (3 H, t, *J* = 7.1 Hz), 2.59 (2 H, q, *J* = 7.3 Hz), 3.86 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 4.83 (2 H, q, *J* = 9.3 Hz), 5.62 (2 H, s), 6.56 (1 H, s), 7.61 (2 H, t, *J* = 7.5 Hz), 7.70 - 7.78 (1 H, m), 8.08 - 8.14 (2 H, m).

Ejemplo de Referencia 61.

Producción de ácido 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

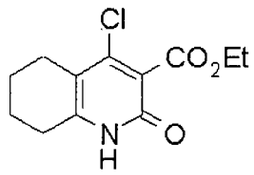


A solución del compuesto del Ejemplo de Referencia 60 (270 mg, 0.581 mmol) y solución acuosa 8N de hidróxido de sodio (1 ml) en etanol (7 ml) se agitó a 6°C durante 1 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 5N, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (235 mg, 93%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.86 (3 H, s), 4.82 (2 H, q, *J* = 9.2 Hz), 5.61 (2 H, s), 6.54 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.77 (1 H, m), 8.07 - 8.16 (2 H, m), 12.74 (1 H, s amplio).

Ejemplo de Referencia 62.

Producción de etil 4-cloro-2-oxo-1,2.5.6.7.8-hexahidroquinolin-3-carboxilato.



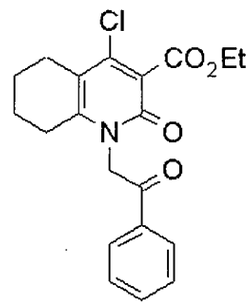
Una mezcla de etil 4-hidroxi-2-oxo-1,2,5,6,7,8-

hexahidroquinolin-3-carboxilato (26.0 g, 110 mmol) y oxicloruro de fósforo (51.3 ml) se agitó a 13°C durante 1.5 hrs. Luego de enfriar, la mezcla de reacción se concentró bajo presión reducida, y ice se agregó al residuo. La mezcla se neutralizó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se lavó en forma consecutiva con solución de hidrógeno carbonato de sodio, agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recolectó por filtración, y se lavó con acetato de etilo-hexano para dar el compuesto del título (4.65 g, 17%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.25 (3 H, t, *J* = 7.1 Hz), 1.61 - 1.74 (4 H, m), 2.37 - 2.45 (2 H, m), 2.51 - 2.57 (2 H, m), 4.24 (2 H, q, *J* = 7.2 Hz), 12.09 (1 H, s).

Ejemplo de Referencia 63.

Producción de etil 4-cloro-2-oxo-1-(2-oxo-2-feniletil)-1,2,5,6,7,8-hexahidroquinolin-3-carboxilato.

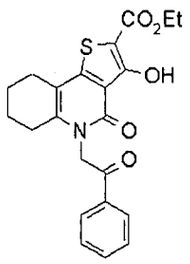


Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (710 mg, 16%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 62 (3.00 g, 11.7 mmol), hidruro de sodio (60% en aceite, 516 mg, 12.9 mmol) y bromuro de fenacilo (2.57 g, 12.9 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.25 (3H, t, *J* = 7.1 Hz), 1.60 - 1.80 (4H, m), 2.50 - 2.65 (4H, m), 4.26 (2H, q, *J* = 7.1 Hz), 5.66 (2H, s), 7.61 (2H, t, *J* = 7.3 Hz), 7.74 (1H, t, *J* = 7.3 Hz), 8.09 (2H, d, *J* = 7.3 Hz).

Ejemplo de Referencia 64.

Producción de etil 3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5,6,7,8,9-hexahidrotieno[3,2-c]quinolin-2-carboxilato.

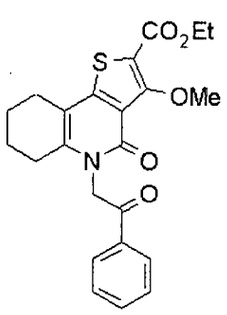


Del mismo modo que en el Ejemplo de Referencia 5, el compuesto del título (751 mg, 100%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 63 (690 mg, 1.85 mmol), 20% solución (1.26 g, 3.69 mmol) de etóxido de sodio en etanol, tioglicolato de etilo (486 µl, 4.43 mmol) y etanol (15 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.29 (3H, t, *J* = 7.0 Hz), 1.65 - 1.85 (4H, m), 2.50 - 2.65 (4H, m), 4.28 (2H, q, *J* = 7.0 Hz), 5.72 (2H, s), 7.62 (2H, t, *J* = 7.7 Hz), 7.73 - 7.78 (1H, m), 8.10 - 8.13 (2H, m), 10.39 (1H, s).

Ejemplo de Referencia 65.

Producción de etil 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5,6,7,8,9-hexahidrotieno[3,2-c]quinolin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (238 mg, 31%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 64 (740 mg, 1.80 mmol), yodometano (168 µl, 2.70 mmol), DBU (404 µl, 2.70 mmol) y DMF (15 ml).

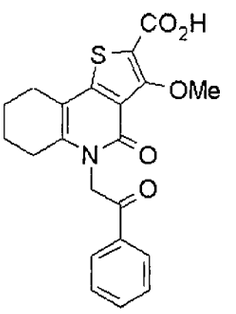
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.31 (3H, t, *J* = 7.0 Hz),

948

1.65 - 1.85 (4H, m), 2.45 - 2.65 (4H, m), 3.89 (3H, s), 4.29 (2H, q, *J* = 7.0 Hz), 5.67 (2H, s), 7.62 (2H, t, *J* = 7.3 Hz), 7.75 (1H, t, *J* = 7.3 Hz), 8.11 (2H, d, *J* = 7.3 Hz).

Ejemplo de Referencia 66.

Producción de ácido 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5,6,7,8,9-hexahidrotieno[3,2-c]quinolin-2-carboxílico.

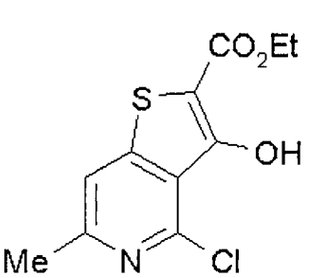


A solución del compuesto del Ejemplo de Referencia 65 (220 mg, 0.517 mmol) y solución acuosa 8N de hidróxido de sodio (1 ml) en etanol (7 ml) se agitó a 6°C durante 1 hrs. La mezcla de reacción se acidificó con ácido clorhídrico 6N (1.5 ml), y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (162 mg, 79%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.66 - 1.88 (4H, m), 2.52 - 2.61 (4H, m), 3.86 (3H, s), 5.66 (2H, s), 7.62 (2H, t, *J* = 7.6 Hz), 7.70 - 7.79 (1H, m), 8.03 - 8.11 (2H, m), 13,12 (1H, s).

Ejemplo de Referencia 67.

Producción de etil 4-cloro-3-hidroxi-6-metiltieno[3,2-c]piridin-2-carboxilato.



A una suspensión de etil 2,4-dicloro-6-metilpiridin-3-carboxilato (10.0 g, 42.7 mmol) en acetonitrilo (45 ml) se

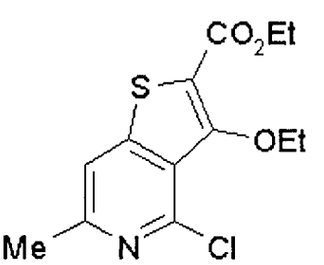
949

agregaron carbonato de potasio (8.85 g, 64.1 mmol) y tioglicolato de etilo (4.68 ml, 42.7 mmol), y la mezcla se agitó durante 15 hrs en condiciones de reflujo. La mezcla de reacción se diluyó con agua (150 ml), ácido clorhídrico 6N (15ml) se agregó y la mezcla se agitó durante 30 min. El sólido precipitado se recolectó por filtración, se lavó con agua y etanol-diisopropil éter (1/1), y se secó bajo presión reducida para dar el compuesto del título (10.9 g, 94%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 (3H, t, *J* = 7.1 Hz), 2.54 (3H, s), 4.36 (2H, q, *J* = 7.1 Hz), 7.87 (1H, s), 10.75 (1H, s).

Ejemplo de Referencia 68.

Producción de etil 4-cloro-3-etoxi-6-metiltieno[3,2-c]piridin-2-carboxilato.

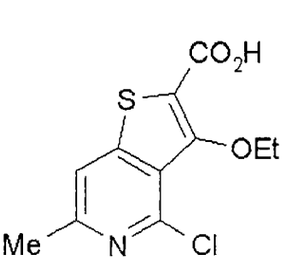


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (4.30 g, 78%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 67 (4.97 g, 18.3 mmol), DBU (4.10 ml, 27.3 mmol) y yodoetano (2.19 ml, 27.3 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.33 (3H, t, *J* = 7.2 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 2.54 (3H, s), 4.25 (2H, q, *J* = 7.0 Hz), 4.34 (2H, q, *J* = 7.1 Hz), 7.92 (1H, s).

Ejemplo de Referencia 69.

Producción de ácido 4-cloro-3-etoxi-6-metiltieno[3,2-c]piridin-2-carboxílico.



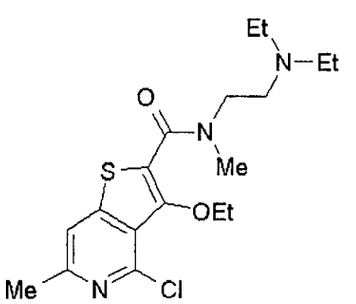
950

Una solución mixta del compuesto del Ejemplo de Referencia 68 (4.30 g, 14.3 mmol) y solución acuosa 8N de hidróxido de sodio (15 ml) en THF (22 ml)-etanol (22 ml) se agitó durante 5 hrs en condiciones de reflujo. La mezcla de reacción se acidificó con ácido clorhídrico 6N (22 ml) y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (3.80 g, 97%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.40 (3H, t, J = 6.9 Hz), 2.54 (3H, s), 4.26 (2H, q, J = 6.9 Hz), 7.90 (1H, s), 13.65 (1H, s).

Ejemplo de Referencia 70.

Producción de 4-cloro-N-[2-(dietilamino)etil]-3-etoxi-N,6-dimetiltieno[3,2-c]piridin-2-carboxamida



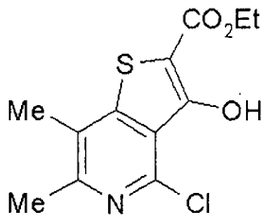
Del mismo modo que en el Ejemplo 25, el compuesto del título (800 mg, 59%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo de Referencia 69 (1.00 g, 3.68 mmol) y N,N-dietil-N'-metiletan-1,2-diamina (773 µl, 4.78 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.65 - 1.10 (6H, m), 1.33 (3H, t, J = 6.9 Hz), 2.20-2.70 (6H, m), 2.53 (3H, s), 3.04 (3H, s), 3.35 - 3,65 (2H, m), 4.05 - 4.20 (2H, m), 7.89 (1H, s).

Ejemplo de Referencia 71.

951

Producción de etil 4-cloro-3-hidroxi-6.7-dimetiltieno[3,2-c]piridin-2-carboxilato.

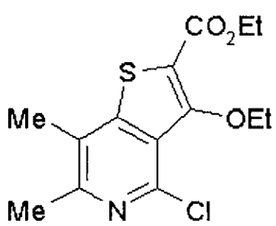


Una solución al 20% (1.73 g, 5.08 mmol) de etóxido de sodio en etanol se diluyó con etanol (5 ml), se agregó y tioglicolato de etilo (610 mg, 5.08 mmol). Se agregó etil 2,4-dicloro-5.6-dimetilpiridin-3-carboxilato (630 mg, 2.54 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 18 hrs. Se agregó ácido clorhídrico 2N (3 ml) a la mezcla de reacción y la mezcla se repartió entre salmuera y acetato de etilo. La fase orgánica se secó sobre sulfato de magnesio y concentró. El sólido obtenido se lavó con diisopropil éter-hexano, y secó bajo presión reducida para dar el compuesto del título (374 mg, 52%) como un polvo blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, J = 7.2 Hz), 2.40 (3H, s), 2.61 (3H, s), 4.44 (2H, q, J = 7.2 Hz), 10.63 (1H, s).

Ejemplo de Referencia 72.

Producción de etil 4-cloro-3-etoxi-6.7-dimetiltieno[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (350 mg, 91%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 71 (350 mg, 1.22 mmol), DBU (380 mg, 2.02 mmol) y yodoetano (315 mg,

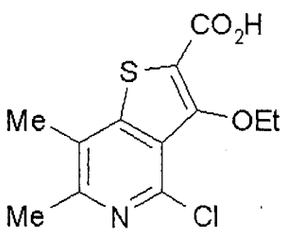
952

2.02 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J* = 7.2 Hz), 1.54 (3H, t, *J* = 7.2 Hz), 2.42 (3H, s), 2.60 (3H, s), 4.31 (2H, q, *J* = 7.2 Hz), 4.41 (2H, q, *J* = 7.2 Hz).

Ejemplo de Referencia 73.

Producción de ácido 4-cloro-3-etoxi-6.7-dimetiltieno[3,2-c]piridin-2-carboxílico.

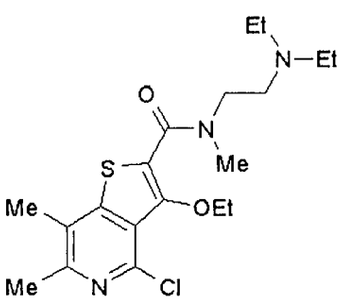


Una solución mixta del compuesto del Ejemplo de Referencia 72 (250 mg, 0.80 mmol) y solución acuosa 4N de hidróxido de sodio (2 ml) en THF (2 ml)-etanol (1 ml) se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se repartió entre ácido clorhídrico 1N y acetato de etilo, y la fase orgánica se secó sobre sulfato de magnesio y concentró bajo presión reducida para dar el compuesto del título (210 mg, 92%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.40 (3H, t, *J* = 7.1 Hz), 2.40 (3H, s), 2.53 (3H, s), 4.25 (2H, q, *J* = 7.0 Hz).

Ejemplo de Referencia 74.

Producción de 4-cloro-N-[2-(dietilamino)etil]-3-etoxi-N,6.7-trimetiltieno[3,2-c]piridin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (230 mg, 79%) se obtuvo como un aceite incoloro a partir

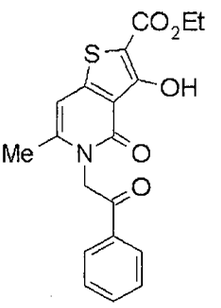
953

del compuesto del Ejemplo de Referencia 73 (210 mg, 0.73 mmol) y N,N-dietil-N'-metiletan-1,2-diamina (144 mg, 1.10 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 0.80 - 1.10 (6H, m), 1.42 (3H, t, *J* = 6.9 Hz), 2.30 - 2.50 (5H, m), 2.60 - 2.80 (7H, m), 3.19 (3H, s), 3.45 - 3.70 (2H, m), 4.18 (2H, q, *J* = 7.0 Hz).

Ejemplo de Referencia 75.

Producción de etil 3-hidroxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato.

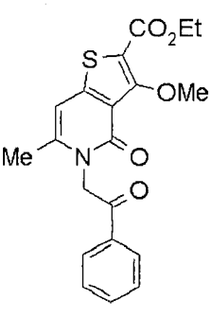


Del mismo modo que en el Ejemplo de Referencia 5, el compuesto del título (8.31 g, 88%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 32 (8.50 g, 25.5 mmol), tioglicolato de etilo (6.70 ml, 61.1 mmol), una solución al 20% (17.3 g, 51.0 mmol) de etóxido de sodio en etanol y etanol (100 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.28 (3 H, t, *J* = 7.2 Hz), 2.33 (3 H, s), 4.27 (2 H, q, *J* = 7.1 Hz), 5.71 (2 H, s), 6.93 (1 H, d, *J* = 0.9 Hz), 7.62 (2 H, t, *J* = 7.5 Hz), 7.69 - 7.83 (1 H, m), 8.01 - 8.21 (2 H, m), 10.34 (1 H, s).

Ejemplo de Referencia 76.

Producción de etil 3-metoxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato.



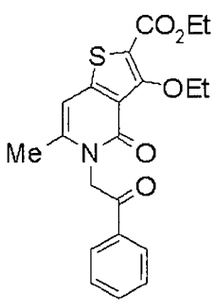
954

Una mezcla del compuesto del Ejemplo de Referencia 75 (3.00 g, 8.08 mmol), sulfato de dimetilo (4.58 ml, 48.4 mmol), carbonato de potasio (3.35 g, 24.2 mmol) y acetona (60 ml) se agitó durante 3 días en condiciones de reflujo. Se agregó agua (120 ml) a la mezcla, y el sólido precipitado se recolectó por filtración, y se lavó con agua, etanol y acetato de etilo para dar el compuesto del título (2.45 g, 79%) como un sólido blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.30 (3 H, t, J = 7.1 Hz), 2.31 (3 H, s), 3.88 (3 H, s), 4.28 (2 H, q, J = 7.2 Hz), 5.66 (2 H, s), 6.85 (1 H, d, J = 0.8 Hz), 7.58 - 7.67 (2 H, m), 7.70 - 7.80 (1 H, m), 8.06 - 8.15 (2 H, m).

Ejemplo de Referencia 77.

Producción de etil 3-etoxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato.



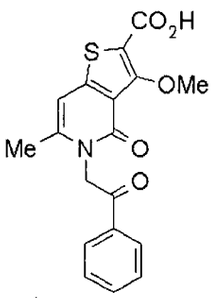
Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (585 mg, 54%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 75 (1.00 g, 2.69 mmol), DBU (604 µl, 4.04 mmol) y yodoetano (323 µl, 4.04 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.23 - 1.35 (6 H, m), 2.31 (3 H, s), 4.14 (2 H, q, J = 7.0 Hz), 4.27 (2 H, q, J = 7.1 Hz), 5.67 (2 H, s), 6.84 (1 H, d, J = 0.8 Hz), 7.57 - 7.67 (2 H, m), 7.71 - 7.79 (1 H, m), 8.07 - 8.15 (2 H, m).

Ejemplo de Referencia 78.

Producción de ácido 3-metoxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-

4,5-dihidrotieno[3,2-c]piridin-2-carboxílico.

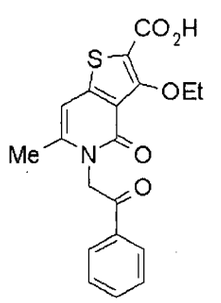


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (1.25 g, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 76 (2.00 g, 5.19 mmol), solución acuosa 8N de hidróxido de sodio (3 ml) y etanol (21 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.31 (3 H, m), 3.86 (3 H, s), 5.66 (2 H, s), 6.83 (1 H, d, J = 0.8 Hz), 7.58 - 7.68 (2 H, m), 7.71 - 7.80 (1 H, m), 8.08 - 8.17 (2 H, m), 13.07 (1 H, s amplio).

Ejemplo de Referencia 79.

Producción de ácido 3-etoxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxílico.



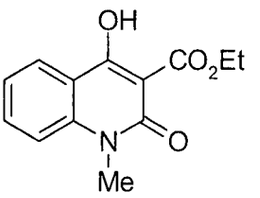
956

Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (311 mg, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 77 (500 mg, 1.25 mmol), solución acuosa 8N de hidróxido de sodio (1 ml) y etanol (7 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.27 (3 H, t, J = 7.0 Hz), 2.30 (3 H, s), 4.14 (2 H, q, J = 7.0 Hz), 5.66 (2 H, s), 6.82 (1 H, s), 7.58 - 7.66 (2 H, m), 7.71 - 7.79 (1 H, m), 8.08 - 8.17 (2 H, m), 13.05 (1 H, s amplio).

Ejemplo de Referencia 80.

Producción de etil 4-hidroxi-1-metil-2-oxo-1,2-dihidroquinolin-3-carboxilato.

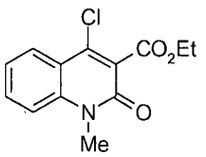


A una solución de malonato de dietilo (68.0 g, 0.425 mol) en DMF (400 ml) se agregó hidruro de sodio (66% en aceite, 10.8 g, 0.30 mol) enfrió con hielo, y la mezcla se agitó a la misma temperatura durante 5 min y a temperatura ambiente durante 15 min. Se agregó anhídrido N-metilisatoico (50.8 g, 0.287 mol) a la mezcla resultante en pequeñas porciones, y la mezcla se agitó a 12°C durante 3 hrs. Se agregó diisopropil éter (500 ml) a la mezcla de reacción, y el sólido precipitado se recolectó por filtración y se lavó con diisopropil éter. El sólido obtenido se suspendió en una mezcla de metanol (250 ml) y agua (500 ml), se agregó ácido clorhídrico 5N (60 ml) gota a gota, y la mezcla se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua, y concentró bajo presión reducida. El residuo se lavó con diisopropil éter para dar el compuesto del título (41.4 g, 58%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.49 (3H, t, *J* = 7.1 Hz), 3.66 (3H, s), 4.51 (2H, q, *J* = 7.1 Hz), 7.23 - 7.30 (1H, m), 7.32 (1H, d, *J* = 8.7 Hz), 7.69 (1H, ddd, *J* = 8.7, 7.1, 1.6 Hz), 8.19 (1H, dd, *J* = 8.0, 1.6 Hz), 14.21 (1H, s).

Ejemplo de Referencia 81.

Producción de etil 4-cloro-1-metil-2-oxo-1,2-dihidroquinolin-3-carboxilato.

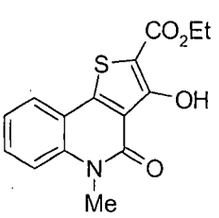


Una mezcla del compuesto del Ejemplo de Referencia 80 (58.0 g, 0.235 mol) y oxicloruro de fósforo (33 ml, 0.35 mol) se agitó a 11°C durante 30 min. La mezcla de reacción se concentró bajo presión reducida, y se agregaron agua helada y acetato de etilo. La fase orgánica se separó, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con agua, solución 1N de hidróxido de sodio (3 veces) y agua, y se concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (47.7 g, 76%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.1 Hz), 3.73 (3H, s), 4.48 (2H, q, *J* = 7.1 Hz), 7.35 (1H, ddd, *J* = 8.7, 7.1, 1.0 Hz), 7.30 (1H, d, *J* = 8.7 Hz), 7.68 (1H, ddd, *J* = 8.7, 7.1, 1.4 Hz), 8.07 (1H, dd, *J* = 8.0, 1.4 Hz).

Ejemplo de Referencia 82.

Producción de etil 3-hidroxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



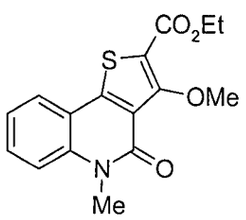
958

Una solución al 20% (23.2 g, 68 mmol) de etóxido de sodio en etanol se diluyó con etanol (70 ml), se agregó tioglicolato de etilo (9.0 ml, 82 mmol) a la solución obtenida, y la mezcla se agitó a temperatura ambiente durante 10 min. El compuesto del Ejemplo de Referencia 81 (9.04 g, 34.0 mmol) se agregó a esta mezcla, y la mezcla se agitó a temperatura ambiente durante 4 hrs. La mezcla de reacción se neutralizó con agua helada y ácido clorhídrico 2N (40 ml) enfrió con hielo, y la mezcla se extrajo dos veces con cloroformo. La fase orgánica combinada se lavó con agua y salmuera, se secó sobre sulfato de sodio, filtró, y concentró bajo presión reducida. El residuo se recristalizó a partir de THF-diisopropil éter para dar el compuesto del título (9.12 g, 88%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz), 3.76 (3H, s), 4.41 (2H, q, *J* = 7.2 Hz), 7.34 (1H, ddd, *J* = 7.9, 7.2, 0.8 Hz), 7.34 - 7.39 (1H, m), 7.63 (1H, ddd, *J* = 8.6, 7.2, 1.4 Hz), 7.83 (1H, dd, *J* = 7.9, 1.4 Hz), 10.76 (1H, s).

Ejemplo de Referencia 83.

Producción de etil 3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



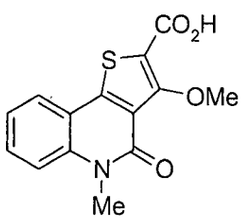
A una suspensión del compuesto del Ejemplo de Referencia 82 (3.04 g, 10.0 mmol) en DMF (30 ml) se agregó DBU (1.65 ml, 11 mmol), y se agregó yodometano (0.81 ml, 13 mmol) a la solución obtenida enfrió con hielo. La mezcla resultante se agitó a temperatura ambiente durante 21 hrs, se agregó agua y el sólido precipitado se recolectó por filtración. Esto se disolvió en etanol con calor, se trató con carbón activado, se filtró, y

concentró bajo presión reducida. El residuo se disolvió en acetato de etilo, y la mezcla se lavó con agua y solución 0.5N de hidróxido de sodio, se filtró a través de celite (nombre comercial), se lavó en forma adicional dos veces con agua, y concentró bajo presión reducida. El residuo se recristalizó a partir de etanol-diisopropil éter para dar el compuesto del título (1.51 g, 48%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz), 3.76 (3H, s), 4.14 (3H, s), 4.40 (2H, q, *J* = 7.2 Hz), 7.24 - 7.31 (1H, m), 7.31 (1H, d, *J* = 8.7 Hz), 7.59 (1H, ddd, *J* = 8.7, 7.3, 1.5 Hz), 7.84 (1H, dd, *J* = 8.1, 1.5 Hz).

Ejemplo de Referencia 84.

Producción de ácido 3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



A una suspensión del compuesto del Ejemplo de Referencia 83 (1.90 g, 5.99 mmol) en THF (20 ml) y etanol (20 ml) se agregó solución 5N de hidróxido de sodio (2.4 ml, 12 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1.5 hrs. Se agregó ácido clorhídrico 1N (13 ml) a la mezcla de reacción, y el sólido precipitado se recolectó por filtración, y recristalizó a partir de metanol para dar el compuesto del título (1.14 g, 66%).

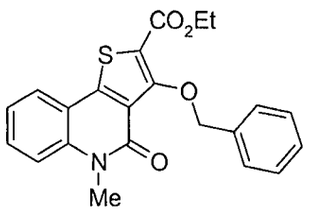
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.66 (3H, d, *J* = 1.1 Hz), 3.95 (3H, s), 7.30 - 7.37 (1H, m), 7.58 - 7.71 (2H, m), 7.94 - 8.00 (1H, m).

Ejemplo de Referencia 85.

Producción de etil 3-(benciloxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-

960

c]quinolin-2-carboxilato.

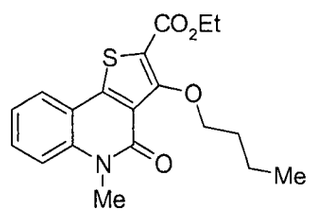


A una suspensión del compuesto del Ejemplo de Referencia 82 (1.00 g, 3.30 mmol) en DMF (10 ml) se agregó DBU (0.592 ml, 3.96 mmol), y se agregó bencilbromuro (0.510 ml, 4.29 mmol) a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 15 hrs. Se agregaron acetato de etilo y agua a la mezcla de reacción y la fase orgánica se separó. La fase acuosa se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua y solución 0.5N de hidróxido de sodio, se filtró a través de Celite (nombre comercial), se lavó en forma adicional con agua, y concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/4 - 1/2 - 2/1) para dar el compuesto del título (980 mg, 75%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.36 (3H, t, *J* = 7.2 Hz), 3.78 (3H, s), 4.36 (2H, q, *J* = 7.2 Hz), 5.34 (2H, s), 7.24 - 7.34 (5H, m), 7.59 (1H, ddd, *J* = 8.6, 7.1, 1.4 Hz), 7.63 - 7.69 (2H, m), 7.85 (1H, dd, *J* = 7.8, 1.4 Hz).

Ejemplo de Referencia 86.

Producción de etil 3-butoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



A una suspensión del compuesto del Ejemplo de Referencia

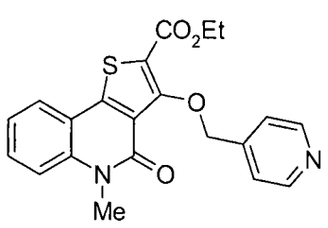
961

82 (1.00 g, 3.30 mmol) en DMF (10 ml) se agregó DBU (0.592 ml, 3.96 mmol), y se agregó 1-yodobutano (0.488 ml, 4.29 mmol) a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 15 hrs. Se agregaron acetato de etilo y agua a la mezcla de reacción, la fase orgánica se separó, y la fase acuosa se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua y solución 0.5N de hidróxido de sodio, se filtró a través de Celite (nombre comercial), se lavó en forma adicional con agua, y concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/4 - 1/2 - 2/1) para dar el compuesto del título (1.05 g, 89%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.5 Hz), 1.42 (3H, t, *J* = 7.2 Hz), 1.50 - 1.66 (2H, m), 1.87 - 1.99 (2H, m), 3.74 (3H, s), 4.28 (2H, t, *J* = 6.6 Hz), 4.39 (2H, q, *J* = 7.2 Hz), 7.27 (1H, ddd, *J* = 8.0, 7.1, 0.9 Hz), 7.30 (1H, d, *J* = 8.1 Hz), 7.58 (1H, ddd, *J* = 8.6, 7.1, 1.4 Hz), 7.81 - 7.86 (1H, m).

Ejemplo de Referencia 87.

Producción de etil 5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



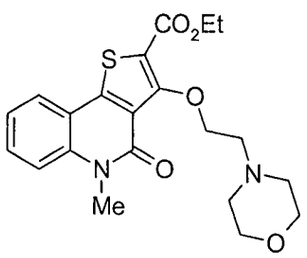
A una suspensión del compuesto del Ejemplo de Referencia 82 (1.00 g, 3.30 mmol) en DMF (20 ml) se agregó DBU (1.18 ml, 7.89 mmol), y 4-(clorometil)piridina clorhidrato (704 mg, 4.29 mmol) se agregó a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 18 hrs, a 45°C durante 2

hrs, y a 6°C durante 18 hrs. Se agregaron DBU (1.18 ml, 7.89 mmol) y 4-(clorometil)piridina clorhidrato (704 mg, 4.29 mmol), y la mezcla se agitó a 6°C durante 10 hrs. Se agregaron cloroformo y agua a la mezcla de reacción, la fase orgánica se separó, y la fase acuosa se extrajo con cloroformo. La fase orgánica combinada se lavó con agua, y concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (678 mg, 53%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.35 (3H, t, *J* = 7.2 Hz), 3.77 (3H, s), 4.37 (2H, q, *J* = 7.2 Hz), 5.36 (2H, s), 7.27 - 7.34 (1H, m), 7.33 (1H, d, *J* = 8.4 Hz), 7.58 - 7.65 (3H, m), 7.86 (1H, dd, *J* = 7.8, 1,2 Hz), 8.61 - 8.65 (2H, m).

Ejemplo de Referencia 88.

Producción de etil 5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



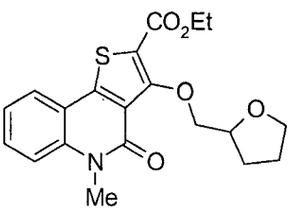
A una suspensión del compuesto del Ejemplo de Referencia 82 (1.00 g, 3.30 mmol) en DMF (20 ml) se agregó DBU (1.18 ml, 7.89 mmol), y se agregó 4-(2-cloroetil)morfolina, clorhidrato (798 mg, 4.29 mmol) a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 17 hrs. Se agregaron cloroformo y agua a la mezcla de reacción y la fase orgánica se separó. La fase acuosa se extrajo con cloroformo. La fase orgánica combinada se lavó con agua, y concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (2.16 g, 85%).

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^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.41 (3H, t, *J* = 7.1 Hz), 2.63 (4H, amplio t, *J* = 4.7 Hz), 2.96 (2H, t, *J* = 5.7 Hz), 3.72 (4H, mplio t, *J* = 4.7 Hz), 3.74 (3H, s), 4.38 (2H, q, *J* = 7.1 Hz), 4.43 (2H, t, *J* = 5.7 Hz), 7.24 - 7.31 (1H, m), 7.30 (1H, d, *J* = 8.5 Hz), 7.58 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz), 7.81 - 7.86 (1H, m).

Ejemplo de Referencia 89

Producción de etil 5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



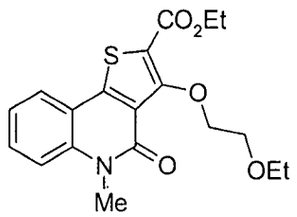
A una suspensión del compuesto del Ejemplo de Referencia 82 (1.00 g, 3.30 mmol) en DMF (20 ml) se agregó DBU (0.740 ml, 4.95 mmol), y 2-(bromometil)tetrahidrofurano (90% que contiene) (0.617 ml, 4.9 mmol) se agregó a la solución obtenida. La mezcla resultante se agitó a 4°C durante 19 hrs y a 8°C durante 23 hrs, se agregaron DBU (0.740 ml, 4.95 mmol) y 2-(bromometil)tetrahidrofurano (90% que contenía) (0.617 ml, 4.9 mmol), y la mezcla se agitó a 8°C durante 66 hrs. Se agregaron acetato de etilo y agua a la mezcla de reacción y la fase orgánica se separó. La fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con solución 0.5N de hidróxido de sodio, se filtró a través de Celite (nombre comercial), se lavó con agua, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=3/17 - 2/1) y se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (821 mg, 64%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz), 1.84 - 2.19 (4H, m), 3.74 (3H, s), 3.76 - 3.85 (1H, m), 3.89 - 3.98 (1H,

m), 4.22 - 4.49 (5H, m), 7.27 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.58 (1H, ddd, *J* = 8.6, 7.1, 1.4 Hz), 7.81 - 7.86 (1H, m).

Ejemplo de Referencia 90.

Producción de etil 3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

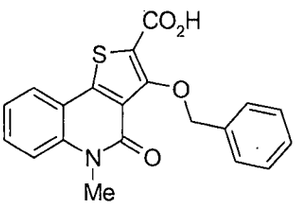


a suspensión del compuesto del Ejemplo de Referencia 82 (1.00 g, 3.30 mmol) en DMF (20 ml) se agregó DBU (1.48 ml, 9.90 mmol), y 1-bromo-2-etoxietano (1.12 ml, 9.93 mmol) se agregó a la solución obtenida. La mezcla resultante se agitó a 6°C durante 24 hrs. Se agregaron acetato de etilo y agua a la mezcla de reacción, la fase orgánica se separó, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con solución 0.5N de hidróxido de sodio, se filtró a través de Celite (nombre comercial), se lavó en forma adicional con agua, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/4 - 1/1) y se cristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (986 mg, 80%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.19 (3H, t, *J* = 7.0 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 3.59 (2H, q, *J* = 7.0 Hz), 3.74 (3H, s), 3.93 (2H, t, *J* = 5.0 Hz), 4.40 (2H, q, *J* = 7.1 Hz), 4.46 (2H, t, *J* = 5.0 Hz), 7.26 - 7.31 (1H, m), 7.30 (1H, d, *J* = 8.5 Hz), 7.58 (1H, ddd, *J* = 8.5, 7.2, 1.4 Hz), 7.84 (1H, dd, *J* = 8.0, 1.4 Hz).

Ejemplo de Referencia 91.

Producción de ácido 3-(benciloxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

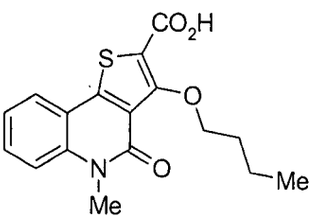


A una solución del compuesto del Ejemplo de Referencia 85 (867 mg, 2.20 mmol) en THF (7 ml) y etanol (7 ml) se agregó solución acuosa 5N de hidróxido de sodio (0.88 ml, 4.4 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 hrs. Se agregó ácido clorhídrico 1N (5.0 ml) a la mezcla de reacción, y el sólido precipitado se recolectó por filtración, se lavó con agua, y se secó al aire para dar el compuesto del título (665 mg, 83%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.69 (3H, s), 5.22 (2H, s), 7.30 - 7.31 (4H, m), 7.57 - 7.72 (4H, m), 7.98 (1H, d, *J* = 8.1 Hz), 13.31 (1H, s amplio).

Ejemplo de Referencia 92.

Producción de ácido 3-butoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

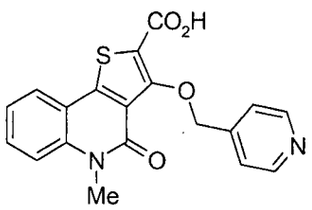


A una solución del compuesto del Ejemplo de Referencia 86 (923 mg, 2.57 mmol) en THF (7 ml) y etanol (7 ml) se agregó solución acuosa 5N de hidróxido de sodio (1.0 ml, 5.0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 hrs. ácido clorhídrico 1N (6.0 ml) se agregó a la mezcla de reacción, y el sólido precipitado se recolectó por filtración, se lavó con agua, y se secó al aire para dar el compuesto del título (872 mg, cuantitativo).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.94 (3H, t, *J* = 7.5 Hz), 1.41 - 1.55 (2H, m), 1.71 - 1.82 (2H, m), 3.65 (3H, s), 4.16 (2H, t, *J* = 6.6 Hz), 7.32 (1H, t, *J* = 7.2 Hz), 7.54 - 7.70 (2H, m), 7.91 - 7.98 (1H, m), 13.21 (1H, s amplio).

Ejemplo de Referencia 93.

Producción de ácido 5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



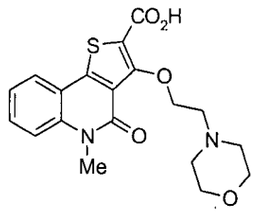
A una suspensión del compuesto del Ejemplo de Referencia 87 (723 mg, 1.83 mmol) en THF (6 ml) y etanol (6 ml) se agregó solución acuosa 5N de hidróxido de sodio (0.74 ml, 3.7 mmol). La mezcla resultante se agitó a temperatura ambiente durante 4 hrs. Se agregó ácido clorhídrico 1N (3.7 ml) a la mezcla de reacción y la mezcla se diluyó con agua. El sólido precipitado se recolectó por filtración, se lavó con agua, y se secó al aire para dar el compuesto del título (424 mg, 63%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.67 (3H, s), 5.28 (2H, s), 7.32 - 7.38 (1H, m), 7.59 - 7.72 (4H, m), 7.98 (1H, dd, *J* = 7.8, 1,2 Hz), 8.59 (2H, dd, *J* = 4.5, 1.5 Hz).

Ejemplo de Referencia 94.

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Producción de ácido 5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

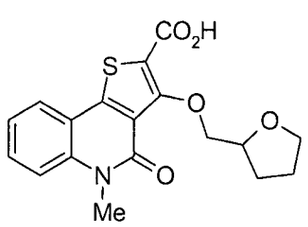


A una suspensión del compuesto del Ejemplo de Referencia 88 (832 mg, 2.00 mmol) en THF (7 ml) y etanol (7 ml) se agregó solución acuosa 5N de hidróxido de sodio (0.80 ml, 4.0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 4 hrs. Se agregó ácido clorhídrico 1N (4.0 ml) a la mezcla de reacción y la mezcla se diluyó con agua, y concentró bajo presión reducida. Metanol se agregó al residuo y la mezcla se concentró bajo presión reducida, y se cristalizó a partir de agua-metanol para dar el compuesto del título (477 mg, 61%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.00 - 3.20 (6H, m), 3.67 (3H, s), 3.84 (4H, amplio t, J = 4.4 Hz), 4.53 (2H, amplio t, J = 5.0 Hz), 7.31 (1H, ddd, J = 8.0, 6.3, 1.8 Hz), 7.55 - 7.67 (2H, m), 7.88 - 7.91 (1H, m).

Ejemplo de Referencia 95.

Producción de ácido 5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



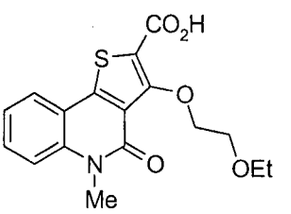
A una suspensión del compuesto del Ejemplo de Referencia 89 (728 mg, 1.88 mmol) en THF (6 ml) y etanol (6 ml) se agregó solución acuosa 5N de hidróxido de sodio (0.76 ml, 3.8 mmol). La mezcla resultante se agitó a temperatura ambiente durante 4 hrs. Se agregó ácido clorhídrico 1N (3.8 ml) a la mezcla de reacción y

la mezcla se diluyó con agua y la mezcla se extrajo 3 veces con cloroformo. La fase orgánica combinada se lavó con una solución de cloruro de sodio acuosos, se secó sobre sulfato de sodio, se filtró, y concentró bajo presión reducida. El sólido obtenido se lavó con diisopropil éter para dar el compuesto del título (659 mg, 97%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.73 - 2.04 (4H, m), 3.56 - 3.78 (2H, m), 3.65 (3H, s), 4.02 - 4.10 (1H, m), 4.19 - 4.30 (2H, m), 7.29 - 7.37 (1H, m), 7.57 - 7.71 (2H, m), 7.92 - 7.99 (1H, m), 13.20 (1H, s amplio).

Ejemplo de Referencia 96.

Producción de ácido 3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



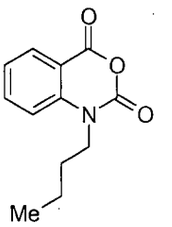
A una suspensión del compuesto del Ejemplo de Referencia 90 (826 mg, 2.20 mmol) en THF (7 ml) y etanol (7 ml) se agregó solución acuosa 5N de hidróxido de sodio (0.88 ml, 4.4 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2.5 hrs, se agregó solución acuosa 5N de hidróxido de sodio (4.4 ml, 22 mmol), y la mezcla se agitó a 5°C durante 3.5 hrs. La mezcla de reacción se acidificó con ácido clorhídrico 1N y se diluyó con agua, y el sólido precipitado se recolectó por filtración, se lavó con agua, y secó al aire para dar el compuesto del título (719 mg, 94%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.03 (3H, t, J = 6.9 Hz), 3.44 (2H, q, J = 6.9 Hz), 3.66 (3H, s), 3.75 (2H, t, J = 5.0 Hz), 4.33 (2H, t, J = 5.0 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.58 - 7.71 (2H, m), 7.96 (1H, d, J = 8.1 Hz), 13.21 (1H, s amplio).

969

Ejemplo de Referencia 97.

Producción de 1-butil-2H-3,1-benzooxazin-2,4(1H)-diona.

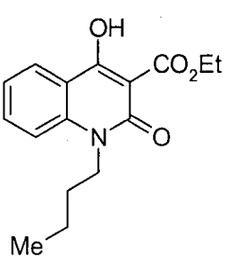


A una solución de anhídrido isatoico (8.16 g, 50.0 mmol) en DMF (100 ml) se agregó hidruro de sodio (66% en aceite, 2.00 g, 55 mmol) enfrió con hielo, y la mezcla se agitó a la misma temperatura durante 10 min. Se agregó 1-Yodobutano (8.5 ml, 75 mmol) a la mezcla resultante y la mezcla se agitó a temperatura ambiente durante 64 hrs. Se agregó agua helada a la mezcla de reacción y la mezcla se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó dos veces con agua y se concentró bajo presión reducida para dar el compuesto del título (10.5 g), que se usó para la siguiente reacción sin purificación.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.3 Hz), 1.48 (2H, sext, *J* = 7.3 Hz), 1.69 - 1.81 (2H, m), 4.02 - 4.10 (2H, m), 7.17 (1H, d, *J* = 8.6 Hz), 7.25 - 7.32 (1H, m), 7.75 (1H, ddd, *J* = 8.6, 7.3, 1.7 Hz), 8.16 (1H, dd, *J* = 7.8, 1.7 Hz).

Ejemplo de Referencia 98.

Producción de etil 1-butil-4-hidroxi-2-oxo-1,2-dihidroquinolin-3-carboxilato.



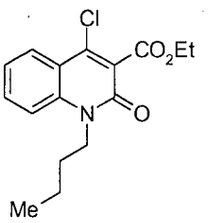
A una solución de malonato de dietilo (12.0 g, 74.9 mmol) en DMF (70 ml) se agregó hidruro de sodio (66% en aceite, 2.00 g, 55 mmol) enfrió con hielo, y la mezcla se agitó a la misma temperatura durante 10 min. una solución del compuesto del

Ejemplo de Referencia 97 (10.5 g) en DMF (20 ml) se agregó gota a gota a la mezcla resultante, y la mezcla se agitó a 12°C durante 6 hrs. La mezcla de reacción se concentró bajo presión reducida, se agregó agua helada al residuo y la fase acuosa obtenida se lavó con dietil éter. La fase acuosa se acidificó en forma débil con ácido clorhídrico 5N (12 ml) enfrió con hielo, y se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua, y concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/9 - 1/2) para dar el compuesto del título (9.96 g, 69%, 2 etapas) como un sólido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 0.99 (3H, t, *J* = 7.3 Hz), 1.482 (2H, sext, *J* = 7.3 Hz), 1.485 (3H, t, *J* = 7.1 Hz), 1.64 - 1.76 (2H, m), 4.17 - 4.26 (2H, m), 4.50 (2H, q, *J* = 7.1 Hz), 7.20 - 7.26 (1H, m), 7.29 (1H, d, *J* = 8.4 Hz), 7.66 (1H, ddd, *J* = 8.6, 7.3, 1.6 Hz), 8.18 (1H, dd, *J* = 8.3, 1.6 Hz), 14.20 (1H, s).

Ejemplo de Referencia 99.

Producción de etil 1-butil-4-cloro-2-oxo-1,2-dihidroquinolin-3-carboxilato.



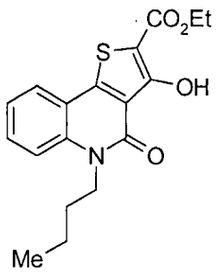
Una mezcla del compuesto del Ejemplo de Referencia 98 (9.73 g, 33.6 mmol) y oxicloruro de fósforo (4.7 ml, 50 mmol) se agitó a 11°C durante 30 min. La mezcla de reacción se concentró bajo presión reducida, y agua helada y acetato de etilo se agregaron. La fase orgánica se separó, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con agua, solución de hidrógeno carbonato de sodio y agua (dos veces), y se concentró bajo presión reducida. El residuo se

sometió a cromatografía en columna con gel de sílice (eluato; acetato de etilo/hexano=1/9 - 1/3), y las fracciones que contenían el producto deseado se combinaron, y se lavaron con solución acuosa 1N de hidróxido de sodio y agua (dos veces). Se eliminó por filtración el material insoluble y concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (6.07 g, 59%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.00 (3H, t, J = 7.3 Hz), 1.42 (3H, t, J = 7.2 Hz), 1.42 - 1.56 (2H, m), 1.67 - 1.79 (2H, m), 4.23 - 4.31 (2H, m), 4.47 (2H, q, J = 7.2 Hz), 7.33 (1H, ddd, J = 8.1, 7.2, 0.9 Hz), 7.37 - 7.31 (1H, m), 7.66 (1H, ddd, J = 8.7, 7.2, 1.4 Hz), 8.07 (1H, dd, J = 8.1, 1.4 Hz).

Ejemplo de Referencia 100.

Producción de etil 5-butil-3-hidroxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

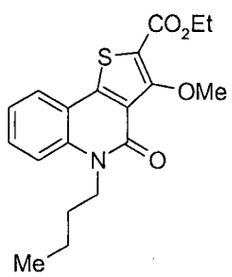


Una solución al 20% (16.0 g, 47 mmol) de etóxido de sodio en etanol se diluyó con etanol (45 ml), se agregó tioglicolato de etilo (6.2 ml, 55 mmol) a la solución obtenida, y la mezcla se agitó a temperatura ambiente durante 10 min. El compuesto del Ejemplo de Referencia 99 (7.21 g, 23.4 mmol) se agregó a esta mezcla, y la mezcla se agitó a temperatura ambiente durante 5 hrs. La mezcla de reacción se neutralizó con agua helada y ácido clorhídrico 2N (25 ml) enfrió con hielo, y la mezcla se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó dos veces con agua, y concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (6.44 g, 80%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.02 (3H, t, *J* = 7.3 Hz), 1.42 (3H, t, *J* = 7.2 Hz), 1.44 - 1.58 (2H, m), 1.71 - 1.83 (2H, m), 4.29 - 4.36 (2H, m), 4.41 (2H, q, *J* = 7.2 Hz), 7.32 (1H, ddd, *J* = 8.0, 7.2, 0.9 Hz), 7.33 - 7.38 (1H, m), 7.61 (1H, ddd, *J* = 8.6, 7.3, 1.6 Hz), 7.81-7.86 (1H, m), 10.81 (1H, s).

Ejemplo de Referencia 101.

Producción de etil 5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



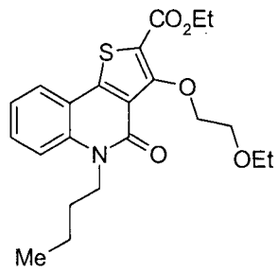
A una suspensión del compuesto del Ejemplo de Referencia 100 (3.11 g, 9.00 mmol) en DMF (30 ml) se agregó DBU (1.62 ml, 10.8 mmol), y se agregó yodometano (1.12 ml, 18.0 mmol) a la solución obtenida. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs, se agregó agua y la mezcla se extrajo dos veces con acetato de etilo. La fase orgánica combinada se lavó con agua y solución 0.5N de hidróxido de sodio, se filtró a través de Celite (nombre comercial), se lavó en forma adicional dos veces con agua, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/4 - 1/1) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (1.03 g, 32%).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.3 Hz), 1.40 - 1.60 (2H, m), 1.42 (3H, t, *J* = 7.2 Hz), 1.69 - 1.81 (2H, m), 4.14 (3H, s), 4.28 - 4.36 (2H, m), 4.40 (2H, q, *J* = 7.2 Hz), 7.22 - 7.29 (1H, m), 7.39 (1H, d, *J* = 8.5 Hz), 7.57 (1H, ddd, *J* = 8.5, 7.1, 1.4 Hz), 7.84 (1H, dd, *J* = 8.0, 1.4 Hz).

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Ejemplo de Referencia 102.

Producción de etil 5-butil-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

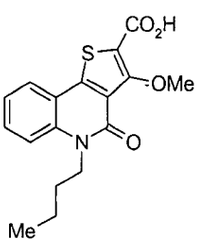


A una suspensión del compuesto del Ejemplo de Referencia 100 (1.14 g, 3.30 mmol) en DMF (20 ml) se agregó DBU (1.48 ml, 9.90 mmol), y 1-bromo-2-etoxietano (1.12 ml, 9.93 mmol) se agregó a la solución obtenida. La mezcla resultante se agitó a 6°C durante 30 hrs y se agregaron acetato de etilo y agua a la mezcla de reacción. La fase orgánica se separó, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con solución 0.5N de hidróxido de sodio y agua, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (eluato; acetato de etilo/hexano=1/4 - 1/2) para dar el compuesto del título (1.28 g, 93%) como un sólido.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.3 Hz), 1.18 (3H, t, *J* = 7.0 Hz), 1.42 (3H, t, *J* = 7.2 Hz), 1.43 - 1.57 (2H, m), 1.65 - 1.79 (2H, m), 3.58 (2H, q, *J* = 7.0 Hz), 3.92 (2H, dd, *J* = 5.6, 4.7 Hz), 4.30 (2H, amplio t, *J* = 7.8 Hz), 4.39 (2H, q, *J* = 7.2 Hz), 4.47 (2H, t, *J* = 5.1 Hz), 7.21 - 7.28 (1H, m), 7.37 (1H, d, *J* = 8.5 Hz), 7.56 (1H, ddd, *J* = 8.5, 7.1, 1.4 Hz), 7.83 (1H, dd, *J* = 8.1, 1.4 Hz).

Ejemplo de Referencia 103.

Producción de ácido 5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

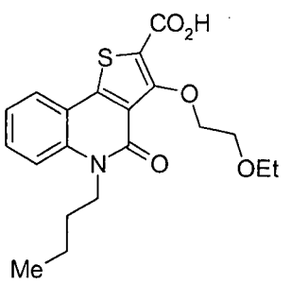


A una suspensión del compuesto del Ejemplo de Referencia 101 (1.81 g, 5.04 mmol) en THF (15 ml) y etanol (15 ml) se agregó solución acuosa 5N de hidróxido de sodio (2.0 ml, 10 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1.5 hrs. La mezcla de reacción se enfrió con hielo, se agregaron ácido clorhídrico 1N (15 ml) y acetato de etilo, y el sólido precipitado se recolectó por filtración, y se lavó con agua y acetato de etilo para dar un sólido. El filtrado se separó, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica combinada se lavó con agua, y se concentró bajo presión reducida. El residuo y el sólido obtenido con anterioridad se combinaron, y la mezcla se recristalizó a partir de metanol-diisopropil éter para dar el compuesto del título (1.43 g, 86%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.95 (3H, t, *J* = 7.3 Hz), 1.43 (2H, sext, *J* = 7.3 Hz), 1.56 - 1.68 (2H, m), 3.95 (3H, s), 4.29 (2H, t, *J* = 7.5 Hz), 7.29 - 7.36 (1H, m), 7.60 - 7.71 (2H, m), 7.95 - 8.00 (1H, m).

Ejemplo de Referencia 104.

Producción de ácido 5-butil-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.



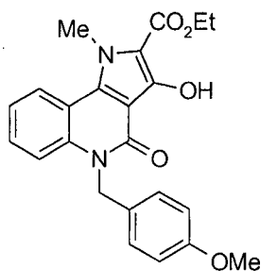
976

A una solución del compuesto del Ejemplo de Referencia 102 (1.16 g, 2.78 mmol) en THF (9 ml) y etanol (9 ml) se agregó solución acuosa 5N de hidróxido de sodio (1.12 ml, 5.6 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2.5 hrs, se agregó solución acuosa 5N de hidróxido de sodio (4.48 ml, 22 mmol), y la mezcla se agitó a 5°C durante 3 hrs. La mezcla de reacción se acidificó con ácido clorhídrico 1N, y se extrajo dos veces con cloroformo. La fase orgánica combinada se lavó con agua, y concentró bajo presión reducida. El residuo se cristalizó a partir de acetato de etilo-diisopropil éter para dar el compuesto del título (965 mg, 89%).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.95 (3H, t, J = 7.3 Hz), 1.02 (3H, t, J = 7.0 Hz), 1.43 (2H, sext, J = 7.3 Hz), 1.56 - 1.68 (2H, m), 3.43 (2H, q, J = 7.0 Hz), 3.74 (2H, t, J = 5.0 Hz), 4.24 - 4.40 (2H, m), 4.30 (2H, t, J = 5.0 Hz), 7.32 (1H, t, J = 7.3 Hz), 7.59 - 7.71 (2H, m), 7.97 (1H, d, J = 7.5 Hz), 13.20 (1H, s amplio).

Ejemplo de Referencia 105.

Producción de etil 3-hidroxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.



977

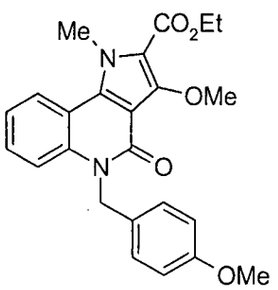
Del mismo modo que en el Ejemplo de Referencia 25, etil 4-[(2-etoxi-2-oxoetil)(metil)amino]-1-(4-metoxibencil)-2-oxo-1,2-dihidroquinolin-3-carboxilato (14.7 g, 63%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 10 (19.2 g, 51.6 mmol).

Del mismo modo que en el Ejemplo de Referencia 26, el compuesto del título (10.35 g, 49%) se obtuvo como un sólido blanco a partir del etil 4-[(2-etoxi-2-oxoetil)(metil)amino]-1-(4-metoxibencil)-2-oxo-1,2-dihidroquinolin-3-carboxilato (14.73 g).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, *J* = 7.1 Hz), 3.69 (3H, s), 4.27 (3H, s), 4.34 (2H, q, *J* = 7.1 Hz), 5.47 (2H, s), 6.86 (2H, d, *J* = 8.7 Hz), 7.16 (2H, d, *J* = 8.7 Hz), 7.27 - 7.30 (1H, m), 7.38 (2H, d, *J* = 3.3 Hz), 8.32 (1H, d, *J* = 8.1 Hz), 9.10 (1H, s).

Ejemplo de Referencia 106.

Producción de etil 3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.



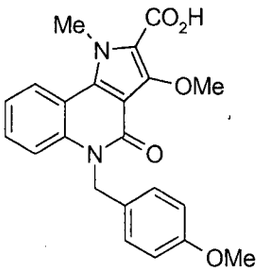
Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (6.51 g, 61%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 105 (10.4 g, 25.5 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, *J* = 7.1 Hz), 3.69 (3H, s), 3.94 (3H, s), 4.26 (3H, s), 4.34 (2H, q, *J* = 7.1 Hz), 5.51 (2H, s amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.15 (1H, d, *J* = 8.4 Hz), 7.25 - 7.31(1H, m), 7.37 (2H, d, *J* = 3.6 Hz), 8.34 (1H, d, *J* = 8.1 Hz).

978

Ejemplo de Referencia 107.

Producción de ácido 3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxílico.

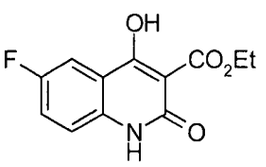


Del mismo modo que en el Ejemplo de Referencia 28, el compuesto del título (5.67 g, 96%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 106 (6.5 g, 15.5 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.70 (3H, s), 3.94 (3H, s), 4.28 (3H, s), 5.51 (2H, s amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.15 (1H, d, *J* = 8.4 Hz), 7.25 - 7.30(1H, m), 7.36 (2H, d, *J* = 3.9 Hz), 8.34 (1H, d, *J* = 8.4 Hz), 12.90 (1H, s amplio).

Ejemplo de Referencia 110.

Producción de etil 6-fluoro-4-hidroxi-2-oxo-1,2-dihidroquinolin-3-carboxilato.



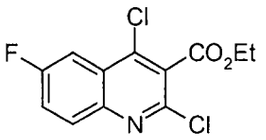
Del mismo modo que en el Ejemplo de Referencia 1, el compuesto del título (8.60 g, 56%) se obtuvo como un sólido amarillo pálido a partir del etil 2-amino-5-fluorobenzoato (10.3 g, 61 mmol), malonato de dietilo (9.2 ml, 61.0 mmol), una solución al 20% (21.0 g, 61.0 mmol) de etóxido de sodio en etanol y etanol (70 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.52 (3H, t, *J* = 7.2 Hz), 4.54 (2H, q, *J* = 7.1 Hz), 7.20 - 7.29 (1H, m), 7.31 - 7.32 (1H, m), 7.75 (1H, dd, *J* = 8.6, 2.7 Hz), 11.02 (1H, s amplio), 14.31 (1H, s).

979

Ejemplo de Referencia 111.

Producción de etil 2,4-dicloro-6-fluoroquinolin-3-carboxilato.

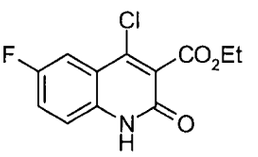


Del mismo modo que en el Ejemplo de Referencia 2, el compuesto del título (2.2 g, 96%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 110 (2.0 g, 7.8 mmol) y oxicloruro de fósforo (9.0 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.46 (3H, t, *J* = 7.1 Hz), 4.54 (2H, q, *J* = 7.2 Hz), 7.54 - 7.68 (1H, m), 7.86 (1H, dd, *J* = 9.1, 2.8 Hz), 8.07 (1H, dd, *J* = 9.2, 5.2 Hz).

Ejemplo de Referencia 112.

Producción de etil 4-cloro-6-fluoro-2-oxo-1,2-dihidroquinolin-3-carboxilato.

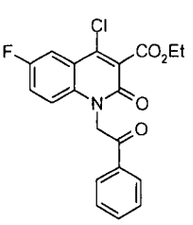


Del mismo modo que en el Ejemplo de Referencia 3, el compuesto del título (1.6 g, 79%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 111 (2.2 g, 7.5 mmol), acetato de sodio (615 mg, 7.5 mmol) y ácido acético (20 ml).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.40 - 1.51 (3H, m), 4.46 - 4.57 (2H, m), 7.36 - 7.36 (2H, m), 7.69 (1H, dd, *J* = 9.1, 1.9 Hz), 12.36 (1H, s amplio).

Ejemplo de Referencia 113.

Producción de etil 4-cloro-6-fluoro-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidroquinolin-3-carboxilato.



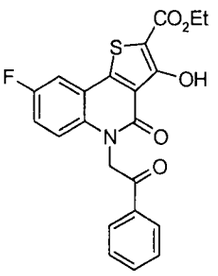
980

Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (1.3 g, 57%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 112 (1.6 g, 5.9 mmol), hidruro de sodio (60% en aceite, 248 mg, 6.2 mmol), bromuro de fenacilo (1.3 g, 6.5 mmol) y DMF (20 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.1 Hz), 4.47 (2H, q, *J* = 7.1 Hz), 5.79 (2H, s), 7.00 (1H, dd, *J* = 9.3, 4.2 Hz), 7.27 - 7.38 (1H, m), 7.39 - 7.61 (2H, m), 7.63 - 7.73 (1H, m), 7.80 (1H, dd, *J* = 9.1, 2.8 Hz), 8.02 - 8.12 (2H, m).

Ejemplo de Referencia 114.

Producción de etil 8-fluoro-3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 5, el compuesto del título (1.3 g, 94%) se obtuvo como un sólido amarillo a partir del compuesto del Ejemplo de Referencia 113 (1.3 g, 3.3 mmol), una solución al 20% (2.3 g, 6.7 mmol) de etóxido de sodio en etanol, tioglicolato de etilo (0.97 g, 8.0 mmol) y etanol (14 ml).

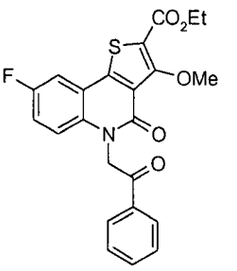
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.32 (3H, t, *J* = 7.1 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 6.02 (2H, s), 7.37 - 7.58 (1H, m), 7.59 - 7.70 (3H, m), 7.72 - 7.82 (1H, m), 8.00 (1H, dd, *J* = 8.7, 2.8 Hz), 8.11 - 8.21 (2H, m), 10.52 (1H, s amplio).

Ejemplo de Referencia 115.

Producción de etil 8-fluoro-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-

791

4,5-dihidrotieno[3,2-c]quinolin-2-carboxilato.

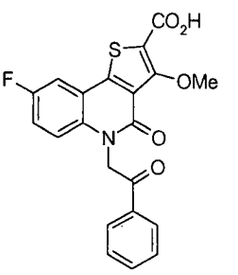


Del mismo modo que en el Ejemplo de Referencia 6, el compuesto del título (880 mg, 65%) se obtuvo como un sólido amarillo a partir del compuesto del Ejemplo de Referencia 114 (1.3 g, 3.1 mmol), yodometano (0.31 ml, 5.0 mmol), DBU (0.75 ml, 5.0 mmol) y DMF (40 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.43 (3H, t, *J* = 7.5 Hz), 4.12 (3H, s), 4.42 (2H, q, *J* = 7.2 Hz), 5.84 (2H, s), 6.98 (1H, dd, *J* = 9.3, 4.2 Hz), 7.16 - 7.25 (1H, m), 7.39 - 7.60 (3H, m), 7.64 - 7.72 (1H, m), 8.03 - 8.15 (2H, m).

Ejemplo de Referencia 116.

Producción de ácido 8-fluoro-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxílico.

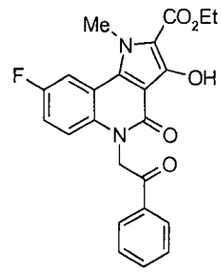


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (602 mg, 73%) se obtuvo como un sólido marrón pálido a partir del compuesto del Ejemplo de Referencia 115 (880 mg, 2.0 mmol), solución acuosa 8N de hidróxido de sodio (5.7 ml), etanol (32 ml) y THF (9.1 ml).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.92 (3H, s), 5.98 (2H, s), 7.39 - 7.60 (2H, m), 7.60 - 7.69 (2H, m), 7.72 - 7.81 (1H, m), 7.91 - 8.01 (1H, m), 8.12 - 8.23 (2H, m).

Ejemplo de Referencia 117.

Producción de etil 8-fluoro-3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.

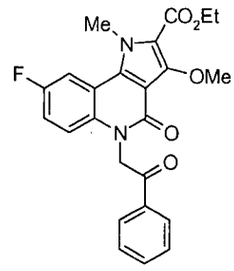


Del mismo modo que en el Ejemplo de Referencia 25, el compuesto del título (4.1 g, 83%) se obtuvo como un sólido marrón pálido a partir del compuesto del Ejemplo de Referencia 113 (4.6 g, 12 mmol), etil éster de sarcosina, clorhidrato (4.5 g, 30 mmol), trietilamina (6.0 ml, 43 mmol), etanol (35 ml), una solución al 20% (3.4 g, 9.9 mmol) de etóxido de sodio en etanol y etanol (35 ml).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.33 (3H, t, J = 8.9 Hz), 4.26 - 4.42 (5H, m), 5.94 (2H, s), 7.33 - 7.50 (2H, m), 7.58 - 7.69 (2H, m), 7.71 - 7.80 (1H, m), 8.03 - 8.23 (3H, m), 9.01 (1H, amplio. s).

Ejemplo de Referencia 118.

Producción de etil 8-fluoro-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxilato.



A solución del compuesto del Ejemplo de Referencia 117 (3.4 g, 8.0 mmol), ácido dimetilsulfúrico (1.1 ml, 12 mmol) y DBU (2.4 ml, 16 mmol) en DMF (100 ml) se agitó a temperatura ambiente durante 2.5 hrs. Se agregaron ácido dimetilsulfúrico

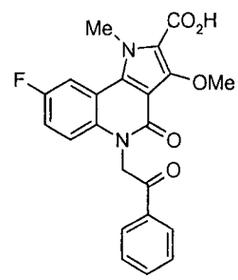
983

(1.1 ml, 12 mmol) y DBU (2.4 ml, 16 mmol) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 día. Se agregaron ácido dimetilsulfúrico (0.75 ml, 8.0 mmol) y DBU (1.8 ml, 11 mmol) en forma adicional, y la mezcla se agitó a temperatura ambiente durante 21 hrs, se diluyó con agua, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (2.8 g, 80%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, J = 7.1 Hz), 3.88 (3H, s), 4.21 - 4.42 (5H, m), 5.96 (2H, s), 7.28 - 7.51 (2H, m), 7.55 - 7.69 (2H, m), 7.71 - 7.81 (1H, m), 7.98 - 8.39 (3H, m).

Ejemplo de Referencia 119.

Producción de ácido 8-fluoro-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxílico.

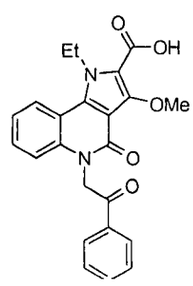


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (2.4 g, 90%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 118 (2.8 g, 6.4 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.85 (3H, s), 4.30 (3H, s), 5.95 (2H, s), 7.19 - 7.39 (2H, m), 7.53 - 7.69 (2H, m), 7.70 - 7.82 (1H, m), 7.97 - 8.26 (3H, m).

Ejemplo de Referencia 120.

Producción de ácido 1-etil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxílico.



984

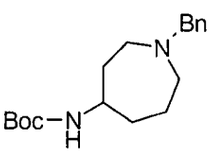
A solución del compuesto del Ejemplo de Referencia 4 (1.0 g, 2.7 mmol), N-etilglicina etil éster clorhidrato (499 mg, 3.0 mmol) y trietilamina (3.8 ml, 27 mmol) en n-butanol (10 ml) se calentó a reflujo durante 6 hrs. Se agregó N- etil éster de etilglicina, clorhidrato (499 mg, 3.0 mmol) y la mezcla se calentó a reflujo durante 17 hrs. Se agregaron etil éster de N-etilglicina, clorhidrato (499 mg, 3.0 mmol) y trietilamina (0.41 ml, 3.0 mmol), y la mezcla se calentó a reflujo durante 6 hrs, y etil éster de N-etilglicina, clorhidrato (499 mg, 3.0 mmol) y trietilamina (0.41 ml, 3.0 mmol) se agregaron, y la mezcla se calentó a reflujo durante 6 hrs. Se agregó agua a la mezcla de reacción, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida. Una mezcla de el sólido obtenido y una solución al 20% (777 mg, 2.3 mmol) de etóxido de sodio en etanol y etanol (150 ml) se agitó a temperatura ambiente durante 5 hrs. Una solución al 20% (777 mg, 2.3 mmol) de etóxido de sodio en etanol se agregó, y la mezcla de reacción se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se diluyó con agua, se neutralizó con ácido clorhídrico 5N, y la mezcla se agitó durante 30 min. El sólido precipitado se recolectó por filtración, se lavó con agua, se secó bajo presión reducida, y recristalizó a partir de DMF-dietil éter. A una solución de el sólido obtenido y DBU (0.19 ml, 1.3 mmol) en DMF (8.0 ml) se agregó ácido dimetilsulfúrico (0.092 ml, 0.97 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 14 hrs. Se agregaron DBU (0.19 ml, 1.3 mmol) y ácido dimetilsulfúrico (0.092 ml, 0.97 mmol) en forma adicional enfrió con hielo, y la mezcla se agitó a

temperatura ambiente durante 4 hrs, y se diluyó con agua. El sólido precipitado se recolectó por filtración, el sólido obtenido se lavó con agua, y se secó bajo presión reducida. Una solución mixta del sólido obtenido y solución acuosa 8N de hidróxido de sodio (1.4 ml) en THF (2.3 ml)-etanol (8.0 ml) se agitó a temperatura ambiente durante 15 hrs. Se agregó solución acuosa 8N de hidróxido de sodio (0.70 ml), y la mezcla se agitó a temperatura ambiente durante 3.5 hrs. Se agregó solución 8N de hidróxido de sodio (0.14 ml) en forma adicional, y la mezcla se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se neutralizó con ácido clorhídrico 1N y concentró bajo presión reducida, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (180 mg, 16%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.51 (3H, t, *J* = 6.5 Hz), 3.86 (3H, s), 4.85 (2H, q, *J* = 7.0 Hz), 5.97 (2H, s), 7.27 - 7.33 (2H, m), 7.34 - 7.54 (1H, m), 7.58 - 7.69 (2H, m), 7.71 - 7.83 (1H, m), 8.01 - 8.45 (3H, m), 12.89 (1H, amplio. s).

Ejemplo de Referencia 121.

Producción de *terc*-butil (1-bencilazepan-4-il)carbamato.



A una solución de 1-bencilazepan-4-amina (400 mg, 2.0 mmol) y trietilamina (0.82 ml, 5.9 mmol) en THF (5.0 ml) se agregó di-*terc*-butilo dicarbonato (591 mg, 2.7 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 4 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre

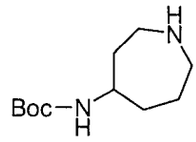
986

sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=10/90 - 100/0) para dar el compuesto del título (447 mg, cuant.) como un aceite incoloro.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.53 - 1.77 (5H, m), 1.78 - 1.93 (1H, m), 2.37 - 2.58 (2H, m), 2.61 - 2.83 (2H, m), 3.61 (2H, s), 3.73 - 4.00 (1H, m), 4.92 - 5.27 (1H, m), 7.07 - 7.34 (5H, m).

Ejemplo de Referencia 122.

Producción de *terc*-butilo azepan-4-ilcarbamato.

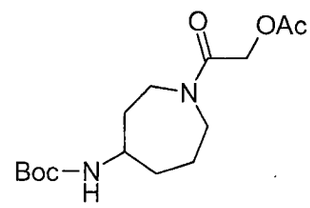


A solución del compuesto del Ejemplo de Referencia 121 (447 mg, 1.5 mmol) y paladio-carbón (65 mg) en etanol (10 ml) se agitó a temperatura ambiente durante 4.5 hrs bajo una atmósfera de hidrógeno. Se eliminó el paladio-carbón por filtración, y el filtrado se concentró bajo presión reducida. El residuo se disolvió en metanol (10 ml), se agregó paladio-carbón (120 mg), y la mezcla se agitó a temperatura ambiente durante 4.5 hrs bajo una atmósfera de hidrógeno. Se eliminó el paladio-carbón por filtración, y el filtrado se concentró bajo presión reducida para dar el compuesto del título (315 mg, cuant.) como un aceite incoloro.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.34 - 1.76 (13H, m), 1.78 - 2.07 (2H, m), 2.39 - 2.70 (1H, m), 2.71 - 3.04 (4H, m), 3.66 - 3.94 (1H, m), 4.60 - 5.01 (1H, m).

Ejemplo de Referencia 123.

Producción de 2-{4-[(*terc*-butoxicarbonil)amino]azepan-1-il}-2-oxoacetato de etilo.

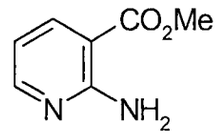


Del mismo modo que en el Ejemplo 544, el compuesto del título (220 mg, 96%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 122 (157 mg, 0.73 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.37 - 1.55 (11H, m), 1.61 - 2.00 (4H, m), 2.07 - 2.23 (4H, m), 3.21 - 3.77 (4H, m), 4.35 - 4.59 (1H, m), 4.59 - 4.81 (2H, m).

Ejemplo de Referencia 124.

Producción de metil 2-aminopiridin-3-carboxilato.

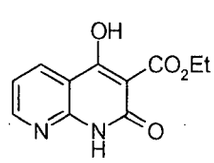


A una solución de ácido 2-aminopiridin-3-carboxílico (4.3 g, 31 mmol) en metanol (62 ml) se agregó gota a gota ácido sulfúrico (31 ml) enfrió con hielo, y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se agitó a 7°C durante 15 hrs, y se neutralizó con bicarbonato de sodio enfrió con hielo. La mezcla de reacción se extrajo dos veces con acetato de etilo, y los extractos se combinaron, y se lavó con salmuera. Los extractos se secaron sobre sulfato de magnesio, y se concentró bajo presión reducida para dar el compuesto del título (4.3 g, 90%) como un sólido blanco.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 3.89 (3H, s), 6.38 (2H, amplio. s), 6.63 (1H, dd, *J* = 7.8, 4.8 Hz), 8.13 (1H, dd, *J* = 7.7, 1.9 Hz), 8.22 (1H, dd, *J* = 4.7, 1.9 Hz).

Ejemplo de Referencia 125.

Producción de etil 4-hidroxi-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxilato.

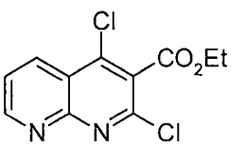


Del mismo modo que en el Ejemplo de Referencia 1, el compuesto del título (2.6 g, 53%) se obtuvo como un sólido rojo pálido a partir del compuesto del Ejemplo de Referencia 124 (3,1 g, 21 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.30 (3H, t, *J* = 7.1 Hz), 4.32 (2H, q, *J* = 7.1 Hz), 7.27 (1H, dd, *J* = 7.9, 4.7 Hz), 8.22 - 8.38 (1H, m), 8.60 (1H, dd, *J* = 4.6, 1.8 Hz), 11.86 (1H, s), 13.29 (1H, amplio. s).

Ejemplo de Referencia 126.

Producción de etil 2,4-dicloro-1,8-naftiridin-3-carboxilato.

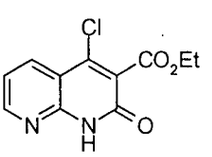


Del mismo modo que en el Ejemplo de Referencia 2, el compuesto del título (2.3 g, 77%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 125 (2.6 g, 11 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.47 (3H, t, *J* = 7.2 Hz), 4.56 (2H, q, *J* = 7.2 Hz), 7.67 (1H, dd, *J* = 8.4, 4.2 Hz), 8.62 (1H, dd, *J* = 8.3, 1.9 Hz), 9.21 (1H, dd, *J* = 4.2, 1.9 Hz).

Ejemplo de Referencia 127.

Producción de etil 4-cloro-2-oxo-1,2-dihidro-1,8-naftiridin-3-carboxilato.



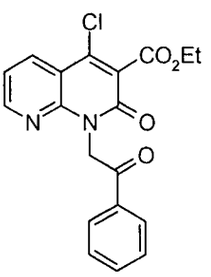
Del mismo modo que en el Ejemplo de Referencia 3, el compuesto del título (1.5 g, 71%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 126 (2.2 g, 8.3 mmol).

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^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.31 (3H, t, *J* = 7.1 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 7.33 (1H, dd, *J* = 8.1, 4.7 Hz), 8.33 (1H, dd, *J* = 8.1, 1.7 Hz), 8.69 (1H, dd, *J* = 4.7, 1.7 Hz), 12.88 (1H, s amplio).

Ejemplo de Referencia 128.

Producción de etil 4-cloro-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidro-1,8-naftiridin-3-carboxilato.

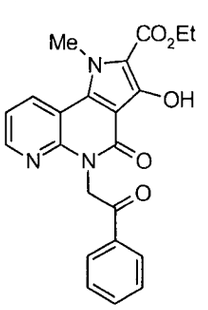


Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (1.1 g, 51%) se obtuvo como un aceite amarillo pálido a partir del compuesto del Ejemplo de Referencia 127 (1.5 g, 5.7 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.1 Hz), 4.48 (2H, q, *J* = 7.1 Hz), 5.98 (2H, s), 7.27 - 7.33 (1H, m), 7.38 - 7.58 (2H, m), 7.59 - 7.69 (1H, m), 8.02 - 8.12 (2H, m), 8.36 (1H, dd, *J* = 8.0, 1.8 Hz), 8.54 (1H, dd, *J* = 4.7, 1.7 Hz).

Ejemplo de Referencia 129.

Producción de etil 3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1,8]naftiridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 25, el compuesto del título (653 mg, 55%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia

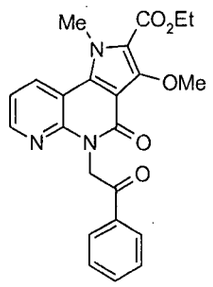
980

128 (1.1 g, 2.9 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.45 (3H, t, *J* = 7.1 Hz), 4.36 (3H, s), 4.46 (2H, q, *J* = 7.2 Hz), 6.00 (2H, s), 7.20 (1H, dd, *J* = 7.9, 4.7 Hz), 7.35 - 7.58 (2H, m), 7.58 - 7.69 (1H, m), 8.02 - 8.15 (2H, m), 8.33 - 8.51 (2H, m), 8.70 (1H, s).

Ejemplo de Referencia 130.

Producción de etil 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1,8]naftiridin-2-carboxilato.

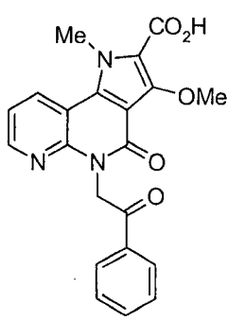


Del mismo modo que en el Ejemplo de Referencia 115, el compuesto del título (420 mg, 79%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 129 (512 mg, 1.3 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, *J* = 7.1 Hz), 3.91 (3H, s), 4.24 - 4.44 (5H, m), 5.97 (2H, s), 7.36 (1H, dd, *J* = 8.1, 4.5 Hz), 7.55 - 7.69 (2H, m), 7.68 - 7.82 (1H, m), 8.06 - 8.24 (2H, m), 8.46 (1H, dd, *J* = 4.6, 1.4 Hz), 8.75 (1H, dd, *J* = 8.1, 1.5 Hz).

Ejemplo de Referencia 131.

Producción de ácido 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1,8]naftiridin-2-carboxílico.



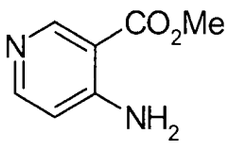
991

Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (264 mg, 75%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 130 (380 mg, 0.91 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.90 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.35 (1H, dd, *J* = 8.1, 4.7 Hz), 7.54 - 7.68 (2H, m), 7.69 - 7.81 (1H, m), 8.03 - 8.27 (2H, m), 8.33 - 8.56 (1H, m), 8.75 (1H, d, *J* = 7.2 Hz), 13.04 (1H, amplio. s).

Ejemplo de Referencia 132.

Producción de metil 4-aminopiridin-3-carboxilato.

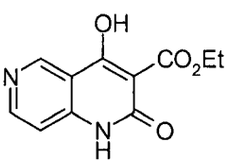


Del mismo modo que en el Ejemplo de Referencia 124, el compuesto del título (4.9 g, 89%) se obtuvo como un sólido amarillo pálido a partir de ácido 4-aminopiridin-3-carboxílico (5.0 g, 36 mmol), ácido sulfúrico (36 ml) y metanol (72 ml).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 3.91 (3H, s), 6.20 (2H, amplio, s), 6.51 (1H, d, *J* = 5.9 Hz), 8.20 (1H, d, *J* = 6.0 Hz), 8.90 (1H, s).

Ejemplo de Referencia 133.

Producción de etil 4-hidroxi-2-oxo-1,2-dihidro-1.6-naftiridin-3-carboxilato.



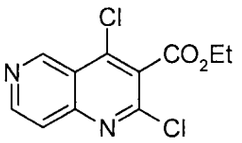
Del mismo modo que en el Ejemplo de Referencia 1, el compuesto del título (3.5 g, 49%) se obtuvo como un polvo amarillo pálido a partir del compuesto del Ejemplo de Referencia 132 (4.7 g, 31 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.28 (3H, t, *J* = 7.1 Hz), 4.26 (2H, q, *J* = 7.0 Hz), 7.20 (1H, d, *J* = 6.0 Hz), 8.50 (1H, d, *J* =

6.0 Hz), 8.92 - 9.09 (1H, m), 11.66 (1H, amplio, s).

Ejemplo de Referencia 134.

Producción de etil 2,4-dicloro-1.6-naftiridin-3-carboxilato.

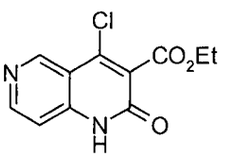


Del mismo modo que en el Ejemplo de Referencia 2, el compuesto del título (2.7 g, 66%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 133 (3.5 g, 15 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.47 (3H, t, *J* = 7.2 Hz), 4.56 (2H, q, *J* = 7.1 Hz), 7.87 (1H, dd, *J* = 5.9, 0.8 Hz), 8.92 (1H, d, *J* = 5.9 Hz), 9.66 (1H, d, *J* = 0.9 Hz).

Ejemplo de Referencia 135.

Producción de etil 4-cloro-2-oxo-1,2-dihidro-1.6-naftiridin-3-carboxilato.

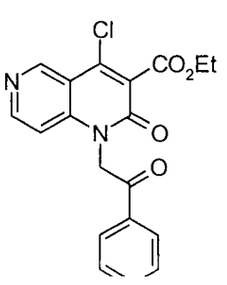


Del mismo modo que en el Ejemplo de Referencia 3, el compuesto del título (733 mg, 30%) se obtuvo como un sólido marrón pálido a partir del compuesto del Ejemplo de Referencia 134 (2.6 g, 9.7 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.31 (3H, t, *J* = 7.1 Hz), 4.36 (2H, q, *J* = 7.1 Hz), 7.29 (1H, d, *J* = 5.7 Hz), 8.63 (1H, d, *J* = 5.7 Hz), 9.06 (1H, s), 12.72 (1H, s amplio).

Ejemplo de Referencia 136.

Producción de etil 4-cloro-2-oxo-1-(2-oxo-2-feniletil)-1,2-dihidro-1.6-naftiridin-3-carboxilato.



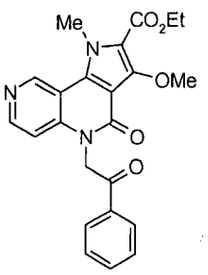
993

Del mismo modo que en el Ejemplo de Referencia 4, el compuesto del título (344 mg, 33%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 135 (710 mg, 2.8 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.42 (3H, t, *J* = 7.2 Hz), 4.48 (2H, q, *J* = 7.2 Hz), 5.73 (2H, s), 6.86 (1H, d, *J* = 5.9 Hz), 7.39 - 7.63 (2H, m), 7.64 - 7.79 (1H, m), 7.95 - 8.19 (2H, m), 8.64 (1H, s amplio), 9.30 (1H, s amplio).

Ejemplo de Referencia 137.

Producción de etil 3-hidroxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1.6]naftiridin-2-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 136 (574 mg, 1.6 mmol), etil éster de sarcosina, clorhidrato (286 mg, 1.9 mmol), trietilamina (0.65 ml, 4.7 mmol), y etanol (29 ml) se calentó a reflujo durante 2.5 hrs. Etil éster de sarcosina, clorhidrato (286 mg, 1.9 mmol) y trietilamina (0.43 ml, 3,1 mmol) se agregaron en forma adicional y la mezcla se calentó a reflujo durante 5.5 hrs. Se agregaron etil éster de sarcosina, clorhidrato (286 mg, 1.9 mmol) y trietilamina (0.65 ml, 4.7 mmol) y la mezcla se calentó a reflujo durante 46 hrs. Se agregó trietilamina (0.65 ml, 4.7 mmol), y la mezcla se calentó a reflujo durante 3 hrs. Se agregó trietilamina (0.65 ml, 4.7 mmol) y la mezcla se calentó a reflujo durante 64 hrs. Se agregó trietilamina (0.65 ml, 4.7 mmol)

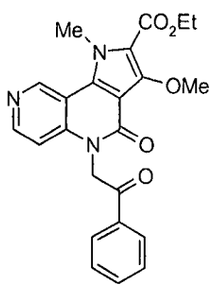
994

en forma adicional y la mezcla se calentó a reflujo durante 3 hrs. se agregó trietilamina (0.65 ml, 4.7 mmol) en forma adicional y la mezcla se calentó a reflujo durante 3 hrs. La mezcla de reacción se concentró bajo presión reducida, se agregó agua al residuo, y la mezcla se acidificó con solución acuosa al 20% de ácido cítrico y se agitó durante 30 min enfrió con hielo. El sólido precipitado se recolectó por filtración, el sólido obtenido se lavó con agua, y se secó bajo presión reducida. El sólido se lavó con solvente mixto de acetato de etilo-hexano y hexano para dar el compuesto del título (485 mg, 77%) como un polvo marrón pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.34 (3H, t, *J* = 7.1 Hz), 4.27 - 4.43 (5H, m), 5.91 (2H, s), 7.32 (1H, d, *J* = 6.0 Hz), 7.58 - 7.69 (2H, m), 7.71 - 7.82 (1H, m), 8.08 - 8.23 (2H, m), 8.50 (1H, d, *J* = 5.9 Hz), 9.07 (1H, s amplio), 9.49 (1H, s).

Ejemplo de Referencia 138.

Producción de etil 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1.6]naftiridin-2-carboxilato.



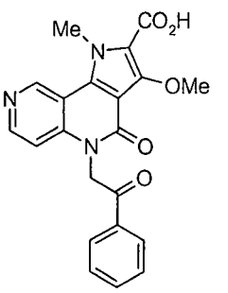
Del mismo modo que en el Ejemplo de Referencia 115, el compuesto del título (313 mg, 64%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 137 (471 mg, 1.2 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 (3H, t, *J* = 6.0 Hz), 3.88 (3H, s), 4.28 - 4.40 (5H, m), 5.94 (2H, s), 7.33 (1H, d, *J* = 6.0 Hz), 7.59 - 7.69 (2H, m), 7.72 - 7.82 (1H, m), 8.11 - 8.22 (2H, m), 8.51 (1H, d, *J* = 6.0 Hz), 9.52 (1H, s).

995

Ejemplo de Referencia 139.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1.6]naftiridin-2-carboxílico ácido.

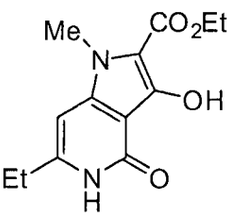


Del mismo modo que en el Ejemplo de Referencia 7, el compuesto del título (259 mg, 92%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 138 (301 mg, 0.72 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.87 (3H, s), 4.36 (3H, s), 5.94 (2H, s), 7.32 (1H, d, *J* = 6.0 Hz), 7.57 - 7.70 (2H, m), 7.71 - 7.83 (1H, m), 8.07 - 8.26 (2H, m), 8.49 (1H, d, *J* = 5.9 Hz), 9.51 (1H, s), 13.01 (1H, amplio, s).

Ejemplo de Referencia 140

Producción de etil 6-etil-3-hidroxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

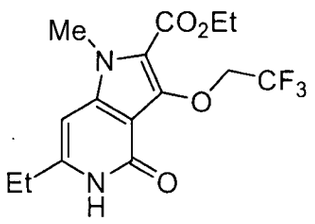


Del mismo modo que en el Ejemplo de Referencia 40, el compuesto del título (4.87 g, 85%) se obtuvo como un polvo marrón a partir del compuesto del Ejemplo de Referencia 38 (5.00 g, 21.8 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.6 Hz), 1.30 (3 H, t, *J* = 7.1 Hz), 2.39 - 2.49 (2 H, m), 3.73 (3 H, s), 4.29 (2 H, q, *J* = 7.1 Hz), 6.25 (1 H, s), 8.87 (1 H, s amplio), 10.81 (1 H, s amplio).

Ejemplo de Referencia 141.

Producción de etil 6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

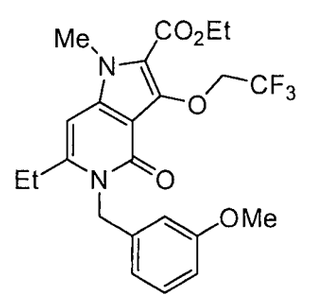


Una mezcla del compuesto del Ejemplo de Referencia 140 (200 mg, 0.757 mmol), carbonato de cesio (271 mg, 0.832 mmol), 2,2,2-trifluoroetil trifluorometanosulfonato (0.109 ml, 0.757 mmol), dimetil sulfóxido (2.0 ml) y DMF (2.0 ml) se agitó a 6°C durante 2 hrs. La mezcla de reacción se diluyó con agua, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua y diisopropil éter, y se secó bajo presión reducida para dar el compuesto del título (161 mg, 61%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, J = 7.5 Hz), 1.27 (3 H, t, J = 7.0 Hz), 2.51 - 2.56 (2 H, m), 3.79 (3 H, s), 4.24 (2 H, q, J = 7.0 Hz), 4.97 (2 H, q, J = 9.3 Hz), 6.38 (1 H, s), 11.06 (1 H, s amplio).

Ejemplo de Referencia 142.

Producción de etil 6-etil-5-(3-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Una mezcla del compuesto del Ejemplo de Referencia 141 (500 mg, 1.44 mmol), *terc*-butóxido de sodio (180 mg, 1.87 mmol), bromuro de litio (250 mg, 2.88 mmol), 1-(clorometil)-3-

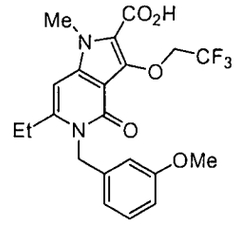
997

metoxibenceno (0.313 ml, 2.16 mmol), DME (8.0 ml) y DMF (2.0 ml) se agitó a 6°C durante 13 hrs. Se agregó agua (50 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=3/97 - 70/30) para dar el compuesto del título (508 mg, 76%) como un aceite amarillo.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.14 - 1.36 (6 H, m), 2.60 (2 H, q, *J* = 7.2 Hz), 3.70 (3 H, s), 3.85 (3 H, s), 4.26 (2 H, q, *J* = 7.2 Hz), 4.89 (2 H, q, *J* = 9.3 Hz), 5.28 (2 H, s amplio), 6.44 - 6.67 (3 H, m), 6.74 - 6.95 (1 H, m), 7.22 (1 H, t, *J* = 7.9 Hz).

Ejemplo de Referencia 143.

Producción de ácido 6-etil-5-(3-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (333 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 142 (508 mg, 1.09 mmol).

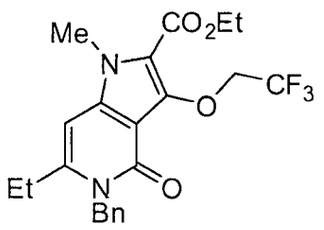
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 2.60 (2 H, q, *J* = 7.3 Hz), 3.70 (3 H, s), 3.85 (3 H, s), 4.87 (2 H, q, *J* = 9.4 Hz), 5.30 (2 H, s amplio), 6.43 - 6.67 (3 H, m), 6.81 (1 H, dd, *J* = 7.9, 2.3 Hz), 7.22 (1 H, t, *J* = 7.9 Hz), 12.70 (1 H, s amplio).

Ejemplo de Referencia 144.

Producción de etil 5-bencil-6-etil-1-metil-4-oxo-3-(2,2,2-

998

trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

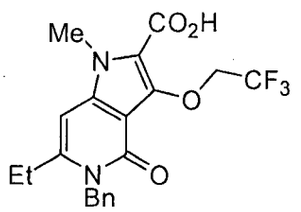


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (312 mg, 62%) se obtuvo como un aceite amarillo a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y bromuro de bencilo (0.207 ml, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.1 Hz), 2.61 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 4.89 (2 H, q, *J* = 9.3 Hz), 5.34 (2 H, s amplio), 6.54 (1 H, s), 7.03 - 7.09 (2 H, m), 7.20 - 7.27 (1 H, m), 7.28 - 7.36 (2 H, m).

Ejemplo de Referencia 145.

Producción de ácido 5-bencil-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



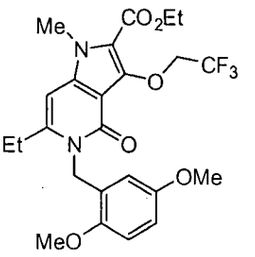
Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (213 mg, 73%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 144 (312 mg, 0.715 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 2.60 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.87 (2 H, q, *J* = 9.3 Hz), 5.34 (2 H, s amplio), 6.52 (1 H, s), 7.01 - 7.10 (2 H, m), 7.17 - 7.39 (3 H, m), 12.73 (1 H, s amplio).

Ejemplo de Referencia 146.

499

Producción de etil 5-(2.5-dimetoxibencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

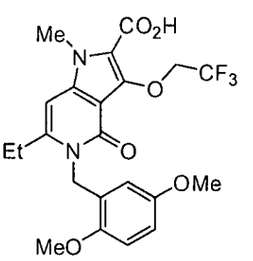


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (121 mg, 21%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y 2-(clorometil)-1,4-dimetoxibenceno (325 mg, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, J = 7.3 Hz), 1.29 (3 H, t, J = 7.2 Hz), 2.53 - 2.61 (2 H, m), 3.56 (3 H, s), 3.83 (3 H, s), 3.86 (3 H, s), 4.26 (2 H, q, J = 7.2 Hz), 4.87 (2 H, q, J = 9.3 Hz), 5.19 (2 H, s amplio), 5.93 (1 H, d, J = 3.0 Hz), 6.58 (1 H, s), 6.79 (1 H, dd, J = 8.9, 3.0 Hz), 6.97 (1 H, d, J = 8.9 Hz).

Ejemplo de Referencia 147.

Producción de ácido 5-(2.5-dimetoxibencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



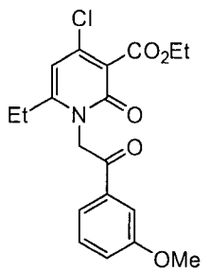
Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (82.7 mg, 72%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 146 (121 mg, 0.244 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, J = 7.3 Hz),

2.52 - 2.60 (2 H, m), 3.56 (3 H, s), 3.83 (3 H, s), 3.86 (3 H, s), 4.85 (2 H, q, *J* = 9.3 Hz), 5.19 (2 H, s amplio), 5.92 (1 H, d, *J* = 3.0 Hz), 6.56 (1 H, s), 6.79 (1 H, dd, *J* = 9.0, 3.0 Hz), 6.97 (1 H, d, *J* = 9.0 Hz), 12.74 (1 H, s amplio).

Ejemplo de Referencia 148.

Producción de etil 4-cloro-6-etil-1-[2-(3-metoxifenil)-2-oxoetil]-2-oxo-1,2-dihidropiridin-3-carboxilato.

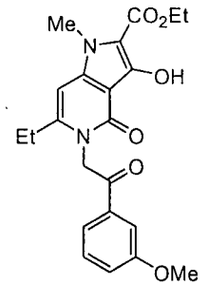


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (879 mg, 53%) se obtuvo como un aceite amarillo a partir del compuesto del Ejemplo de Referencia 38 (1.00 g, 4.35 mmol) y 2-bromo-1-(3-metoxifenil)etanona (1.99 g, 8.71 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ 1.13 (3 H, t, *J* = 7.3 Hz), 1.24 (3 H, t, *J* = 7.1 Hz), 2.61 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.25 (2 H, q, *J* = 7.1 Hz), 5.60 (2 H, s), 6.44 (1 H, s), 7.28 - 7.35 (1 H, m), 7.38 - 7.59 (2 H, m), 7.66 - 7.74 (1 H, m).

Ejemplo de Referencia 149.

Producción de etil 6-etil-3-hidroxi-5-[2-(3-metoxifenil)-2-oxoetil]-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

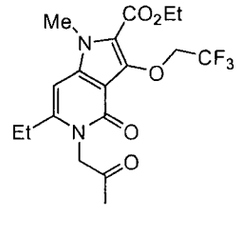


Del mismo modo que en el Ejemplo de Referencia 40, el compuesto del título (526 mg, 55%) se obtuvo como un polvo verde a partir del compuesto del Ejemplo de Referencia 148 (879 mg, 2.33 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.31 (3 H, t, *J* = 7.1 Hz), 2.52 - 2.61 (2 H, m), 3.80 (3 H, s), 3.85 (3 H, s), 4.30 (2 H, q, *J* = 7.1 Hz), 5.54 (2 H, s), 6.43 (1 H, s), 7.26 - 7.36 (1 H, m), 7.38 - 7.60 (2 H, m), 7.68 - 7.76 (1 H, m), 8.89 (1 H, s amplio).

Ejemplo de Referencia 150.

Producción de etil 6-etil-5-[2-(3-metoxifenil)-2-oxoetil]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



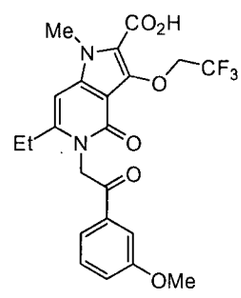
1002

Una mezcla del compuesto del Ejemplo de Referencia 149 (470 mg, 1.14 mmol), carbonato de cesio (446 mg, 1.37 mmol), 2,2,2-trifluoroetil trifluorometanosulfonato (0.197 ml, 1.37 mmol) y DMF (4.7 ml) se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se diluyó con agua, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, diisopropil éter y etanol, y se secó bajo presión reducida para dar el compuesto del título (423 mg, 75%) como un polvo verde.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 1.28 (3 H, t, *J* = 7.2 Hz), 2.59 (2 H, q, *J* = 7.3 Hz), 3.83 - 3.90 (6 H, m), 4.26 (2 H, q, *J* = 7.2 Hz), 4.83 (2 H, q, *J* = 9.3 Hz), 5.61 (2 H, s), 6.55 (1 H, s), 7.27 - 7.34 (1 H, m), 7.38 - 7.61 (2 H, m), 7.68 - 7.76 (1 H, m).

Ejemplo de Referencia 151.

Producción de ácido 6-etil-5-[2-(3-metoxifenil)-2-oxoetil]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



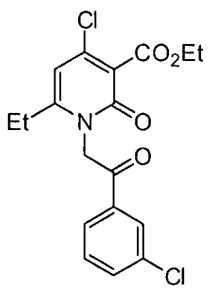
Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (300 mg, 86%) se obtuvo como un polvo marrón a partir del compuesto del Ejemplo de Referencia 150 (370 mg, 0.748 mmol).

1003

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.83 - 3.91 (6 H, m), 4.82 (2 H, q, *J* = 9.3 Hz), 5.60 (2 H, s), 6.54 (1 H, s), 7.26 - 7.37 (1 H, m), 7.37 - 7.62 (2 H, m), 7.67 - 7.83 (1 H, m), 12.70 (1 H, s amplio).

Ejemplo de Referencia 152.

Producción de etil 4-cloro-1-[2-(3-clorofenil)-2-oxoetil]-6-etil-2-oxo-1,2-dihidropiridin-3-carboxilato.

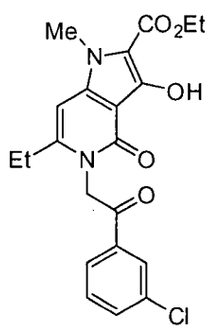


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (486 mg, 29%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 38 (1.50 g, 6.53 mmol) y 2-bromo-1-(3-clorofenil)etanona (2.02 g, 8.65 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.14 (3 H, t, *J* = 7.3 Hz), 1.24 (3 H, t, *J* = 7.1 Hz), 2.63 (2 H, q, *J* = 7.3 Hz), 4.25 (2 H, q, *J* = 7.1 Hz), 5.61 (2 H, s), 6.45 (1 H, s), 7.59 - 7.70 (1 H, m), 7.77 - 7.86 (1 H, m), 8.00 - 8.07 (1 H, m), 8.08 - 8.17 (1 H, m).

Ejemplo de Referencia 153.

Producción de etil 5-[2-(3-clorofenil)-2-oxoetil]-6-etil-3-hidroxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



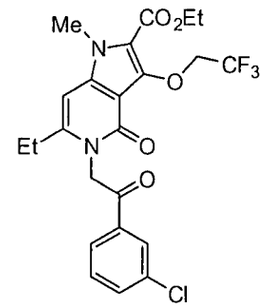
1004

Del mismo modo que en el Ejemplo de Referencia 40, el compuesto del título (460 mg, 87%) se obtuvo como un polvo verde a partir del compuesto del Ejemplo de Referencia 152 (486 mg, 1.27 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.31 (3 H, t, *J* = 7.0 Hz), 2.57 (2 H, q, *J* = 7.3 Hz), 3.80 (3 H, s), 4.30 (2 H, q, *J* = 7.0 Hz), 5.53 (2 H, s), 6.44 (1 H, s), 7.61 - 7.68 (1 H, m), 7.80 (1 H, ddd, *J* = 7.8, 2.0, 0.9 Hz), 8.05 (1 H, dt, *J* = 7.8, 0.9 Hz), 8.13 (1 H, t, *J* = 2.0 Hz), 8.90 (1 H, s).

Ejemplo de Referencia 154.

Producción de etil 5-[2-(3-clorofenil)-2-oxoetil]-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 150, el compuesto del título (348 mg, 63%) se obtuvo como un polvo verde a partir del compuesto del Ejemplo de Referencia 153 (460 mg, 1.10 mmol).

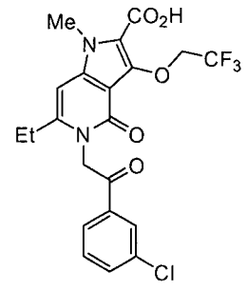
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 1.28 (3 H, t, *J* = 7.1 Hz), 2.60 (2 H, q, *J* = 7.3 Hz), 3.86 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 4.83 (2 H, q, *J* = 9.3 Hz), 5.61 (2 H, s), 6.56 (1 H, s), 7.61 - 7.69 (1 H, m), 7.78 - 7.84 (1 H, m), 8.03 - 8.09 (1 H, m), 8.14 (1 H, t, *J* = 1.7 Hz).

Ejemplo de Referencia 155.

Producción de ácido 5-[2-(3-clorofenil)-2-oxoetil]-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-

1005

carboxílico.

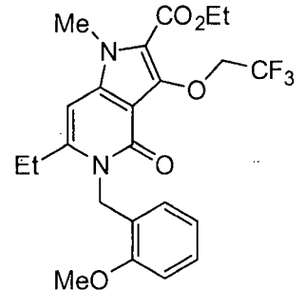


Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (192 mg, 59%) se obtuvo como un polvo marrón a partir del compuesto del Ejemplo de Referencia 154 (348 mg, 0.698 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 2.60 (2 H, q, *J* = 7.3 Hz), 3.86 (3 H, s), 4.81 (2 H, q, *J* = 9.2 Hz), 5.60 (2 H, s), 6.55 (1 H, s), 7.58 - 7.71 (1 H, m), 7.76 - 7.86 (1 H, m), 8.00 - 8.10 (1 H, m), 8.14 (1 H, t, *J* = 1.7 Hz), 12.72 (1 H, s amplio).

Ejemplo de Referencia 156.

Producción de etil 6-etil-5-(2-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



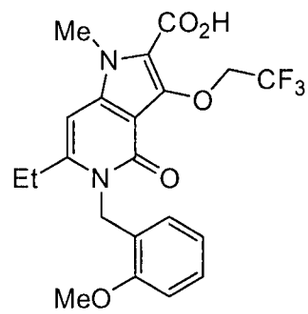
Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (138 mg, 26%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y 1-(clorometil)-2-metoxibenceno (272 mg, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.1 Hz), 2.53 - 2.61 (2 H, m), 3.86 (3 H, s), 3.88 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 4.86 (2 H, q, *J* = 9.3 Hz), 5.22

(2 H, s amplio), 6.41 (1 H, dd, *J* = 7.5, 1,2 Hz), 6.57 (1 H, s), 6.82 (1 H, td, *J* = 7.5, 0.9 Hz), 7.01 - 7.09 (1 H, m), 7.18 - 7.28 (1 H, m).

Ejemplo de Referencia 157.

Producción de 6-etil-5-(2-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico ácido.

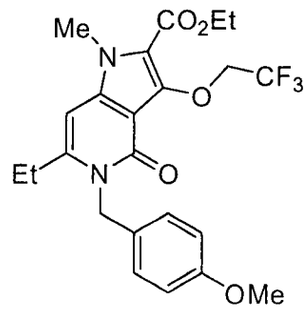


Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (104 mg, 80%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 156 (138 mg, 0.296 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 2.53 - 2.60 (2 H, m), 3.86 (3 H, s), 3.88 (3 H, s), 4.84 (2 H, q, *J* = 9.3 Hz), 5.22 (2 H, s amplio), 6.40 (1 H, dd, *J* = 7.5, 1.3 Hz), 6.55 (1 H, s), 6.82 (1 H, td, *J* = 7.5, 0.9 Hz), 7.00 - 7.11 (1 H, m), 7.16 - 7.31 (1 H, m), 12.72 (1 H, s amplio).

Ejemplo de Referencia 158.

Producción de etil 6-etil-5-(4-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



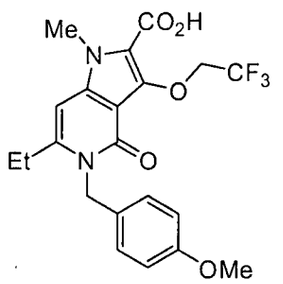
1007

Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (175 mg, 43%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (300 mg, 0.866 mmol) y 1-(clorometil)-4-metoxibenceno (0.175 ml, 1.30 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.2 Hz), 1.29 (3 H, t, *J* = 7.2 Hz), 2.62 (2 H, q, *J* = 7.2 Hz), 3.71 (3 H, s), 3.84 (3 H, s), 4.26 (2 H, q, *J* = 7.2 Hz), 4.90 (2 H, q, *J* = 9.3 Hz), 5.26 (2 H, s amplio), 6.51 (1 H, s), 6.82 - 6.92 (2 H, m), 6.97 - 7.08 (1 H, m).

Ejemplo de Referencia 159.

Producción de ácido 6-etil-5-(4-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

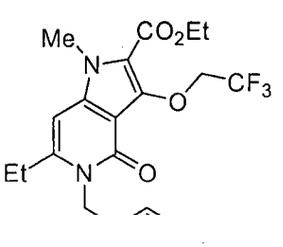


Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (157 mg, 96%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 158 (175 mg, 0.375 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 2.62 (2 H, q, *J* = 7.3 Hz), 3.71 (3 H, s), 3.84 (3 H, s), 4.88 (2 H, q, *J* = 9.3 Hz), 5.26 (2 H, s amplio), 6.49 (1 H, s), 6.81 - 6.92 (2 H, m), 6.96 - 7.09 (2 H, m), 12.70 (1 H, s amplio).

Ejemplo de Referencia 160.

Producción de etil 5-(2-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



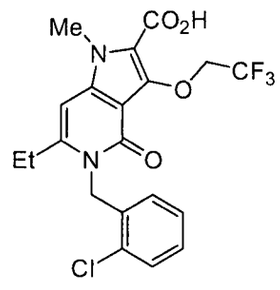
1008

Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (163 mg, 30%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y 1-cloro-2-(clorometil)benceno (0.226 ml, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.1 Hz), 2.53 - 2.62 (2 H, m), 3.87 (3 H, s), 4.27 (2 H, q, *J* = 7.1 Hz), 4.86 (2 H, q, *J* = 9.3 Hz), 5.32 (2 H, s), 6.55 (1 H, dd, *J* = 7.6, 1.5 Hz), 6.62 (1 H, s), 7.21 - 7.33 (2 H, m), 7.52 (1 H, dd, *J* = 7.7, 1.3 Hz).

Ejemplo de Referencia 161.

Producción de ácido 5-(2-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (138 mg, 90%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 160 (163 mg, 0.346 mmol).

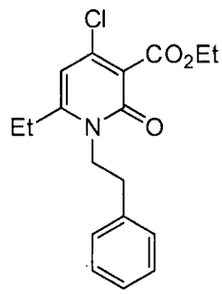
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 2.52 - 2.62 (2 H, m), 3.87 (3 H, s), 4.83 (2 H, q, *J* = 9.3 Hz), 5.32 (2 H, s), 6.50 (1 H, dd, *J* = 7.7, 1.6 Hz), 6.60 (1 H, s), 7.22 - 7.33 (2 H, m), 7.52 (1 H, dd, *J* = 7.7, 1.3 Hz), 12.76 (1 H, s

1009

amplio).

Ejemplo de Referencia 162.

Producción de etil 4-cloro-6-etil-2-oxo-1-(2-feniletil)-1,2-dihidropiridin-3-carboxilato.

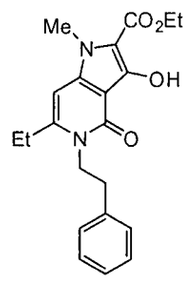


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (480 mg, 16%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 38 (2.00 g, 8.71 mmol) y (2-bromoetil)benceno (1.77 ml, 11.3 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.14 (3 H, t, J = 7.3 Hz), 1.28 (3 H, t, J = 7.1 Hz), 2.63 (2 H, q, J = 7.3 Hz), 2.85 - 2.93 (2 H, m), 4.07 - 4.15 (2 H, m), 4.29 (2 H, q, J = 7.1 Hz), 6.30 (1 H, s), 7.19 - 7.28 (3 H, m), 7.28 - 7.38 (2 H, m).

Ejemplo de Referencia 163.

Producción de etil 6-etil-3-hidroxi-1-metil-4-oxo-5-(2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 40, el compuesto del título (481 mg, 80%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 162 (480 mg, 1.44 mmol).

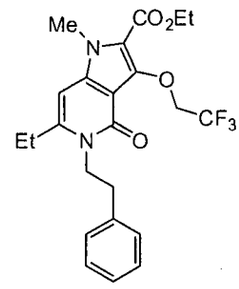
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.20 (3 H, t, J = 7.3 Hz), 1.31 (3 H, t, J = 7.1 Hz), 2.63 (2 H, q, J = 7.3 Hz), 2.80 - 2.94 (2

1010

H, m), 3.75 (3 H, s), 4.01 - 4.16 (2 H, m), 4.30 (2 H, q, *J* = 7.1 Hz), 6.34 (1 H, s), 7.11 - 7.31 (5 H, m), 8.94 (1 H, s amplio).

Ejemplo de Referencia 164.

Producción de etil 6-etil-1-metil-4-oxo-5-(2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

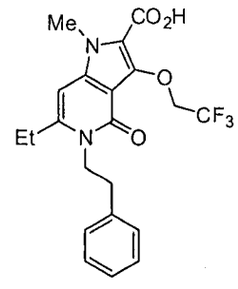


Del mismo modo que en el Ejemplo de Referencia 150, el compuesto del título (185 mg, 31%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 163 (482 mg, 1.31 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.22 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.2 Hz), 2.67 (2 H, q, *J* = 7.3 Hz), 2.82 - 2.94 (2 H, m), 3.82 (3 H, s), 4.10 - 4.20 (2 H, m), 4.26 (2 H, q, *J* = 7.2 Hz), 4.90 (2 H, q, *J* = 9.3 Hz), 6.46 (1 H, s), 7.15 - 7.38 (5 H, m).

Ejemplo de Referencia 165.

Producción de ácido 6-etil-1-metil-4-oxo-5-(2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (143 mg, 83%) se obtuvo como un polvo marrón a partir del compuesto del Ejemplo de Referencia 164 (185 mg, 0.411 mmol).

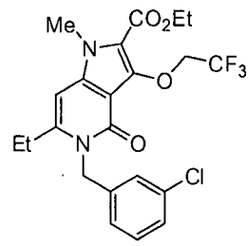
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.21 (3 H, t, *J* = 7.2 Hz),

1011

2.66 (2 H, q, *J* = 7.2 Hz), 2.81 - 2.94 (2 H, m), 3.81 (3 H, s), 4.05 - 4.30 (2 H, m), 4.89 (2 H, q, *J* = 9.3 Hz), 6.44 (1 H, s), 7.09 - 7.38 (5 H, m), 12.67 (1 H, s amplio).

Ejemplo de Referencia 166.

Producción de etil 5-(3-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

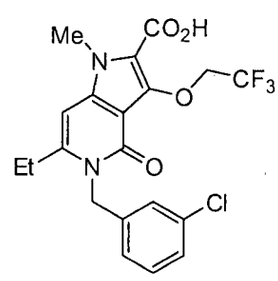


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (325 mg, 60%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y 1-cloro-3-(clorometil)benceno (357 mg, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.1 Hz), 2.60 (2 H, q, *J* = 7.1 Hz), 3.85 (3 H, s), 4.26 (2 H, q, *J* = 7.3 Hz), 4.88 (2 H, q, *J* = 9.3 Hz), 5.33 (2 H, s amplio), 6.56 (1 H, s), 6.96 - 7.05 (1 H, m), 7.10 - 7.18 (1 H, m), 7.27 - 7.33 (2 H, m).

Ejemplo de Referencia 167.

Producción de ácido 5-(3-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



Del mismo modo que en el Ejemplo de Referencia 49, el

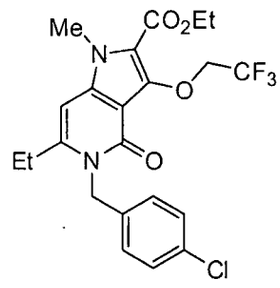
1012

compuesto del título (281 mg, 92%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 166 (325 mg, 0.690 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.2 Hz), 2.60 (2 H, q, *J* = 7.2 Hz), 3.85 (3 H, s), 4.86 (2 H, q, *J* = 9.3 Hz), 5.34 (2 H, s amplio), 6.54 (1 H, s), 6.95 - 7.05 (1 H, m), 7.10 - 7.18 (1 H, m), 7.26 - 7.33 (2 H, m), 12.74 (1 H, s).

Ejemplo de Referencia 168.

Producción de etil 5-(4-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

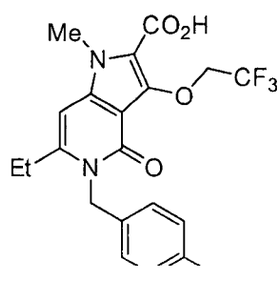


Del mismo modo que en el Ejemplo de Referencia 142, el compuesto del título (213 mg, 39%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 141 (400 mg, 1.16 mmol) y 1-cloro-4-(clorometil)benceno (357 mg, 1.74 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 1.29 (3 H, t, *J* = 7.1 Hz), 2.60 (2 H, q, *J* = 7.1 Hz), 3.85 (3 H, s), 4.26 (2 H, q, *J* = 7.3 Hz), 4.88 (2 H, q, *J* = 9.3 Hz), 5.32 (2 H, s amplio), 6.55 (1 H, s), 7.03 - 7.16 (2 H, m), 7.66 - 7.33 (2 H, m).

Ejemplo de Referencia 169.

Producción de ácido 5-(4-clorobencil)-6-etil-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



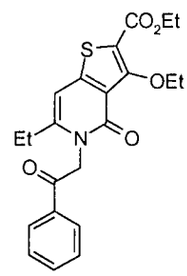
1013

Del mismo modo que en el Ejemplo de Referencia 49, el compuesto del título (188 mg, 94%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 168 (213 mg, 0.452 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 2.59 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 4.86 (2 H, q, *J* = 9.3 Hz), 5.32 (2 H, s amplio), 6.53 (1 H, s), 7.01 - 7.20 (2 H, m), 7.28 - 7.39 (2 H, m), 12.75 (1 H, s amplio).

Ejemplo de Referencia 170.

Producción de etil 3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 5, etil 6-etil-3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato se obtuvo a partir del compuesto del Ejemplo de Referencia 39 (3.6 g, 10.3 mmol), tioglicolato de etilo (14.4 ml, 103 mmol) y trietilamina (2.3 ml, 20.6 mmol). El Compuesto del título (900 mg, 47%) se obtuvo como un sólido blanco a partir del etil 6-etil-3-hidroxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxilato obtenido de este modo (1.8 g, 4.7 mmol) por un método similar al del Ejemplo de Referencia 43.

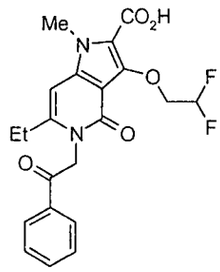
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 1.23 - 1.36 (6 H, m), 2.61 (2 H, q, *J* = 7.3 Hz), 4.14 (2 H, q, *J* =

1014

7.1 Hz), 4.28 (2 H, q, *J* = 7.0 Hz), 5.65 (2 H, s), 6.83 (1 H, s), 7.62 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.79 (1 H, m), 8.12 (2 H, d, *J* = 7.2 Hz).

Ejemplo de Referencia 171.

Producción de ácido 3-(2,2-difluoroetoxi)-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



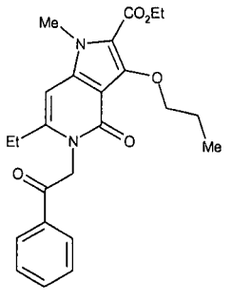
Del mismo modo que en el Ejemplo de Referencia 56, etil 3-(2,2-difluoroetoxi)-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato se obtuvo a partir del compuesto del Ejemplo de Referencia 40 (500 mg, 1.31 mmol), 2,2-difluoroetil trifluorometanosulfonato (336 mg, 1.57 mmol) y carbonato de cesio (554 mg, 1.70 mmol). El Compuesto del título (314 mg, 83%) se obtuvo como un polvo blanco a partir del así obtenido etil 3-(2,2-difluoroetoxi)-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato (400 mg, 0.90 mmol) por aplicación de un método similar al del Ejemplo de Referencia 59.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.2 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.85 (3 H, s), 4.40 (2 H, td, *J* = 14.6, 1.2 Hz), 5.60 (2 H, s), 6.26 (1 H, tt, *J* = 55.0, 3.9 Hz), 6.77 (1H, s), 7.58 - 7.76 (3 H, m), 8.12 (2 H, d, *J* = 7.5 Hz), 12.50 - 12.70 (1H, amplio).

Ejemplo de Referencia 172.

Producción de etil 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.

1015

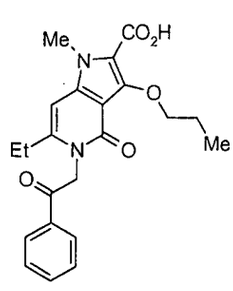


Del mismo modo que en el Ejemplo de Referencia 56, el compuesto del título (177 mg, 83%) se obtuvo como un polvo marrón a partir del compuesto del Ejemplo de Referencia 40 (191 mg, 0.50 mmol), dipropil sulfato (364 mg, 2.0 mmol), carbonato de potasio (414 mg, 3.0 mmol) y acetona (20 ml).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.01 (3 H, t, *J* = 7.5 Hz), 1.28 (3H, t, *J* = 7.3 Hz), 1.40 (3H, t, *J* = 7.5 Hz), 1.75 - 1.89 (2H, m), 2.51 (2 H, q, *J* = 7.2 Hz), 3.88 (3 H, s), 4.21 (2 H, t, *J* = 6.7 Hz), 4.36 (2H, q, *J* = 7.2 Hz), 5.59 (2 H, s), 6.19 (1 H, s), 7.37 - 7.56 (2 H, m), 7.59 - 7.67 (1 H, m), 8.02 - 8.09 (2H, m).

Ejemplo de referencia 173.

Producción de ácido 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



Del mismo modo que en el Ejemplo de Referencia 59, el compuesto del título (237 mg, 93%) se obtuvo como polvo Amarillo pálido a partir del compuesto del Ejemplo de Referencia 172 (274 mg, 0.65 mmol).

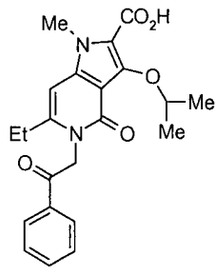
^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.91 (3 H, t, *J* = 7.5 Hz), 1.18 (3H, t, *J* = 7.3 Hz), 1.55 - 1.70 (2H, m), 2.57 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 4.07 (2 H, t, *J* = 6.5 Hz), 5.58 (2 H, s), 6.47 (1 H, s), 7.56 - 7.66 (2 H, m), 7.69 - 7.78 (1 H, m), 8.07 - 8.16 (2H,

1016

m), 12.42 (1 H, s).

Ejemplo de Referencia 174.

Producción de ácido 6-etil-1-metil-3-(1-metiletoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

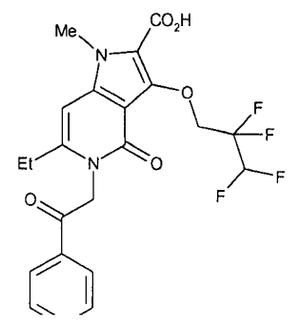


Del mismo modo que en el Ejemplo de Referencia 56, etil 6-etil-1-metil-3-(1-metiletoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato (291 mg, 46%) se obtuvo como un polvo violeta pálido a partir del compuesto del Ejemplo de Referencia 40 (574 mg, 1.50 mmol), carbonato de potasio (1.04 g, 7.5 mmol) y diisopropil sulfato (1.37 g, 7.5 mmol). El Compuesto del título (242 mg, 97%) se obtuvo como polvo sin color a partir del así obtenido etil 6-etil-1-metil-3-(1-metiletoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato (267 mg, 0.63 mmol) por aplicación de un método similar al del Ejemplo de Referencia 59.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.23 (9 H, m), 2.57 (2 H, q, J = 7.5 Hz), 3.84 (3 H, s), 4.65 - 4.80 (1H, m), 5.58 (2 H, s), 6.47 (1 H, s), 7.56 - 7.66 (2 H, m), 7.69 7.78 (1 H, m), 8.07 - 8.16 (2H, m), 12.29 (1 H, s).

Ejemplo de Referencia 175.

Producción de ácido 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,3.3-tetrafluoropropoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.



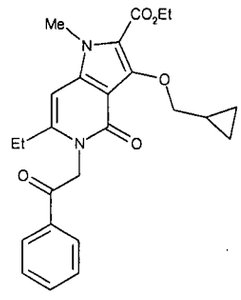
(107

Del mismo modo que en el Ejemplo de Referencia 150, etil 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,3.3-tetrafluoropropoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato (460 mg, 93%) se obtuvo como un polvo gris a partir del compuesto del Ejemplo de Referencia 40 (382 mg, 1.00 mmol), 2,2,3.3-tetrafluoropropil trifluorometansulfonato (913 mg, 3.46 mmol), carbonato de cesio (391 mg, 1.20 mmol) y DMF (10 ml). El compuesto del título (310 mg, 95%) se obtuvo como un polvo gris a partir del así obtenido etil 6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,3.3-tetrafluoropropoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato (348 mg, 0.70 mmol) por aplicación de un método similar al del Ejemplo de Referencia 59.

^{1}H-NMR (300 MHz, DEMO-d_6) δ:1.19 (3 H, t, *J* = 7.3 Hz), 2.58 (2 H, q, *J* = 7.3 Hz), 3.86 (3 H, s), 4.70 (2H, t, *J* = 13.1 Hz), 5.62 (2 H, s), 6.54 (1 H, s), 6.73 (1H, tt, *J* = 52.6, 6.1 Hz), 7.56 - 7.66 (2H, m), 7.69 - 7.79 (1H, m), 8.07 - 8.17 (2H, m), 12.93 (1H, s amplio).

Ejemplo de Referencia 176.

Producción de etil 3-(cyclopropylmethoxi)-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxilato.



Del mismo modo que en el Ejemplo de Referencia 150, el compuesto del título (65 mg, 15%) se obtuvo como un polvo

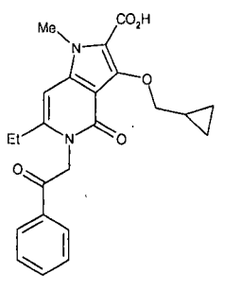
1018

Amarillo a partir del compuesto del Ejemplo de Referencia 40 (382 mg, 1.00 mmol), carbonato de cesio (358 mg, 1,10 mmol), ciclopropilmetil metansulfonato (750 mg, 5.00 mmol) y DMF (10 ml).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.29 - 0.36 (2 H, m), 0.49 - 0.57 (2H, m), 1.24 - 1.37 (1H, m), 1.28 (3H, t, *J* = 7.3 Hz), 1.41 (3H, t, *J* = 7.1 Hz), 2.51 (2 H, q, *J* = 7.3 Hz), 3.88 (3 H, s), 4.10 (2 H, d, *J* = 7.2 Hz), 4.37 (2H, q, *J* = 7.1 Hz), 5.59 (2H, s), 6.19 (1H, s), 7.37 - 7.55 (2H, m), 7.59 - 7.67 (1H, m), 8.02 - 8.10 (2H, m).

Ejemplo de Referencia 177.

Producción de ácido 3-(ciclopropilmetoxi)-6-etil-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxílico.

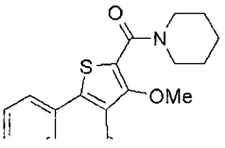


Del mismo modo que en el Ejemplo de Referencia 59, el compuesto del título (112 mg, 83%) se obtuvo como un polvo incoloro a partir del compuesto del Ejemplo de Referencia 176 (144 mg, 0.33 mmol).

^{1}H-NMR (300 MHz, DEMO-d_6) δ: 0.17 - 0.27 (2H, m), 0.39 - 0.48 (2H, m), 1.03 - 1.22 (1H, m), 1.18 (3H, t, *J* = 7.3 Hz), 2.56 (2 H, q, *J* = 7.3 Hz), 3.84 (3 H, s), 3.94 (2H, d, *J* = 7.0 Hz), 5.58 (2 H, s), 6.46 (1H, s), 7.56 - 7.65 (2H, m), 7.69 - 7.77 (1H, m), 8.07 - 8.15 (2H, m), 12.43 (1H, s amplio).

Ejemplo 1.

Producción de 3-metoxi-5-(2-oxo-2-feniletil)-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.



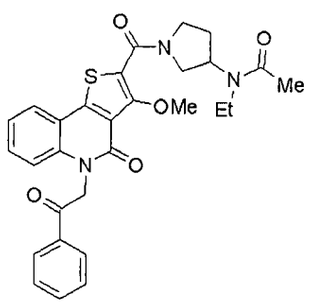
1019

A solución (0.10 M, 0.600 ml, 60 μmol) del compuesto del Ejemplo de Referencia 7 en DMF se diluyó con DMF (0.200 ml), se agregaron y una solución (1.0 M, 0.063 ml, 63 μmol) de piperidina en DMF y una solución (0.50 M, 0.126 ml, 63 μmol) de HOBt y WSCD en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 13 hrs. Se agregaron diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) a la mezcla de reacción, y la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar de la fase acuosa, y concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (8.5 mg, 31%).

LC/EM 461 (M+H).

Ejemplo 2.

Producción de N-etil-N-(1-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}pirrolidin-3-il)acetamida.



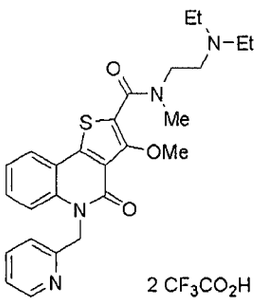
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N-etil-N-pirrolidin-3-ilacetamida.

LC/EM 532 (M+H).

1020

Ejemplo 3.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato.

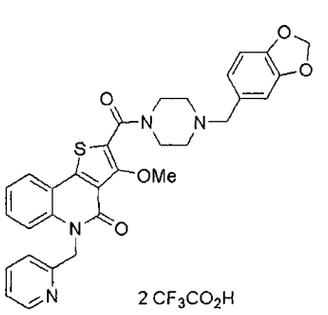


A una solución (0.12 M, 0.40 ml, 48 μmol) del compuesto del Ejemplo de Referencia 19 en DMF se agregaron una solución (0.66 M, 0.10 ml, 63 μmol) de N,N-dietil-N'-metiletan-1,2-diamina en DMF y una solución (0.39 M, 0.20 ml, 78 μmol) de HOBt y WSCD en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) se agregaron a la mezcla de reacción, y la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar de la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (33.2 mg, 98%).

LC/EM 479 (M+H).

Ejemplo 4.

Producción de 2-{[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]carbonil}-3-metoxi-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato.



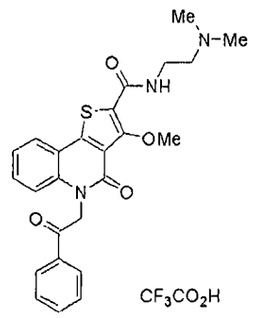
1021

Del mismo modo que en el Ejemplo 3, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-(1,3-benzodioxol-5-ilmetil)piperazina.

LC/EM 569 (M+H).

Ejemplo 5.

Producción de N-[2-(dimetilamino)etil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



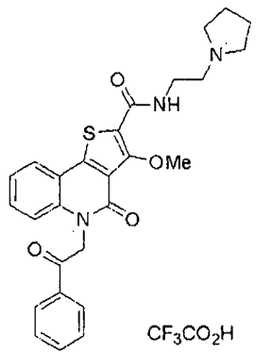
A una solución (0.15 M, 0.40 ml, 60 µmol) del compuesto del Ejemplo de Referencia 7 en DMF se agregaron una solución (0.66 M, 0.10 ml, 63 µmol) de N,N-dimetiletan-1,2-diamina en DMF y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y WSCD en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Se agregaron diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) a la mezcla de reacción, y la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar de la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (25.2 mg, 73%).

LC/EM 464 (M+H).

Ejemplo 6.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

1022

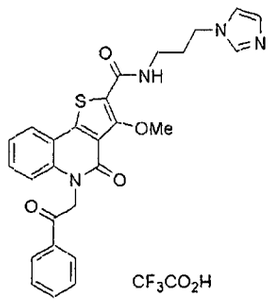


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-pirrolidin-1-iletanamina.

LC/EM 490 (M+H).

Ejemplo 7.

Producción de N-[3-(1H-imidazol-1-il)propil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

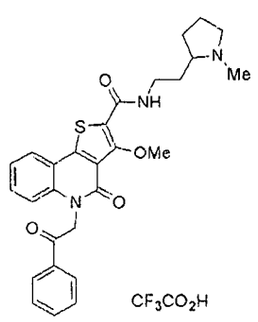


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 501 (M+H).

Ejemplo 8.

Producción de 3-metoxi-N-[2-(1-metilpirrolidin-2-il)etil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



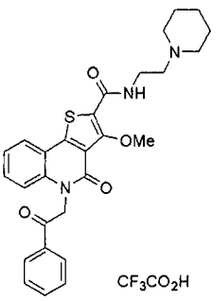
1023

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-(1-metilpirrolidin-2-il)etanamina.

LC/EM 504 (M+H).

Ejemplo 9.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

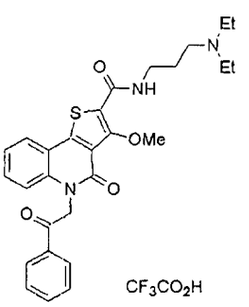


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-piperidin-1-iletanamina.

LC/EM 504 (M+H).

Ejemplo 10.

Producción de N-[3-(dietilamino)propil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



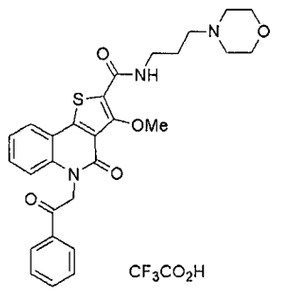
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N,N-dietilpropano-1,3-diamina.

LC/EM 506 (M+H).

1024

Ejemplo 11.

Producción de 3-metoxi-N-(3-morfolin-4-ilpropil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

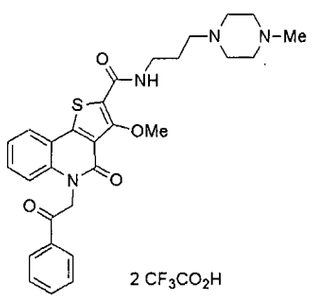


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-morfolin-4-ilpropan-1-amina.

LC/EM 520 (M+H).

Ejemplo 12.

Producción de 3-metoxi-N-[3-(4-metilpiperazin-1-il)propil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato.

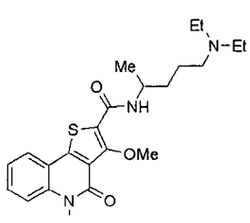


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-(4-metilpiperazin-1-il)propan-1-amina.

LC/EM 533 (M+H).

Ejemplo 13.

Producción de N-[4-(dietilamino)-1-metilbutil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



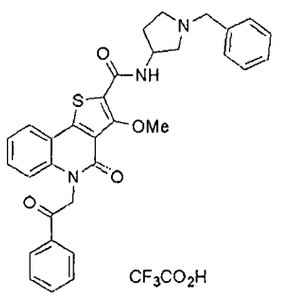
1025

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N1,N1-dietilpentano-1,4-diamina.

LC/EM 534 (M+H).

Ejemplo 14.

Producción de N-(1-bencilpirrolidin-3-il)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

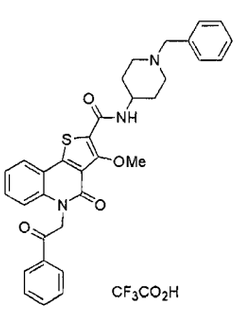


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-bencilpirrolidin-3-amina.

LC/EM 552 (M+H).

Ejemplo 15.

Producción de N-(1-bencilpiperidin-4-il)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



Del mismo modo que en el Ejemplo 5, el compuesto del

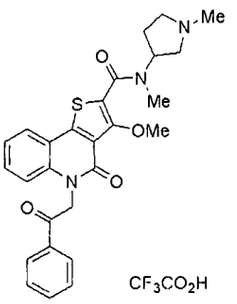
1026

título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-bencilpiperidin-4-amina.

LC/EM 566 (M+H).

Ejemplo 16.

Producción de 3-metoxi-N-metil-N-(1-metilpirrolidin-3-il)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

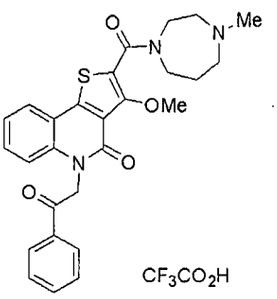


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N,1-dimetilpirrolidin-3-amina.

LC/EM 490 (M+H).

Ejemplo 17.

Producción de 3-metoxi-2-[(4-metil-1,4-diazepan-1-il)carbonil]-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

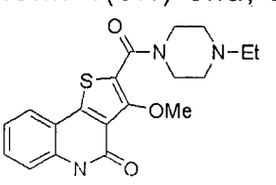


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-metil-1,4-diazepano.

LC/EM 490 (M+H).

Ejemplo 18.

Producción de 2-[(4-etilpiperazin-1-il)carbonil]-3-metoxi-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.



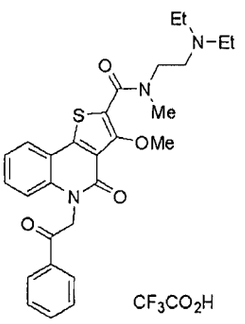
1027

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-etilpiperazina.

LC/EM 490 (M+H).

Ejemplo 19.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

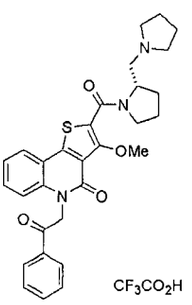


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 506 (M+H).

Ejemplo 20.

Producción de 3-metoxi-5-(2-oxo-2-feniletil)-2-{[(2S)-2-(pirrolidin-1-ilmetil)pirrolidin-1-il]carbonil}tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.



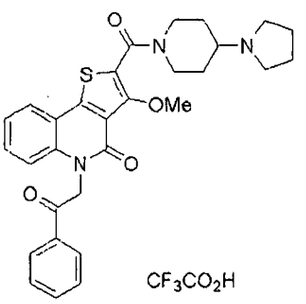
1028

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-[(2S)-pirrolidin-2-ilmetil]pirrolidina.

LC/EM 530 (M+H).

Ejemplo 21.

Producción de 3-metoxi-5-(2-oxo-2-feniletil)-2-[(4-pirrolidin-1-ilpiperidin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

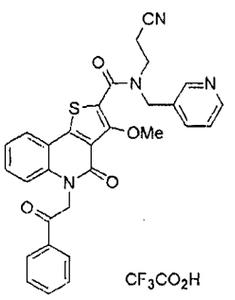


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 4-pirrolidin-1-ilpiperidina.

LC/EM 530 (M+H).

Ejemplo 22.

Producción de N-(2-cianoetil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-3-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-[(piridin-3-ilmetil)amino]propanonitrilo.

LC/EM 537 (M+H).

Ejemplo 23.

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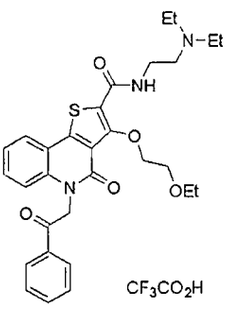
Producción de 2-{[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]carbonil}-3-metoxi-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-(1,3-benzodioxol-5-ilmetil)piperazina.

LC/EM 596 (M+H).

Ejemplo 24.

Producción de N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

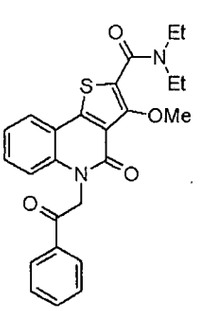


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N,N-dietiletan-1,2-diamina.

LC/EM 550 (M+H).

Ejemplo 25.

Producción de N,N-dietil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



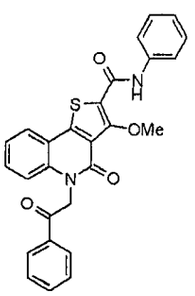
1030

A una solución del compuesto del Ejemplo de Referencia 7 (130 mg, 0.33 mmol), dietilamina (36 mg, 0.49 mmol) y HOBt (67 mg, 0.49 mmol) en DMF (4 ml) se agregó WSCD (94 mg, 0.49 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo), y el aceite obtenido se recristalizó a partir de acetato de etilo-dietil éter para dar el compuesto del título (104 mg, 70%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 (6H, t, *J* = 7.1 Hz), 3.39 - 3.50 (4H, m), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 7.8 Hz), 7.56 (1H, td, *J* = 8.7, 1.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.75 (1H,d, *J* = 7.5 Hz), 7.96 (1H, dd, *J* = 7.8, 1.2 Hz), 8.18 (2H, d, *J* = 7.5 Hz).

Ejemplo 26.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N,N-fenil-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (163 mg, 63%) se obtuvo como cristales naranja pálido a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y anilina (48 µl, 0.51 mmol).

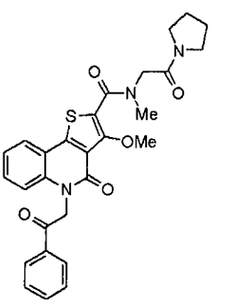
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 4.15 (3H, s), 6.02 (2H, s),

1031

7.12 - 7.21 (1H, m), 7.32 - 7.34 (3H, m), 7.38 - 7.55 (1H, m), 7.56 - 7.70 (3H, m), 7.71 - 7.82 (3H, m), 8.09 (1H, dd, *J* = 7.9, 1.3 Hz), 8.14 - 8.24 (2H, m), 9.74 (1H, s).

Ejemplo 27.

Producción de 3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-oxo-2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Una solución mixta del compuesto del Ejemplo 120 (400 mg, 0.81 mmol) y una solución acuosa 2N de hidróxido de sodio (10 ml) en THF (10 ml)-etanol (5 ml) se agitó a temperatura ambiente durante 2 hrs. La mezcla de reacción se neutralizó con ácido clorhídrico 2N (10 ml), y concentró bajo presión reducida. El residuo se repartió entre salmuera y acetato de etilo, y la fase acuosa se extrajo con acetato de etilo. La fase orgánica se combinó, se secó sobre sulfato de magnesio, y concentró bajo presión reducida para dar N-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}-N-metilglicina (380 mg, 100%) como un sólido blanco.

El compuesto del título (84 mg, 40%) se obtuvo como cristales blancos a partir del así obtenido N-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}-N-metilglicina (190 mg, 0.41 mmol) y pirrolidina (44 mg, 0.61 mmol) por aplicación de un método similar al del Ejemplo 25.

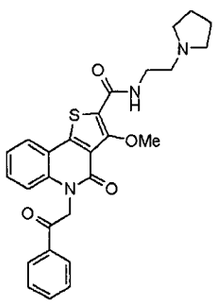
^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.75 - 2.05 (4H, m), 3.20 (1H, s), 3.27 (2H, s), 3.45 - 3.56 (4H, m), 4.01 (1H, s), 4.13 (2H, s), 4.23 (0.6H, s amplio), 4.29 (1,4H, s), 5.86 (2H, s), 7.03 (1H, d, *J*

1032

= 8.4 Hz), 7.23 - 7.28 (1H, m), 7.35 (1H, t, *J* = 8.0 Hz), 7.55 (2H, t, *J* = 7.5 Hz), 7.67 (1H, t, *J* = 7.2 Hz), 7.82 (1H, dd, *J* = 8.1, 1.2 Hz), 8.10 - 8.12 (2H, m).

Ejemplo 28.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

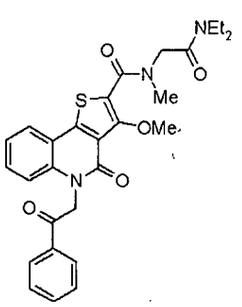


Del mismo modo que en el Ejemplo 25, el compuesto del título (1.54g, 67%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (1.85 g, 4.69 mmol) y 1-(2-aminoetil)pirrolidina (642 mg, 5.63 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.72 (4H, s amplio), 2.45 - 2.60 (4H, amplio), 2.64 (2H, t, *J* = 6.3 Hz), 3.44 (2H, t, *J* = 5.9 Hz), 4.01 (3H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.8 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.55 - 7.67 (3H, m), 7.70 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 8.1, 1.5 Hz), 8.16 - 8.19 (3H, m).

Ejemplo 29.

Producción de N-[2-(dietilamino)-2-oxoetil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (124 mg, 58%) se obtuvo como cristales blancos a partir de

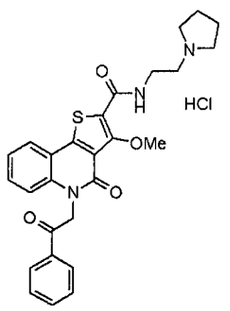
1033

N-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}-N-metilglicina (190 mg, 0.41 mmol) obtenida en el Ejemplo 27 y dietilamina (45 mg, 0.61 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.05 - 1.31 (6H, m), 3.18 (1.2H, s), 3.26 (1.8H, s), 3.34 - 3.47 (4H, m), 4.01 (1.2H, s), 4.10 (1.8H, s), 4.30 (0.8H, s), 4.36 (1.2H, s), 5.85 (2H, s), 7.03 (1H, d, *J* = 8.4 Hz), 7.23 - 7.28 (1H, m), 7.36 (1H, t, *J* = 7.3 Hz), 7.55 (2H, t, *J* = 7.5 Hz), 7.67 (1H, t, *J* = 7.3 Hz), 7.82 (1H, d, *J* = 6.9 Hz), 8.11 (2H, d, *J* = 7.2 Hz).

Ejemplo 30.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo 28 (200 mg, 0.41 mmol) en acetato de etilo (25 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.11 ml). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (162 mg, 75%) como un polvo blanco.

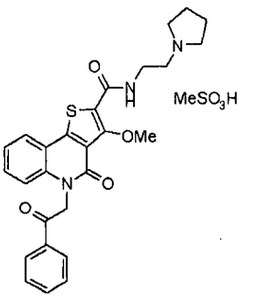
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.77 - 2.10 (4H, m), 2.95 - 3.10 (2H, amplio), 3.29 - 3.40 (2H, m), 3.55 - 3.75 (4H, m), 4.07 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.3 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.3 Hz), 8.06 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.19 (2H, m), 8.31 (1H, t, *J* = 6.0 Hz), 10.33 (1H, s amplio).

Ejemplo 31.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-

1034

1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, metansulfonato.

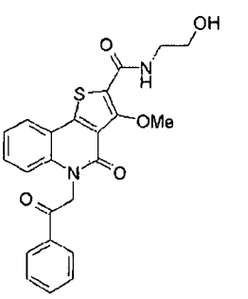


A una solución del compuesto del Ejemplo 28 (200 mg, 0.41 mmol) en acetato de etilo (25 ml) se agregó una solución de ácido metansulfónico (39 mg, 0.41 mmol) en acetato de etilo (5 ml). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (197 mg, 82%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.65 - 2.10 (4H, m), 2.30 (3H, s), 3.00 - 3.20 (2H, amplio), 3.35 - 3.45 (2H, amplio), 3.60 - 3.75 (4H, m), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.2 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.5 Hz), 8.06 (1H, dd, *J* = 7.8, 1,2 Hz), 8.16 - 8.19 (2H, m), 8.29 (1H, t, *J* = 5.9 Hz), 9.30 - 9.45 (1H, amplio).

Ejemplo 32.

Producción de N-(2-hidroxietil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (65.8 mg, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (89.0 mg, 0.226 mmol) y 2-aminoetanol (16.3 µl,

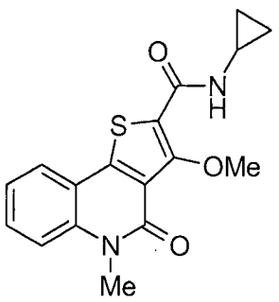
1035

0.271 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.40 - 3.46 (2H, m), 3.54 - 3.59 (2H, m), 4.03 (3H, s), 4.87 (1H, t, *J* = 5.3 Hz), 5.99 (2H, s), 7.32 - 7.38 (1H, m), 7.38 - 7.67 (4H, m), 7.74 - 7.79 (1H, m), 8.00 - 8.06 (2H, m), 8.16 - 8.19 (2H, m).

Ejemplo 33.

Producción de N-ciclopropil-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

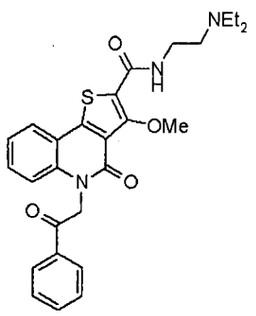


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y ciclopropanamina.

LC/EM 329 (M+H).

Ejemplo 34.

Producción de N-[2-(dietilamino)etil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (500 mg, 80%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (500 mg, 1.27 mmol) y N,N-dietiletilendiamina (220 mg, 1.90 mmol).

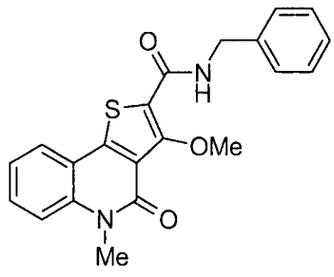
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.00 (6H, t, *J* = 7.1 Hz),

1036

2.50 - 2.62 (6H, m), 3.37 - 3.42 (2H, m), 4.03 (3H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.3 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.55 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 7.8, 1.5 Hz), 8.12 (1H, t, *J* = 5.1 Hz), 8.16 - 8.19 (2H, m).

Ejemplo 35.

Producción de N-bencil-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

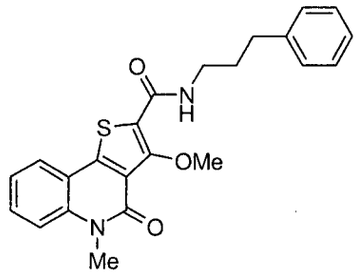


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-fenilmetanamina.

LC/EM 379 (M+H).

Ejemplo 36.

Producción de 3-metoxi-5-metil-4-oxo-N-(3-fenilpropil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



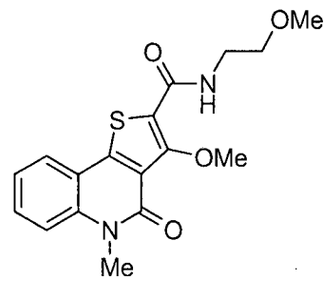
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-fenilpropan-1-amina.

LC/EM 407 (M+H).

Ejemplo 37.

Producción de 3-metoxi-N-(2-metoxietil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

1037

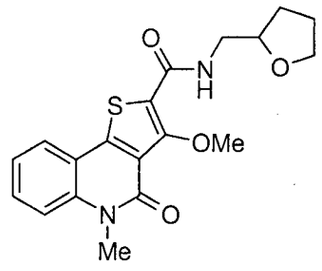


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-metoxietanamina.

LC/EM 347 (M+H).

Ejemplo 38.

Producción de 3-metoxi-5-metil-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

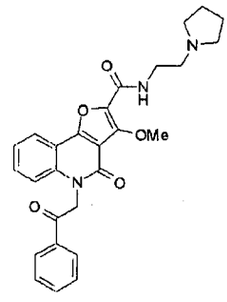


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 373 (M+H).

Ejemplo 39.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrofuro[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (125 mg, 66%) se obtuvo como un polvo blanco a partir del

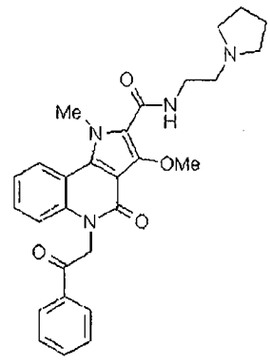
1038

compuesto del Ejemplo de Referencia 24 (150 mg, 0.397 mmol) y 1-(2-aminoetil)pirrolidina (65.4 µl, 0.516 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.69 - 1.73 (4H, m), 2.49 - 2.51 (4H, m), 2.61 (2H, t, *J* = 6.6 Hz), 3.40 - 3.46 (2H, m), 4.15 (3H, s), 6.00 (2H, s), 7.33 (1H, t, *J* = 8.1 Hz), 7.54 (1H, d, *J* = 8.4 Hz), 7.60 - 7.67 (3H, m), 7.74 - 7.79 (1H, m), 8.06 (1H, t, *J* = 8.6 Hz), 8.15 - 8.19 (3H, m).

Ejemplo 40.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

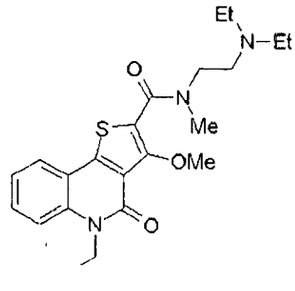


Del mismo modo que en el Ejemplo 25, el compuesto del título (145 mg, 78%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (150 mg, 0.384 mmol) y 1-(2-aminoetil)pirrolidina (63.3 µl, 0.499 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.65 - 1.75 (4H, m), 2.48 - 2.55 (4H, m), 2.62 (2H, t, *J* = 6.2 Hz), 3.39 - 3.45 (2H, m), 3.97 (3H, s), 4.37 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.61 - 7.66 (2H, m), 7.73 - 7.78 (1H, m), 8.16 - 8.18 (3H, m), 8.39 (1H, dd, *J* = 8.1, 1.2 Hz).

Ejemplo 41.

Producción de 5-(ciclopropilmetil)-N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



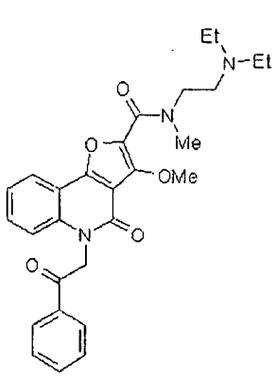
1039

A una solución del compuesto del Ejemplo 121 (400 mg, 1.03 mmol) en DMF (5 ml) se agregó hidruro de sodio (60% en aceite, 45.4 mg, 1.14 mmol) enfrió con hielo, y la mezcla se agitó durante 15 min. Ciclopropilmetilbromuro (120 µl, 1.24 mmol) se agregó a la mezcla resultante enfrió con hielo, y la mezcla se agitó durante 15 hrs. La mezcla de reacción se agregó a agua, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=3/7) para dar el compuesto del título (320 mg, 70%) como un aceite incoloro.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.45 - 0.50 (4H, m), 0.70 - 1.05 (6H, amplio), 1.23 - 1.31 (1H, m), 2.25 - 2.70 (6H, amplio), 3.06 (3H, s), 3.40 - 3.60 (2H, amplio), 3.89 (3H, s), 4.27 (2H, d, *J* = 6.9 Hz), 7.30 - 7.35 (1H, m), 7.62 - 7.68 (1H, m), 7.76 (1H, d, *J* = 8.4 Hz), 7.91 (1H, dd, *J* = 7.8, 1.2 Hz).

Ejemplo 42.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrofuro[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (130 mg, 80%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo de Referencia 24 (130 mg, 0.344

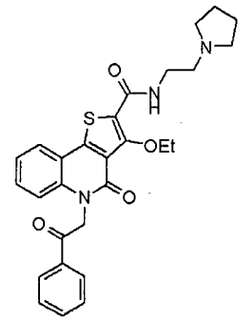
1090

mmol) y N,N-dietil-N'-metiletilendiamina (72.3 µl, 0.477 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.75 - 0.90 (3H, amplio), 0.90 - 1.05 (3H, amplio), 2.25 - 2.40 (2H, amplio), 2.45 - 2.70 (4H, amplio), 2.95 - 3.30 (3H, amplio), 3.52 (2H, t, *J* = 6.5 Hz), 4.04 (3H, s), 5.99 (2H, s), 7.37 - 7.32 (1H, m), 7.52 (1H, d, *J* = 8.7 Hz), 7.57 - 7.67 (3H, m), 7.74 - 7.79 (1H, m), 8.04 (1H, d, *J* = 7.5 Hz), 8.16 - 8.19 (2H, m).

Ejemplo 43.

Producción de 3-etoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

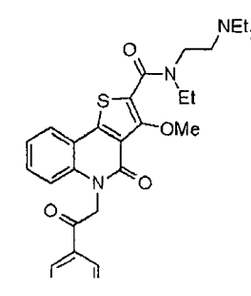


Del mismo modo que en el Ejemplo 25, el compuesto del título (126 mg, 67%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 9 (150 mg, 0.37 mmol) y 1-(2-aminoetil)pirrolidina (63 mg,0.55 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.39 (3H, t, *J* = 7.0 Hz), 1.72 (4H, s amplio), 2.40 - 2.60 (4H, amplio), 2.63 (2H, t, *J* = 6.0Hz), 3.40 - 3.47 (2H, m), 4.31 (2H, q, *J* = 7.0 Hz), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.8 Hz), 7.38 (1H, d, *J* = 8.4 Hz), 7.56 (1H, dd, *J* = 7.2, 1.5 Hz), 7.64 (2H, t, *J* = 8.4 Hz), 7.77 (1H, t, *J* = 7.2 Hz), 8.05 (1H, dd, *J* = 8.1, 1.5 Hz), 8.10 (1H, amplio t), 8.16 - 8.19 (2H, m).

Ejemplo 44.

Producción de N-[2-(dietilamino)etil]-N-etil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



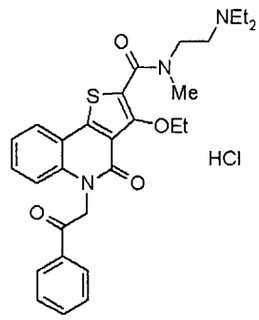
1041

Del mismo modo que en el Ejemplo 25, el compuesto del título (150 mg, 56%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y N,N,N'-trietiletilendiamina (110 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.10 (6H, amplio), 1.14 (3H, amplio t), 2.20 - 2.70 (6H, amplio), 3.40 - 3.60 (4H, amplio), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, *J* = 7.5 Hz), 7.37 (1H, d, *J* = 8.1 Hz), 7.55 (1H, td, *J* = 7.8, 1.5 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 7.95 (1H, dd, *J* = 7.8, 1.5 Hz), 8.16 - 8.19 (2H, m).

Ejemplo 45.

Producción de N-[2-(dietilamino)etil]-3-etoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo de Referencia 9 (150 mg, 0.37 mmol), N,N-dietil-N'-metiletilendiamina (72 mg, 0.55 mmol) y HOBt (74 mg, 0.55 mmol) en DMF (5 ml) se agregó WSCD (105 mg, 0.55 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía

1042

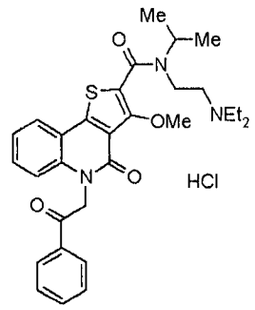
con gel de sílice (eluato; acetato de etilo/hexano=1/1) para dar un sólido no cristalino blanco (180 mg).

A una solución del sólido no cristalino blanco (180 mg) en acetato de etilo (5 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.1 ml). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (173 mg, 83%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.35 (9H, m), 3.12 - 3.40 (9H, amplio), 3.84 (2H, t, *J* = 7.2 Hz), 4.14 (2H, q, *J* = 7.0 Hz), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.55 - 7.67 (3H, m), 7.75 - 7.80 (1H, m), 7.98 (1H, dd, *J* = 8.1, 1.5 Hz), 8.16 - 8.19 (2H, m), 9.85 - 10,10 (1H, amplio).

Ejemplo 46.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-(1-metiletil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



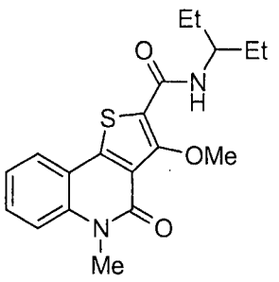
Del mismo modo que en el Ejemplo 45, el compuesto del título (164 mg, 56%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y N,N-dietil-N'-isopropiletilendiamina (120 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.35 (12H, m), 3.15 - 3.40 (6H, amplio), 3.65 - 3.80 (2H, m), 3.89 (3H, s), 4.10 - 4.30 (1H, amplio), 5.99 (2H, s), 7.33 (1H, t, *J* = 7.5 Hz), 7.39 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.97 (1H, dd, *J* = 7.2, 1,2 Hz), 8.16 - 8.19 (2H, m), 9.95 - 10.10 (1H, amplio).

1043

Ejemplo 47.

Producción de N-(1-etilpropil)-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

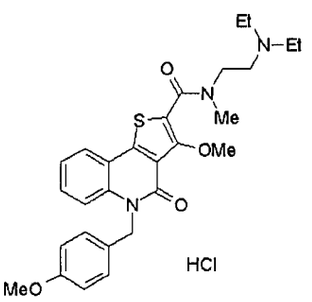


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y pentan-3-amina.

LC/EM 359 (M+H).

Ejemplo 48.

Producción de N-[2-(dietilamino)etil]-3-metoxi-5-(4-metoxibencil)-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 25, N-[2-(dietilamino)etil]-3-metoxi-5-(4-metoxibencil)-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (4.90 g, 85%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo de Referencia 13 (4.50 g, 11.4 mmol) y N,N-dietil-N'-metiletilendiamina (2.40 ml, 14.8 mmol).

El compuesto del título (490 mg, 91%) se obtuvo como un polvo blanco a partir del así obtenido N-[2-(dietilamino)etil]-3-metoxi-5-(4-metoxibencil)-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (500 mg, 0.985 mmol) por aplicación de

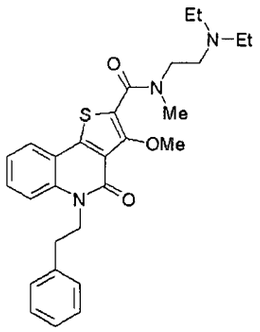
1044

un método similar al del Ejemplo 30.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.35 (6H, amplio), 3.13 (3H, s), 3.10 - 3.40 (6H, amplio), 3.70 (3H, s), 3.87 (2H, t, *J* = 6.6 Hz), 3.96 (3H, s), 5.52 (2H, s), 6.87 (2H, d, *J* = 8.6 Hz), 7.20 (2H, d, *J* = 8.6 Hz), 7.30 (1H, t, *J* = 7.2 Hz), 7.39 - 7.58 (2H, m), 7.92 (1H, d, *J* = 7.8 Hz), 10.55 (1H, s).

Ejemplo 49.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

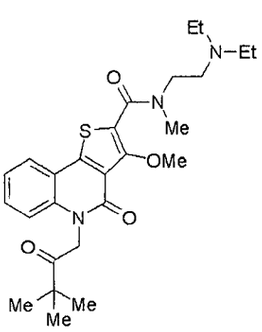


Del mismo modo que en el Ejemplo 41, el compuesto del título (45.1 mg, 28%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 121 (125 mg, 0.323 mmol) y (2-bromoetil)benceno (53.5 µl, 0.387 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.75 - 1.05 (6H, amplio), 2.25 - 2.70 (6H, amplio), 2.92 - 2.97 (2H, m), 3.05 (3H, s), 3.40 - 3.55 (2H, amplio), 3.88 (3H, s), 4.50 (2H, t, *J* = 6.5 Hz), 7.20 - 7.26 (1H, m), 7.30 - 7.36 (5H, m), 7.63 - 7.75 (2H, m), 7.92 (1H, dd, *J* = 7.8, 1.5 Hz).

Ejemplo 50.

Producción de N-[2-(dietilamino)etil]- 5-(3.3-dimetil-2-oxobutil)-3-metoxi-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

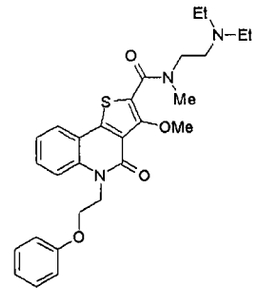


Del mismo modo que en el Ejemplo 41, el compuesto del título (45.1 mg, 28%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 121 (125 mg, 0.323 mmol) y 1-bromo-3.3-dimetilbutan-2-ona (57.9 µl, 0.441 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.10 (6H, amplio), 1.30 (9H, s), 2.20 - 2.40 (6H, amplio), 3.06 (3H, s), 3.40 - 3.60 (2H, amplio), 3.87 (3H, s), 5.47 (2H, s), 7.28 - 7.34 (2H, m), 7.55 - 7.61 (1H, m), 7.92 (1H, dd, *J* = 7.8, 1.2 Hz).

Ejemplo 51.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(2-fenoxietil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

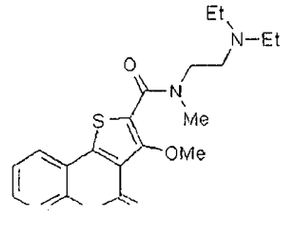


Del mismo modo que en el Ejemplo 41, el compuesto del título (75.1 mg, 43%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 121 (135 mg, 0.348 mmol) y (2-bromoetoxi)benceno (105 mg, 0.522 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.10 (6H, amplio), 2.20 - 2.70 (6H, amplio), 3.05 (3H, s), 3.40 - 3,60 (2H, amplio), 3.91 (3H, s), 4.30 (2H, t, *J* = 5.9 Hz), 4.73 (2H, t, *J* = 5.9 Hz), 6.88 - 6.93 (3H, m), 7.22 - 7.36 (3H, m), 7.65 (1H, t, *J* = 8.0 Hz), 7.83 (1H, d, *J* = 8.7 Hz), 7.91 (1H, d, *J* = 7.8 Hz).

Ejemplo 52.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-[2-oxo-2-(fenilamino)etil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



1046

A una solución del compuesto del Ejemplo 122 (150 mg, 0.336 mmol), anilina (39.8 mg, 0.437 mmol) y HOBt (68.2 mg, 0.505 mmol) en DMF (3 ml) se agregó WSCD (96.8 mg, 0.505 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=1/1) para dar N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-[2-oxo-2-(fenilamino)etil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida como un aceite incoloro.

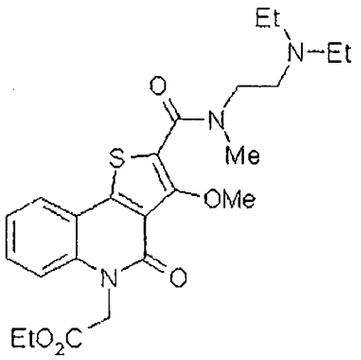
El compuesto del título (65.2 mg, 35%) se obtuvo como un polvo blanco a partir del así obtenido N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-[2-oxo-2-(fenilamino)etil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida por aplicación de un método similar al del Ejemplo 30.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.35 (6H, amplio), 3.12 (3H, s), 3.15 - 3.40 (6H, amplio), 3.75 - 3.90 (2H, amplio), 3.92 (3H, s), 5.22 (2H, s), 7.07 (1H, t, *J* = 7.5 Hz), 7.29 - 7.38 (3H, m), 7.53 - 7.66 (4H, m), 7.96 (1H, dd, *J* = 7.5, 1.4 Hz), 9.76 (1H, s), 10.51 (1H, s).

Ejemplo 53.

Producción de etil [2-{[2-(dietilamino)etil](metil)carbamoil}-3-metoxi-4-oxotieno[3,2-c]quinolin-5(4H)-il]acetato.

(1047)

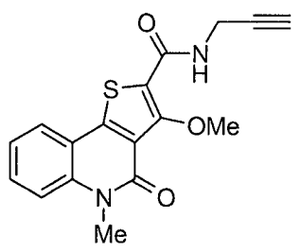


Del mismo modo que en el Ejemplo 41, el compuesto del título (680 mg, 83%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 121 (670 mg, 1.73 mmol) y etil bromoacetato (229 µl, 2.08 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.10 (6H, amplio), 1.23 (3H, t, *J* = 7.1 Hz), 2.25 - 2.70 (6H, m), 3.06 (3H, s), 3.40 - 3.60 (2H, amplio), 3.89 (3H, s), 4.18 (2H, q, *J* = 7.1 Hz), 5.16 (2H, s), 7.34 (1H, t, *J* = 7.7 Hz), 7.51 (1H, d, *J* = 8.1 Hz), 7.61 (1H, t, *J* = 8.1 Hz), 7.94 (1H, d, *J* = 7.7 Hz).

Ejemplo 54.

Producción de 3-metoxi-5-metil-4-oxo-N-prop-2-in-1-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

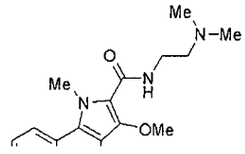


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y prop-2-in-1-amina.

LC/EM 327 (M+H).

Ejemplo 55.

Producción de N-[2-(dimetilamino)etil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



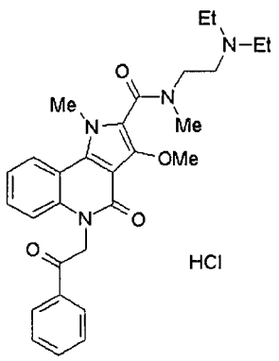
1048

Del mismo modo que en el Ejemplo 25, el compuesto del título (65.0 mg, 61%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (90.0 mg, 0.231 mmol) y N,N-dimetiletilendiamina (25.2 µl, 0.300 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.22 (6H, s), 2.44 (2H, t, *J* = 6.2 Hz), 3.37 - 3.43 (2H, m), 3.98 (3H, s), 4.38 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1H, m), 8.11 - 8.19 (3H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 56.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N,1-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 25, N-[2-(dietilamino)etil]-3-metoxi-N,1-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo de Referencia 28 (90.0 mg, 0.231 mmol) y N,N-dietil-N'-metiletilendiamina (48.6 µl, 0.300 mmol).

El compuesto del título (75.1 mg, 60%) se obtuvo como un

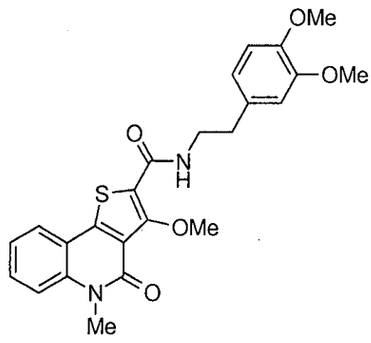
1049

polvo blanco a partir del así obtenido N-[2-(dietilamino)etil]-3-metoxi-N,1-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida por aplicación de un método similar al del Ejemplo 30.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.31 (6H, amplio), 2.95 - 3.40 (9H, amplio), 3.80 - 3.95 (5H, m), 4.03 (3H, s), 5.98 (2H, s), 7.29 - 7.50 (3H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.16 - 8.19 (2H, m), 8.34 (1H, dd, *J* = 8.3, 1.1 Hz), 9.80 - 10.15 (1H, amplio).

Ejemplo 57.

Producción de N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

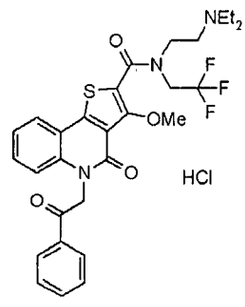


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-(3.4-dimetoxifenil)etanamina.

LC/EM 453 (M+H).

Ejemplo 58.

Producción de N-[2-(dietilamino)etil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2,2,2-trifluoroetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



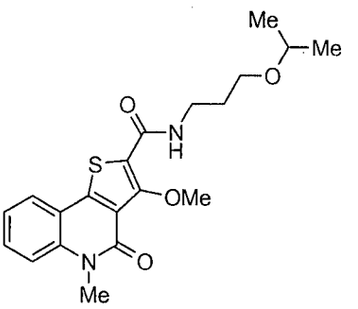
1050

Del mismo modo que en el Ejemplo 45, el compuesto del título (12 mg, 7%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (116 mg, 0.29 mmol) y N,N-dietil-N'-(2,2,2-trifluoroetil)etilendiamina (70 mg, 0.35 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 0.80 - 1.10 (6H, amplio), 2.30 - 2.70 (6H, amplio), 3.75 (2H, t, *J* = 5.6 Hz), 4.02 (3H, s), 4.44 (2H, amplio d, *J* = 7.8 Hz), 5.86 (2H, s), 7.04 (1H, d, *J* = 8.4 Hz), 7.26 (1H, t, *J* = 7.8 Hz), 7.37 (1H, td, *J* = 8.7, 1.5 Hz), 7.56 (2H, t, *J* = 7.5 Hz), 7.65 - 7.70 (1H, m), 7.83 (1H, dd, *J* = 7.8, 1.5 Hz), 8.11 (2H, d, *J* = 7.2 Hz).

Ejemplo 59.

Producción de 3-metoxi-5-metil-N-[3-(1-metiletoxi)propil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

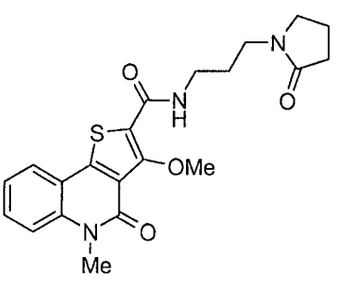


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-(1-metiletoxi)propan-1-amina.

LC/EM 389 (M+H).

Ejemplo 60.

Producción de 3-metoxi-5-metil-4-oxo-N-[3-(2-oxopirrolidin-1-il)propil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



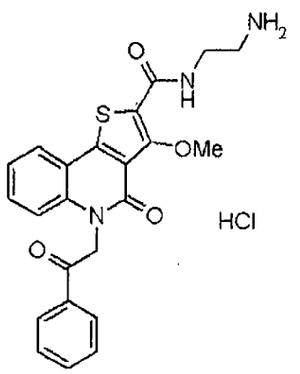
Del mismo modo que en el Ejemplo 1, el compuesto del

título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-(3-aminopropil)pirrolidin-2-ona.

LC/EM 414 (M+H).

Ejemplo 61.

Producción de N-(2-aminoetil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

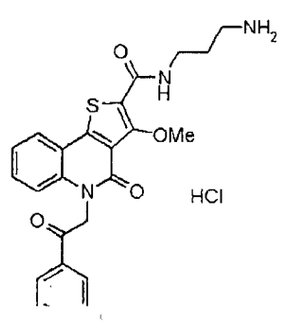


A solución del compuesto del Ejemplo 64 (90 mg, 0.17 mmol) y solución 4N de hidrógeno cloruro de acetato de etilo (10 ml) en acetato de etilo (20 ml) se agitó a temperatura ambiente durante 5 hrs. El precipitado se recolectó por filtración, se lavó con acetato de etilo y dietil éter, y secó bajo presión reducida para dar el compuesto del título (78 mg, 97%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.02 (2H, t, *J* = 6.0 Hz), 3.62 (2H, q, *J* = 6.0 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.3 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 7.57 - 7.59 (3H, m), 7.65 (1H, t, *J* = 7.5 Hz), 7.94 (3H, s amplio), 8.06 (1H, dd, *J* = 8.1, 1.5 Hz), 8.16 - 8.23 (3H, m).

Ejemplo 62.

Producción de N-(3-aminopropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



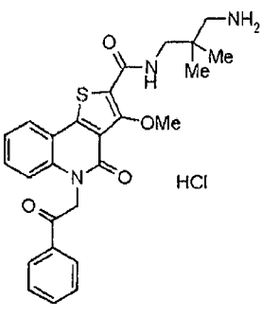
1052

Del mismo modo que en el Ejemplo 61, el compuesto del título (121 mg, 100%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 65 (130 mg, 0.24 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.80 - 1.90 (2H, m), 2.85 (2H, t, *J* = 7.3 Hz), 3.33 - 3.49 (2H, m), 4.04 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.3 Hz), 7.50 (1H, d, *J* = 8.1 Hz), 7.56 - 7.67 (3H, m), 7.75 - 7.80 (4H, m), 8.05 (1H, dd, *J* = 7.8, 1,2 Hz), 8.16 - 8.23 (3H, m).

Ejemplo 63.

Producción de N-(3-amino-2,2-dimetilpropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida clorhidrato.



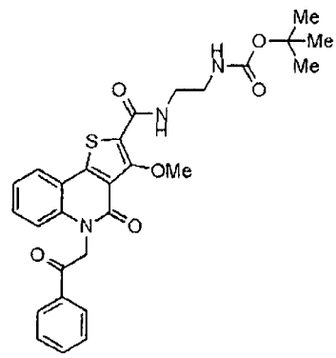
1053

Del mismo modo que en el Ejemplo 61, el compuesto del título (123 mg, 92%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 66 (150 mg, 0.26 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.01 (6H, s), 2.69 (2H, q, *J* = 6.0 Hz), 3.32 (2H, d, *J* = 6.6 Hz), 4.08 (3H, s), 6.01 (2H, s), 7.34 (1H, t, *J* = 7.8 Hz), 7.51 (1H, d, *J* = 8.1 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.2 Hz), 7.90 (3H, s amplio), 8.06 (1H, dd, *J* = 8.1, 1.5 Hz), 8.17 - 8.19 (3H, m).

Ejemplo 64.

Producción de *terc*-butil [2-({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)etil]carbamato.

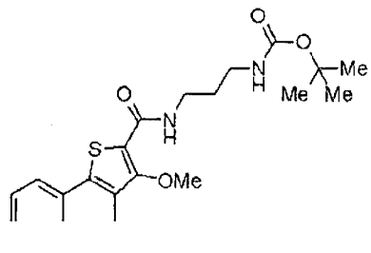


Del mismo modo que en el Ejemplo 25, el compuesto del título (136 mg, 50%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y ter-butil N-(2-aminoetil)carbamato (122 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.37 (9H, s), 3.10 - 3.20 (2H, m), 3.37 - 3.41 (2H, m), 4.04 (3H, s), 6.00 (2H, s), 6.99 (1H, amplio t), 7.35 (1H, t, *J* = 7.3 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.55-7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.04 - 8.07 (2H, m), 8.16 - 8.19 (2H, m).

Ejemplo 65.

Producción de *terc*-butil [3-({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)propil]carbamato.



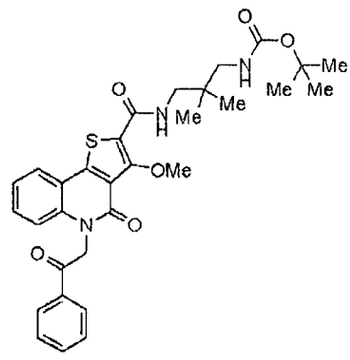
1054

Del mismo modo que en el Ejemplo 25, el compuesto del título (136 mg, 50%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y *terc*-butil N-(3-aminopropil)carbamato (133 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 (9H, s), 1.60 - 1.70 (2H, m), 2.90 - 3.00 (2H, m), 3.25 - 3.35 (2H, m), 4.05 (3H, s), 6.00 (2H, s), 6.91 (1H, amplio t), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.55 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.2 Hz), 8.05 (1H, dd, *J* = 7.8, 1,2 Hz), 8.17 - 8.19 (3H, m).

Ejemplo 66.

Producción de *terc*-butil [3-({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)-2,2-dimetilpropil]carbamato.



Del mismo modo que en el Ejemplo 25, el compuesto del título (205 mg, 69%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y 1-boc-amino-2,2-dimetil-1,3-propanodiamina (154 mg, 0.76 mmol).

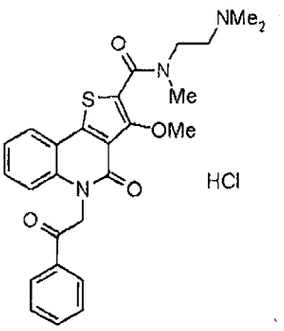
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.42 (9H, s), 2.81 (2H, d, *J*

1055

= 6.3 Hz), 3.13 (2H, d, *J* = 6.3 Hz), 4.09 (3H, s), 6.00 (2H, s), 7.11 (1H, amplio t), 7.35 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 8.1, 1.5 Hz), 8.16 - 8.19 (2H, m), 8.37 (1H, amplio t).

Ejemplo 67.

Producción de N-[2-dimetilaminoetil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol), N,N,N'-trimetiletilendiamina (78 mg, 0.76 mmol) y HOBt (103 mg, 0.76 mmol) en DMF (5 ml) se agregó WSCD (145 mg, 0.76 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 24 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, lavó con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=2/1) para dar N-[2-dimetilaminoetil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (180 mg) como una sustancia amorfa sin color.

A una solución de la N-[2-(dimetilaminoetil)]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (180 mg, 0.38 mmol) en acetato de etilo (10 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.1 ml), y el precipitado obtenido se recolectó por

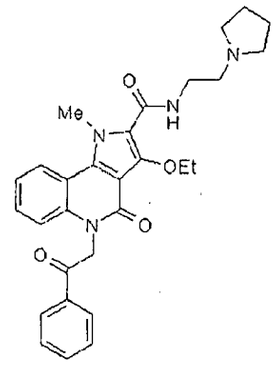
1036

filtración, se lavó con dietil éter, y secó bajo presión reducida para dar el compuesto del título (144 mg, 55%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 (6H, t, *J* = 7.1 Hz), 3.10 (3H, s), 3.39 - 3.50 (4H, m), 3.87 (3H, s), 5.98 (2H, s), 7.33 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 7.8 Hz), 7.56 (1H, td, *J* = 8.7, 1.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.75 (1H,d, *J* = 7.5 Hz), 7.96 (1H, dd, *J* = 7.8, 1.2 Hz), 8.18 (2H, d, *J* = 7.5 Hz).

Ejemplo 68.

Producción de 3-etoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (44.0 mg, 18%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 30 (200 mg, 0.495 mmol) y 1-(2-aminoetil)pirrolidina (82.1 µl, 0.644 mmol).

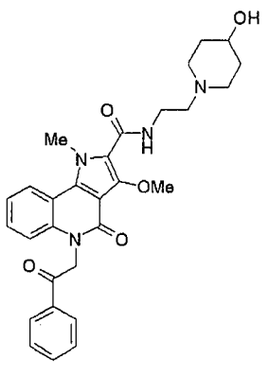
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 (3H, t, *J* = 7.0 Hz), 1.65 - 1.75 (4H, amplio), 2.40 - 2.55 (4H, amplio), 2.62 (2H, t, *J* = 6.0 Hz), 3.05 - 3.47 (2H, m), 4.29 (2H, q, *J* = 7.0 Hz), 4.39 (3H, s), 5.96 (2H, s), 7.29 - 7.39 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.63 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.12 - 8.19 (3H, m), 8.38 (1H, d, *J* = 8.4 Hz).

Ejemplo 69.

Producción de N-[2-(4-hidroxipiperidin-1-il)etil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-

1057

carboxamida.

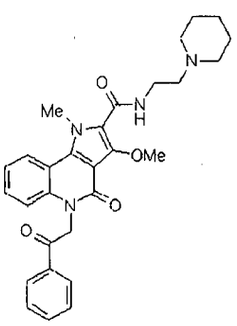


Del mismo modo que en el Ejemplo 25, el compuesto del título (210 mg, 79%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 4-(2-aminoetil)ciclohexanol (96.0 mg, 0.606 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.50 (2H, amplio), 1.70 - 1.80 (2H, amplio), 2.00 - 2.15 (2H, amplio), 2.45 - 2.55 (2H, amplio), 2.70 - 2.85 (2H, amplio), 3.35 - 3.50 (3H, m), 4.01 (3H, s), 4.38 (3H, s), 4.56 (1H, d, *J* = 4.5 Hz), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.64 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.2 Hz), 8.12 - 8.19 (3H, m), 8.38 (1H, d, *J* = 8.4 Hz).

Ejemplo 70.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piperidin-1-iletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



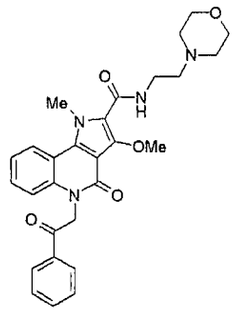
1058

Del mismo modo que en el Ejemplo 25, el compuesto del título (230 mg, 90%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-(2-aminoetil)piperidina (94.9 µl, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.30 - 1.65 (6H, amplio), 2.30 - 2.60 (6H, amplio), 3.40 - 3.45 (2H, m), 4.01 (3H, s), 4.38 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.78 (1H, m), 8.11 - 8.19 (3H, m), 8.38 (1H, dd, *J* = 8.4, 1,2 Hz).

Ejemplo 71.

Producción de 3-metoxi-1-metil-N-(2-morfolin-4-iletil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

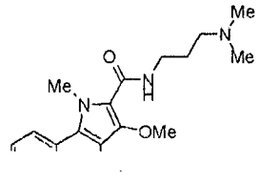


Del mismo modo que en el Ejemplo 25, el compuesto del título (210 mg, 82%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-(2-aminoetil)morfolina (87.3 µl, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.40 - 2.55 (6H, amplio), 3.40 – 3.50 (2H, amplio), 3.61 (4H, t, *J* = 4.2 Hz), 4.01 (3H, s), 4.37 (3H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.38 (1H, t, *J* = 7.7 Hz), 7.64 (2H, t, *J* = 7.3 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.12 - 8.19 (3H, m), 8.38 (1H, d, *J* = 8.4 Hz).

Ejemplo 72.

Producción de N-[3-(dimetilamino)propil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



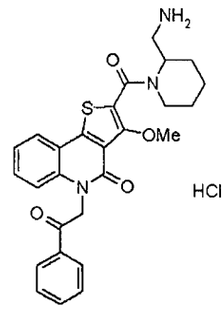
1059

Del mismo modo que en el Ejemplo 25, el compuesto del título (163 mg, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y N,N-dimetilpropano-1,3-diamina (80.0 µl, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.75 - 1.84 (2H, m), 2.43 (6H, s), 2.65 (2H, t, *J* = 7.2 Hz), 3.34 - 3.41 (2H, m), 4.00 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.74 - 7.78 (1H, m), 8.11 - 8.19 (3H, m), 8.37 (1H, dd, *J* = 8.4, 1,2 Hz).

Ejemplo 73.

Producción de 2-{[2-(aminometil)piperidin-1-il]carbonil}-3-metoxi-5-(2-oxo-2-feniletil)tieno [3,2-c]quinolin-4(5H)-ona, clorhidrato.



A una solución del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol), 2-(boc-aminometil)piperidina (122 mg, 0.58 mmol) y HOBt (77 mg, 0.58 mmol) en DMF (5 ml) se agregó WSCD (109 mg, 0.58 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó

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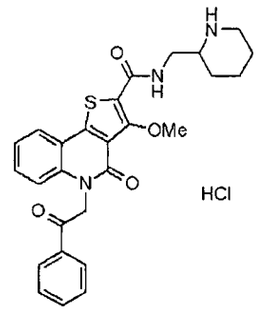
con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=1/1 a 2/1) para dar *terc*-butil [(1-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}piperidin-2-il)metil]carbamato (150 mg) como un aceite incoloro.

A solución del *terc*-butil [(1-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}piperidin-2-il)metil]carbamato obtenido (150 mg) y solución 4N de hidrógeno cloruro de acetato de etilo (8 ml) en acetato de etilo (15 ml) se agitó a temperatura ambiente durante 18 hrs. El precipitado obtenido se recolectó por filtración, se lavó con dietil éter, y secó bajo presión reducida para dar el compuesto del título (133 mg, 67%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.90 (6H, m), 3.00 - 3.15 (2H, m), 3.20 - 3.30 (1H, m), 3.60 - 3.80 (1H, m), 3.90 (3H, s), 4.75 - 4.90 (1H, amplio), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.3 Hz), 7.38 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.3 Hz), 7.85 - 8.00 (4H, m), 8.16 - 8.19 (2H, m).

Ejemplo 74.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(piperidin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



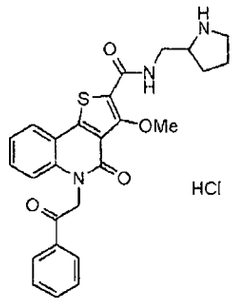
Del mismo modo que en el Ejemplo 73, el compuesto del título (95 mg, 53%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 2-aminometil-N-boc-piperidina (122 mg, 0.57 mmol).

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^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.44 - 1.91 (6H, m), 2.85 (1H, q, *J* = 12.0 Hz), 3.26 (2H, d, *J* = 12.0 Hz), 3.47 - 3.55 (1H, m), 3.62 - 3.69 (1H, m), 4.06 (3H, s), 6.01 (2H, s), 7.36 (1H, t, *J* = 7.5 Hz), 7.51 (1H, d, *J* = 8.1 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.3 Hz), 8.07 (1H, dd, *J* = 7.8, 1.2 Hz), 8.18 (2H, d, *J* = 8.4 Hz), 8.27 (1H, t, *J* = 6.2 Hz), 8.50 - 8.70 (1H, m), 8.70 - 8.85 (1H, m).

Ejemplo 75.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(pirrolidin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

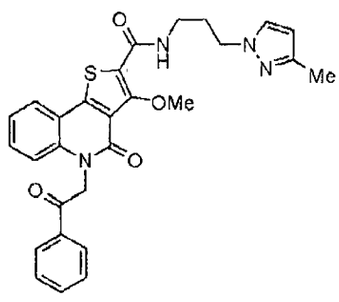


Del mismo modo que en el Ejemplo 73, el compuesto del título (126 mg, 65%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 2-aminometil-N-boc-pirrolidina (122 mg, 0.57 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.63 - 1.75 (1H, m), 1.83 - 2.10 (3H, m), 3.11 - 3.27 (2H, m), 3.61 - 3.76 (3H, m), 4.08 (3H, s), 6.01 (2H, s), 7.36 (1H, t, *J* = 7.5 Hz), 7.51 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.5 Hz), 8.07 (1H, dd, *J* = 7.8, 1,2 Hz), 8.16 - 8.19 (2H, m), 8.40 (1H, t, *J* = 5.9 Hz), 8.80 - 9.20 (2H, amplio).

Ejemplo 76.

Producción de 3-metoxi-N-[3-(3-metil-1H-pirazol-1-il)propil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



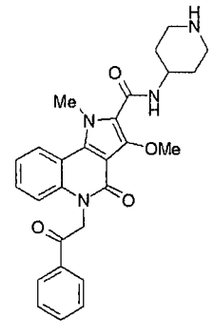
1062

Del mismo modo que en el Ejemplo 25, el compuesto del título (113 mg, 58%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y (3-metilpirazol-1-il)propanamina (79 mg, 0.57 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 2.02 (2H, t, *J* = 6.9 Hz), 2,15 (3H, s), 3.26 - 3.35 (2H, m), 4.04 (3H, s), 4.09 (2H, t, *J* = 6.9 Hz), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.55 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 8.1, 1.2 Hz), 8.03 - 8.19 (4H, m).

Ejemplo 77.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, *terc*-butil 4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato (615 mg) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (404 mg, 1.00 mmol) y 4-amino-1-boc-piperidina (260 mg, 1.33 mmol).

El así obtenido *terc*-butilo 4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato (610 mg) y ácido trifluoroacético (5 ml) se agitaron a temperatura ambiente durante 2 hrs. La mezcla de reacción se concentró bajo presión reducida, solución de hidrógeno carbonato de sodio se agregó, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera,

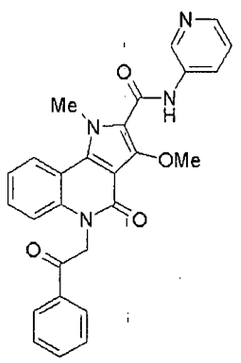
1063

se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=20/1), y el sólido obtenido se recristalizó a partir de acetato de etilo-etanol para dar el compuesto del título (430 mg, 85%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.34 - 1.46 (2H, m), 1.78 - 1.84 (2H, m), 1.90 - 2.20 (1H, amplio), 2.50 - 2.60 (2H, m), 2.85 - 3.00 (2H, amplio), 3.80 - 3.95 (1H, m), 3.98 (3H, s), 4.32 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 7.86 (1H, d, *J* = 7.8 Hz), 8.16 - 8.18 (2H, m), 8.37 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 78.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-piridin-3-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



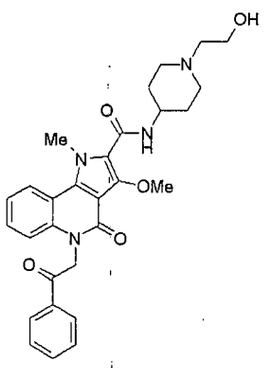
Una mezcla del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol), 3-aminopiridina (60.6 mg, 0.644 mmol), HATU (245 mg, 0.644 mmol), N,N'-diisopropiletilamina (336 µl, 1.93 mmol), y DMF (5 ml) se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de THF para dar el compuesto del título (83.0 mg, 36%) como cristales blancos.

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^{1}H-RMN (300 MHz, DEMO-d_6) δ: 4.07 (3H, s), 4.33 (3H, s), 6.00 (2H, s), 7.32 - 7.34 (3H, m), 7.39 - 7.54 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 8.17 - 8.22 (3H, m), 8.33 (1H, dd, *J* = 8.3, 1,1 Hz), 8.41 (1H, dd, *J* = 8.3, 1,1 Hz), 8.91 (1H, d, *J* = 2.1 Hz), 10.31 (1H, s).

Ejemplo 79.

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Una mezcla del compuesto del Ejemplo 77 (200 mg, 0.399 mmol), 2-bromoetanol (42.5 µl, 0.599 mmol), carbonato de potasio (248 mg, 1.80 mmol) y DMF (5 ml) se agitó a 10°C durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo-etanol para dar el compuesto del título (68.0 mg, 33%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.51 - 1.62 (2H, m), 1.75 - 1.90 (2H, amplio), 2.18 (2H, t, *J* = 10. 5 Hz), 2.40 (2H, t, *J* = 5.9 Hz), 2.70 - 2.85 (2H, amplio), 3.47- 3.52 (2H, m), 3.75 - 3.90 (1H, amplio), 3.98 (3H, s), 4.32 - 4.38 (4H, m), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.37 (1H, t, *J* = 7.6 Hz), 7.63 (2H, t, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.1 Hz), 7.87 (1H, d, *J* = 7.5 Hz), 8.17 (2H, d, *J* =

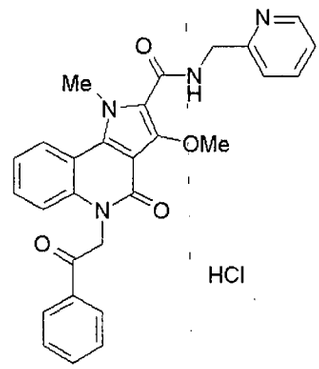
1065

7.6 Hz), 8.37 (1H, d, *J* = 8.4 Hz).

2) El polvo blanco se recristalizó a partir de etanol-agua para dar el compuesto del título como cristales blancos. Punto de fusión: 202°C

Ejemplo 80.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 25, 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 2-(aminometil)piridina (69.6 mg, 0.644 mmol).

El Compuesto del título (222 mg, 87%) se obtuvo como un polvo blanco a partir de la así obtenida 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida por aplicación de un método similar al del Ejemplo 30.

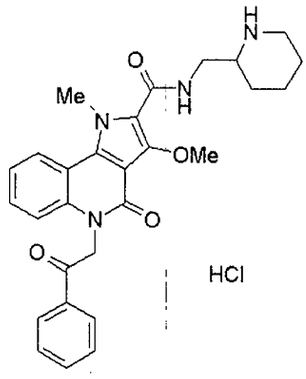
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 4.08 (3H, s), 4.34 (3H, s), 4.85 (2H, d, *J* = 5.7 Hz), 5.98 (2H, s), 7.30 - 7.32 (2H, m), 7.37 - 7.52 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.74 - 7.85 (3H, m), 8.16 - 8.19 (2H, m), 8.31 - 8.40 (2H, m), 8.77 - 8.84 (2H, m).

Ejemplo 81.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-

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(piperidin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.

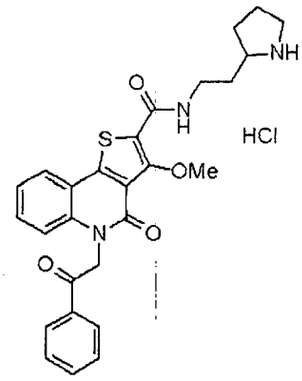


Del mismo modo que en el Ejemplo 73, el compuesto del título (230 mg, 89%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 2-(aminometil)-1-N-boc-piperidina (138 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.95 (6H, amplio), 2.70 - 2.95 (1H, amplio), 3.15 - 3.35 (2H, amplio), 3.46 - 3.69 (2H, m), 4.03 (3H, s), 4.36 (3H, s), 5.98 (2H, s), 7.30 - 7.31 (2H, m), 7.37 - 7.52 (1H, m), 7.64 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.16 - 8.25 (3H, m), 8.39 (1H, dd, *J* = 8.3, 1,1 Hz), 8.55 - 8.75 (1H, amplio), 8.75 - 8.90 (1H, amplio).

Ejemplo 82.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carboxamida, clorhidrato.



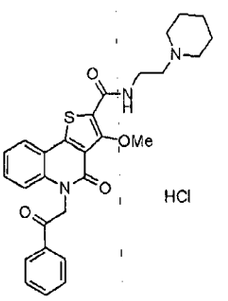
Del mismo modo que en el Ejemplo 73, el compuesto del título (114 mg, 47%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 2-aminoetil-N-boc-pirrolidina (122 mg, 0.57 mmol).

1067

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.65 (1H, m), 1.80 - 2.10 (5H, m), 2.14 - 2.25 (1H, m), 3.10 – 3.20 (2H, m), 3.35 - 3.60 (2H, m), 4.05 (3H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 8.7 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.20 (3H, m), 8.50 - 9.50 (2H, amplio).

Ejemplo 83.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

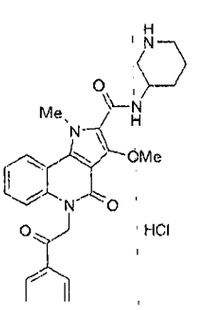


Del mismo modo que en el Ejemplo 67, el compuesto del título (147 mg, 53%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y 1-(2-aminoetil)piperidina (98 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.30 - 1.50 (1H, m), 1.65 - 1.80 (5H, m), 2.85 - 3.00 (2H, m), 3.26 (2H, amplio d, *J* = 5.1 Hz), 3.53 (2H, amplio d, *J* = 11.1 Hz), 3.73 (2H, q, *J* = 5.7 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.06 (1H, dd, *J* = 8.1, 1.5 Hz), 8.16 (1H, d, *J* = 1.5 Hz), 8.19 (1H, s), 8.40 (1H, t, *J* = 5.7 Hz), 9.80 - 9.90 (1H, amplio).

Ejemplo 84.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-3-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.

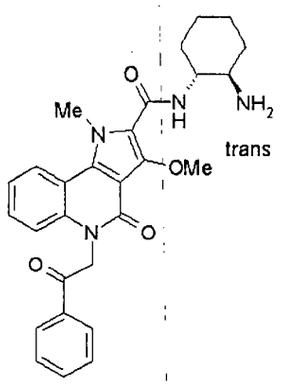


Del mismo modo que en el Ejemplo 73, el compuesto del título (67.1 mg, 27%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 3-amino-1-N-boc-piperidina (129 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.55 - 2.05 (4H, m), 2.75 - 3.00 (2H, m), 3.20 (1H, d, *J* = 13.2 Hz), 3.25 - 3.40 (1H, amplio), 3.99 (3H, s), 4.20 - 4.30 (1H, amplio), 4.31 (3H, s), 5.98 (2H, s), 7.30 - 7.31 (2H, m), 7.36 - 7.52 (1H, m), 7.64 (2H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1H, m), 8.05 (1H, d, *J* = 8.1 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.4 Hz), 8.85 - 9.05 (2H, amplio).

Ejemplo 85.

Producción de N-[trans-2-aminociclohexil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 73, N-[trans-2-aminociclohexil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato se obtuvo a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y N-boc-trans-1,2-diaminociclohexano(138 mg, 0.644 mmol).

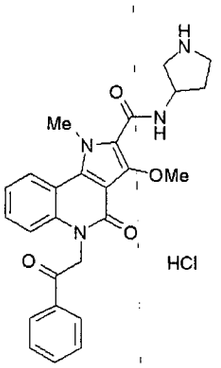
1069

Al así obtenido N-[trans-2-aminociclohexil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato se agregó solución de hidrógeno carbonato de sodio, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=20/1), y el sólido obtenido se recristalizó a partir de acetato de etilo-etanol para dar el compuesto del título (80.0 mg, 33%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.40 (4H, amplio), 1.50 - 1.75 (4H, amplio), 1.70 - 1.90 (1H, amplio), 1.90 - 2.05 (1H, amplio), 2.45 - 2.60 (1H, amplio), 3.45 - 3.60 (1H, amplio), 3.97 (3H, s), 4.30 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.37 (1H, t, J = 7.7 Hz), 7.63 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.3 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.17 (2H, d, J = 7.7 Hz), 8.37 (1H, d, J = 8.1 Hz).

Ejemplo 86.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-pirrolidin-3-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



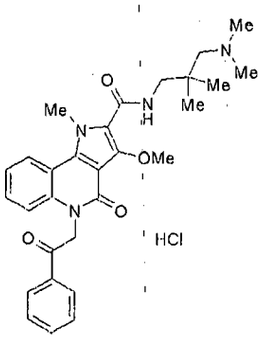
Del mismo modo que en el Ejemplo 73, el compuesto del título (122 mg, 50%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y

3-amino-1-N-boc-pirrolidina (120 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.94 - 2.05 (1H, m), 2.20 - 2.32 (1H, m), 3.17 - 3.49 (4H, m), 4.00 (3H, s), 4.30 (3H, s), 4.58 - 4.69 (1H, m), 5.98 (2H, s), 7.30 - 7.30 (2H, m), 7.36 - 7.52 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.16 - 8.19 (2H, m), 8.26 (1H, d, *J* = 6.9 Hz), 8.38 (1H, dd, *J* = 8.3, 1,1 Hz), 9.10 - 9.30 (2H, amplio).

Ejemplo 87.

Producción de N-[3-(dimetilamino)-2,2-dimetilpropil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 25, N-[3-(dimetilamino)-2,2-dimetilpropil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol).

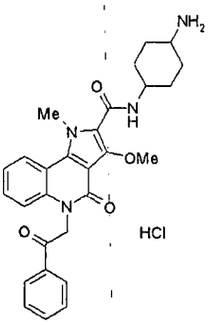
El compuesto del título (203 mg, 76%) se obtuvo como un polvo blanco a partir del así obtenido N-[3-(dimetilamino)-2,2-dimetilpropil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida por aplicación de un método similar al del Ejemplo 30.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.12 (6H, s), 2.86 (3H, s), 2.87 (3H, s), 3.03 - 3.07 (2H, amplio), 3.33 - 3.40 (2H, amplio), 4.04 (3H, s), 4.30 (3H, s), 5.99 (2H, s), 7.30 - 7.31 (2H, m), 7.36 - 7.52 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.16 - 8.21 (3H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz), 9.50 - 9.70

(1H, amplio).

Ejemplo 88.

Producción de N-(4-aminociclohexil)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.

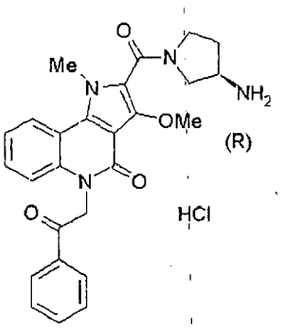


Del mismo modo que en el Ejemplo 73, el compuesto del título (121 mg, 47%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butil (4-aminociclohexil)carbamato (138 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.18 - 1.34 (1H, amplio), 1.55 - 1.75 (1H, amplio), 1.75 - 1.90 (2H, amplio), 1.95 - 2.20 (1H, amplio), 2.60 - 2.81 (2H, m), 3.15 - 3.45 (3H, m), 4.01 (3H, s), 4.30 (3H, s), 5.98 (2H, s), 7.30 - 7.30 (2H, m), 7.36 - 7.51 (1H, m), 7.64 (2H, t, J = 7.5 Hz), 7.74 - 7.79 (1H, m), 8.16 - 8.20 (3H, m), 8.38 (1H, dd, J = 8.3, 1.4 Hz), 8.65 - 8.95 (2H, amplio).

Ejemplo 89.

Producción de 2-{[(3R)-3-aminopirrolidin-1-il]carbonil}-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato.



Del mismo modo que en el Ejemplo 73, el compuesto del

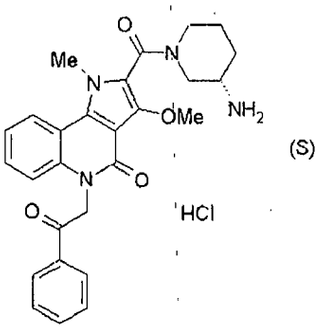
1072

título (190 mg, 78%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butilo (3R)-pirrolidin-3-ilcarbamato (120 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.95 - 2.15 (1H, m), 2.15 - 2.40 (1H, m), 3.57 - 3.92 (8H, m), 4.03 - 4.10 (3H, amplio), 5.98 (2H, s), 7.28 - 7.30 (2H, m), 7.34 - 7.39 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.16 - 8.19 (2H, m), 8.30 - 8.50 (4H, amplio).

Ejemplo 90.

Producción de 2-{[(3S)-3-aminopiperidin-1-il]carbonil}-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato.



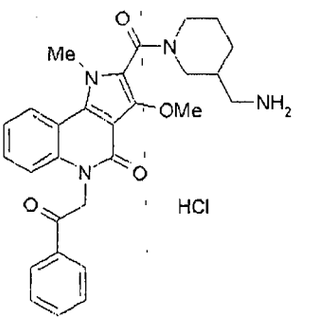
Del mismo modo que en el Ejemplo 73, el compuesto del título (190 mg, 78%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butil (3S)-piperidin-3-ilcarbamato (120 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.45 - 2.00 (3H, amplio), 2.00 - 2.15 (1H, amplio), 2.75 - 3.30 (4H, amplio), 3.65 - 3.85 (0.5H, amplio), 3.91 (3H, s), 4.03 (3H, s), 4.40 - 4.75 (0.5H, amplio), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.34 - 7.39 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.10 - 8.20 (5H, amplio), 8.34 (1H, d, *J* = 7.8 Hz).

Ejemplo 91.

Producción de 2-{[3-(aminometil)piperidin-1-il]carbonil}-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato.

1073

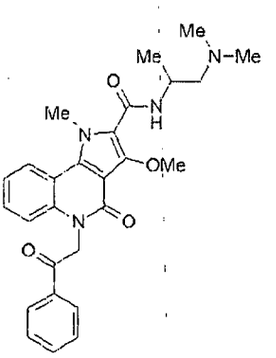


Del mismo modo que en el Ejemplo 73, el compuesto del título (170 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butil (piperidin-3-ilmetil)carbamato (143 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.60 (2H, amplio), 1.60 - 2.00 (3H, amplio), 2.55 - 3.05 (3H, amplio), 3.10 - 3.30 (1H, amplio), 3.60 - 3.80 (1H, amplio), 3.90 (3H, s), 4.01 (3H, s), 4.25 - 4.60 (1H, amplio), 5.98 (2H, s), 7.28 - 7.39 (2H, m), 7.36 (1H, t, *J* = 7.7 Hz), 7.64 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.1 Hz), 7.90 - 8.25 (5H, amplio), 8.33 (1H, d, *J* = 8.1 Hz).

Ejemplo 92.

Producción de N-[2-(dimetilamino)-1-metiletil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (67.0 mg, 29%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (440 mg, 1.01 mmol) y 1-(dimetilamino)isopropilamina (68.1 mg, 0.666 mmol).

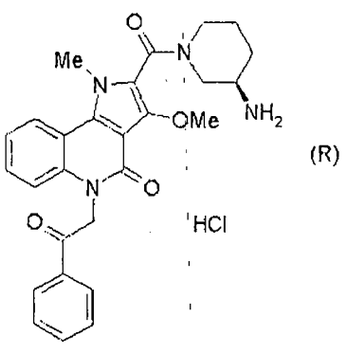
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 (3H, d, *J* = 6.0 Hz),

1074

2.20 (6H, s), 2.20 - 2.27 (1H, m), 2.39 - 2.46 (1H, m), 3.97 (3H, s), 3.98 - 4.10 (1H, m), 4.36 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 7.96 (1H, d, *J* = 6.6 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.1, 1.2 Hz).

Ejemplo 93.

Producción de 2-{[(3R)-3-aminopiperidin-1-il]carbonil}-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato.

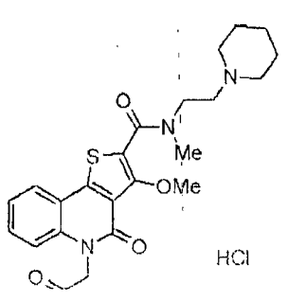


Del mismo modo que en el Ejemplo 73, el compuesto del título (190 mg, 75%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butilo (3R)-piperidin-3-ilcarbamato (133 mg, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.45 - 2.00 (3H, amplio), 2.00 - 2.15 (1H, amplio), 2.75 - 3.30 (4H, amplio), 3.65 - 3.85 (0.5H, amplio), 3.91 (3H, s), 4.03 (3H, s), 4.40 - 4.75 (0.5H, amplio), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.34 - 7.39 (1H, m), 7.64 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.10 - 8.30 (5H, amplio), 8.34 (1H, d, *J* = 8.1 Hz).

Ejemplo 94.

Producción de 3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



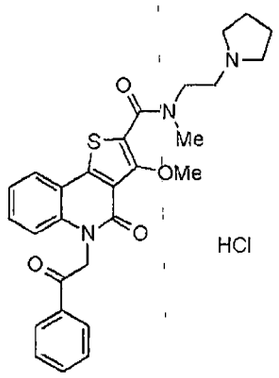
1075

Del mismo modo que en el Ejemplo 67, el compuesto del título (154 mg, 73%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 1-(2-N'-metilaminoetil)piperidina (108 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.25 - 1.45 (1H, m), 1.60 - 1.90 (4H, m), 2.80 - 3.00 (2H, amplio), 3.11 (3H, s), 3.35 - 3.40 (2H, m), 3.40 - 3.65 (2H, amplio), 3.80 - 3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.38 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.98 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.19 (3H, m), 9.75 - 9.90 (1H, amplio).

Ejemplo 95.

Producción de 3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 67, el compuesto del título (153 mg, 74%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 1-(2-N'-metilaminoetil)pirrolidina (98 mg, 0.76 mmol).

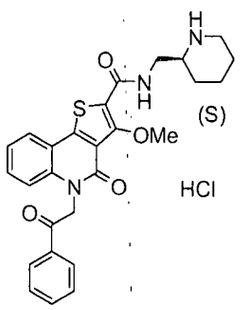
^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.75 - 2.10 (4H, m), 2.90 - 3.15 (5H, m), 3.35 - 3.50 (2H, m), 3.50 - 3.80 (2H, amplio), 3.83 - 3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.38 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.97 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.19

1076

(2H, m), 10.35 - 10.65 (1H, amplio).

Ejemplo 96.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-[(2S)-piperidina-1-ilmetil]-4,5-dihidrotieno[3,2-c]quinolin-1-carboxamida, clorhidrato.

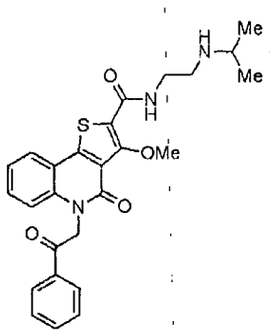


Del mismo modo que en el Ejemplo 73, el compuesto del título (80 mg, 57%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (107 mg, 0.27 mmol) y (S)-2-(boc-aminometil)piperidina (58 mg, 0.27 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.35 - 1.90 (6H, m), 3.00 - 3.40 (4H, m), 3.90 (3H, s), 4.70 - 4.90 (1H, amplio), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.38 - 7.67 (4H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.95 - 8.19 (6H, m).

Ejemplo 97.

Producción de 3-metoxi-N-{2-[(1-metiletil)amino]etil}-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



A una solución mixta del compuesto del Ejemplo 61 (150 mg, 0.32 mmol) y acetona (0.2 ml) en metanol (5 ml)-DMF (5 ml) se agregó cianoborohidruro de sodio (20 mg, 0.32 mmol), y la mezcla se agitó a temperatura ambiente durante 24 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio,

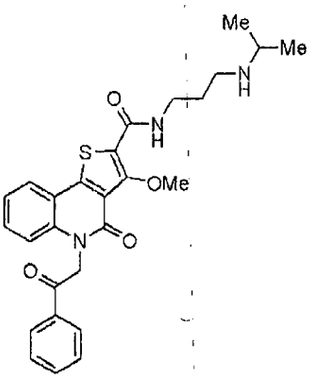
1077

y se extrajo dos veces con acetato de etilo. El extracto se combinó, lavó con salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido blanco obtenido se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (69 mg, 45%) como cristales blancos.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.09 (6H, d, *J* = 6.3 Hz), 2.83 - 2.89 (3H, m), 3.57 (2H, q, *J* = 5.7 Hz), 4.16 (3H, s), 5.87 (2H, s), 7.02 (1H, d, *J* = 8.4 Hz), 7.26 - 7.28 (1H, m), 7.34 - 7.50 (1H, m), 7.56 (2H, t, *J* = 7.5 Hz), 7.66 (1H, t, *J* = 7.5 Hz), 7.91 (1H,dd, *J* = 8.1, 1.2 Hz), 8.10 - 8.13 (3H, m).

Ejemplo 98.

Producción de 3-metoxi-N-{3-[(1-metiletil)amino]propil}-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



1023 Del mismo modo que en el Ejemplo 97, el compuesto del título (9 mg, 5%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 62 (190 mg, 0.38 mmol).

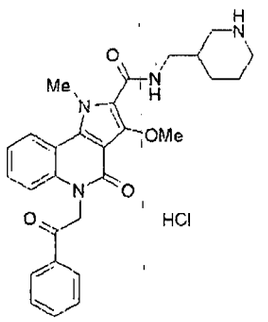
^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.08 (6H, d, *J* = 6.3 Hz), 1.75 - 1.88 (2H, m), 2.73 (2H, t, *J* = 6.9 Hz), 2.76 - 2.85 (1H, m), 3.58 (2H, q, *J* = 6.4 Hz), 4.14 (3H, s), 5.87 (2H, s), 7.02 (1H, d, *J* = 8.7 Hz), 7.20 - 7.28 (1H, m), 7.34 - 7.50 (1H, m), 7.56 (2H, t, *J* = 7.5 Hz), 7.65 - 7.68 (1H, m), 7.80 (1H, amplio t), 7.91 (1H, dd, *J* = 7.8, 1.2 Hz), 8.10 - 8.13

1078

(2H, m).

Ejemplo 99.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(piperidin-3-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.

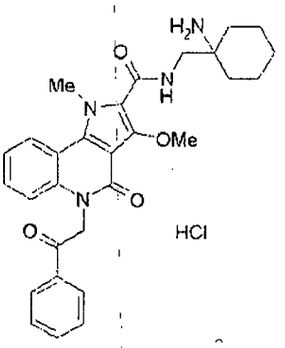


Del mismo modo que en el Ejemplo 73, el compuesto del título (190 mg, 75%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butil 3-(aminometil)piperidina-1-carboxilato (143 mg, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.35 (1H, amplio), 1.50 - 1.90 (3H, amplio), 1.95 - 2.15 (1H, amplio), 2.64 (1H, t, *J* = 6.2 Hz), 2.78 (1H, t, *J* = 5.7 Hz), 3.15 - 3.45 (4H, amplio), 4.01 (3H, s), 4.30 (3H, s), 5.98 (2H, s), 7.29 -7.31 (2H, m), 7.38 (1H, t, *J* = 7.6 Hz), 7.64 (2H, t, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.16 - 8.19 (3H, m), 8.37 (1H, d, *J* = 8.1 Hz), 8.55 - 8.85 (2H, amplio).

Ejemplo 100.

Producción de N-[(1-aminociclohexil)metil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



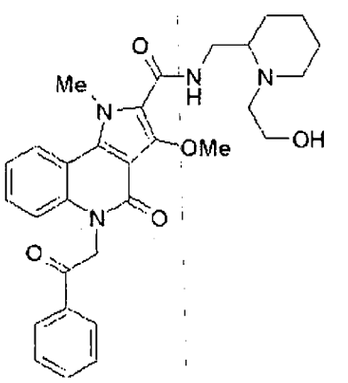
Del mismo modo que en el Ejemplo 73, el compuesto del

título (80.0 mg, 30%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y *terc*-butil [1-(aminometil)ciclohexil]carbamato (147 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.25 - 1.70 (10H, amplio), 3.61 (2H, d, *J* = 6.3 Hz), 4.04 (3H, s), 4.34 (3H, s), 5.98 (2H, s), 7.31 - 7.32 (2H, m), 7.50 (1H, t, *J* = 7.6 Hz), 7.64 (2H, t, *J* = 7.6 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 7.80 - 8.00 (3H, amplio), 8.16 - 8.22 (3H, m), 8.39 (1H, d, *J* = 8.4 Hz).

Ejemplo 101.

Producción de N-{[1-(2-hidroxietil)piperidin-2-il]metil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



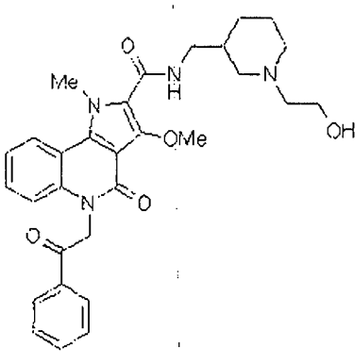
Del mismo modo que en el Ejemplo 79, el compuesto del título (47.1 mg, 39%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 81 (200 mg, 0.399 mmol) y 2-bromoetanol (24.2 µl, 0.341 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.75 (6H, amplio), 2.20 - 3,10 (5H, amplio), 3.40 - 3.65 (4H, amplio), 3.98 - 4.05 (3H, amplio), 4.15 - 4.50 (4H, amplio), 5.98 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.64 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.00 - 8.20 (3H, m), 8.39 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 102.

Producción de N-{[1-(2-hidroxietil)piperidin-3-il]metil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-

c]quinolin-2-carboxamida.

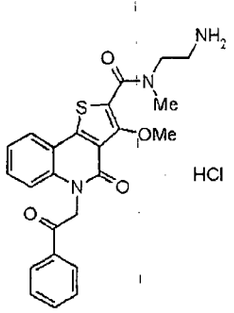


Del mismo modo que en el Ejemplo 79, el compuesto del título (85.2 mg, 50%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 99 (160 mg, 0.306 mmol) y 2-bromoetanol (65.0 µl, 0.918 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.90 - 1.10 (1H, amplio), 1.35 - 1.55 (1H, amplio), 1.55 - 1.90 (4H, amplio), 1.96 (1H, t, *J* = 7.1 Hz), 2.36 (2H, t, *J* = 6.3 Hz), 2.72 (1H, d, *J* = 9.9 Hz), 2.83 (1H, d, *J* = 7.5 Hz), 3.15 - 3.30 (2H, amplio), 3.45 - 3.51 (2H, m), 3.99 (3H, s), 4.30 - 4.34 (4H, m), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.37 (1H, t, *J* = 7.7 Hz), 7.63 (2H, t, *J* = 7.7 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.02 (1H, t, *J* = 6.0 Hz), 8.17 (2H, d, *J* = 7.7 Hz), 8.37 (1H, d, *J* = 8.1 Hz).

Ejemplo 103.

Producción de N-(2-aminoetil)-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo de Referencia 7 (300 mg, 0.76 mmol), 1-boc-amino-2-metilaminoetano clorhidrato (321 mg, 1.52 mmol), trietilamina (154 mg, 1.52 mmol) y HOBt

1081

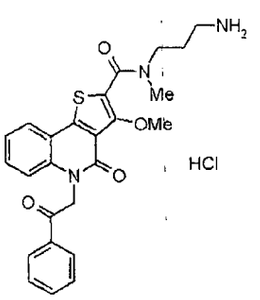
(206 mg, 1.52 mmol) en DMF (10 ml) se agregó WSCD (290 mg, 1.52 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=2/1) para dar *terc*-butil {2-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]etil}carbamato (230 mg) como un aceite incoloro.

Una solución del *terc*-butil {2-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]etil}carbamato obtenido (230 mg) y solución 4N de hidrógeno cloruro de acetato de etilo (8 ml) en acetato de etilo (15 ml) se agitó a temperatura ambiente durante 2 hrs. El precipitado obtenido se recolectó por filtración, se lavó con dietil éter, y se secó bajo presión reducida para dar el compuesto del título (178 mg, 48%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.00 - 3.10 (5H, m), 3.60 - 3.75 (2H, m), 3.89 (3H, s), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.7 Hz), 7.56 (1H, d, *J* = 7.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.2 Hz), 7.80 - 7.98 (4H, m), 8.17 (2H, d, *J* = 7.5 Hz).

Ejemplo 104.

Producción de N-(3-aminopropil)-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



5108

A una solución del compuesto del Ejemplo de Referencia 7 (300 mg, 0.76 mmol), 1-boc-amino-3-metilaminopropano (286 mg, 1.52 mmol) y HOBt (206 mg, 1.52 mmol) en DMF (10 ml) se agregó WSCD (290 mg, 1.52 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=2/1) para dar *terc*-butil {3-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]propil}carbamato (230 mg)*como un sólido no cristalino blanco.

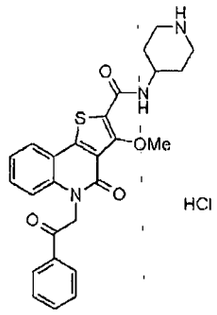
A solución del *terc*-butil {3-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]propil}carbamato obtenido (230 mg) y solución 4N de hidrógeno cloruro de acetato de etilo (8 ml) en acetato de etilo (15 ml) se agitó a temperatura ambiente durante 2 hrs. El precipitado obtenido se recolectó por filtración, se lavó con dietil éter, y se secó bajo presión reducida para dar el compuesto del título (216 mg, 54%) como un polvo blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.80 - 2.00 (2H, m), 2.70 - 2.90 (2H, amplio), 3.06 (3H, s), 3.45 - 3.60 (2H, m), 3.89 (3H, s), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.38 - 7.67 (4H, m), 7.75 - 7.79 (4H, m), 7.97 (1H, d, *J* = 7.8 Hz), 8.17-8.19 (2H, m).

Ejemplo 105.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

1083

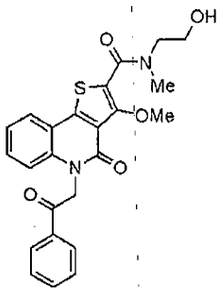


Del mismo modo que en el Ejemplo 73, el compuesto del título (222 mg, 57%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (300 mg, 0.76 mmol) y 4-amino-1-boc-piperidina (305 mg, 1.52 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.70 - 1.95 (2H, m), 2.05 (2H, d, *J* = 11.1 Hz), 3.04 (2H, t, *J* = 11.1 Hz), 3.29 (2H, d, *J* = 14.7 Hz), 4.03 - 4.12 (4H, m), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.59 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.90 (1H, d, *J* = 7.2 Hz), 8.05 (1H, dd, *J* = 8.1, 1.2 Hz), 8.18 (2H, d, *J* = 7.5 Hz), 8.70 - 8.85 (2H, amplio).

Ejemplo 106.

Producción de N-(2-hidroxietil)-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (1,16 g, 68%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (1.50 g, 3.80 mmol) y N-metil-2-aminoetanol (428 mg, 5.70 mmol).

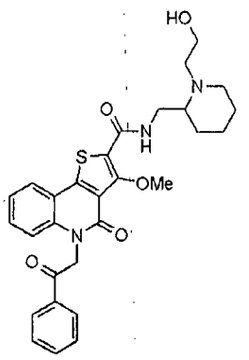
^{1}H-RMN (300 MHz, $CDCl_3$) δ: 3.00 - 3,10 (1H, amplio), 3.21 (3H, s), 3.65 - 3.80 (2H, amplio), 3.80 - 4.00 (2H, amplio), 4.04 (3H, s), 5.86 (2H, s), 7.03 (1H, d, *J* = 8.4 Hz), 7.26 (1H, t, *J* = 7.5 Hz), 7.37 (1H, td, *J* = 7.8, 1.5 Hz), 7.53 - 7.59 (2H, m), 7.65 - 7.71

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(1H, m), 7.83 (1H, dd, *J* = 9.0, 1.2 Hz), 8.10 - 8.13 (2H, m).

Ejemplo 107.

Producción de N-{[1-(2-hidroxietil)piperidin-2-il]metil}-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

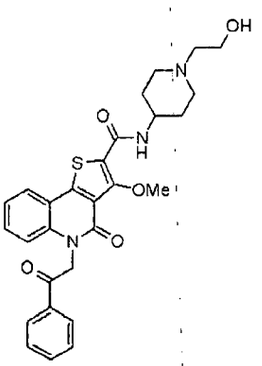


Del mismo modo que en el Ejemplo 101, el compuesto del título (29 mg, 29%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 74 (100 mg, 0.19 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.50 (3H, m), 1.50 - 1.80 (3H, m), 2.27 (1H, t, *J* = 9.5 Hz), 2.35 - 2.60 (3H, m), 2.75 - 2.90 (1H, m), 2.95 (2H, d, *J* = 12.0 Hz), 3.45 - 3.60 (4H, m), 4.44 (1H, t, *J* = 5.4 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.57 (1H, d, *J* = 7.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, d, *J* = 7.2 Hz), 8.10 (1H, t, *J* = 4.2 Hz), 8.18 (2H, d, *J* = 7.2 Hz).

Ejemplo 108.

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 101, el compuesto del

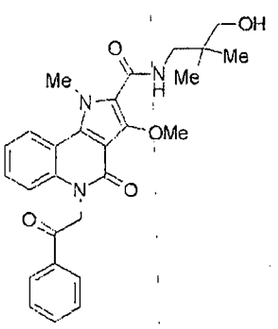
1085

título (41 mg, 27%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 105 (150 mg, 0.29 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.55 - 1.75 (2H, m), 1.84 (2H, d, *J* = 9.6 Hz), 2.18 (2H, t, *J* = 10.2 Hz), 2.37 - 2.44 (2H, m), 2.77 (2H, d, *J* = 10.8 Hz), 3.46 - 3.52 (2H, m), 3.75 - 3.85 (1H, m), 4.04 (3H, s), 4.38 (1H, t, *J* = 5.4 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.57 (1H, dd, *J* = 7.2, 1.5 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.71 - 7.80 (2H, m), 8.05 (1H, dd, *J* = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m).

Ejemplo 109.

Producción de N-(3-hidroxi-2,2-dimetilpropil)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

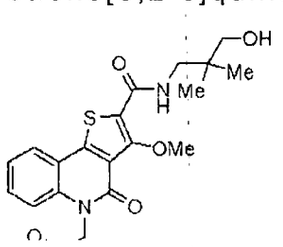


Del mismo modo que en el Ejemplo 25, el compuesto del título (190 mg, 62%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 3-amino-2,2-dimetil-1-propanol (66.4 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.88 (6H, s), 3.22 - 3.24 (4H, m), 4.02 (3H, s), 4.34 (3H, s), 4.78 (1H, t, *J* = 8.3 Hz), 5.98 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.10 - 8.19 (3H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 110.

Producción de N-(3-hidroxi-2,2-dimetilpropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



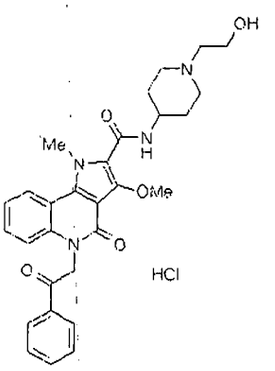
1086

Del mismo modo que en el Ejemplo 25, el compuesto del título (251 mg, 69%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (300 mg, 0.76 mmol) y 3-amino-2,2-dimetil-1-propanol (118 mg, 1.14 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 0.89 (6H, s), 3.25 - 3.35 (4H, m), 4.04 (3H, s), 4.99 (1H, t, *J* = 4.8 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.57 (1H, dd, *J* = 7.2, 1.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m), 8.29 (1H, t, *J* = 5.7 Hz).

Ejemplo 111.

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo 79 (150 mg, 0.290 mmol) en acetato de etilo (4 ml)/etanol (6 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (80.0 µl). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (72 mg, 45%) como un polvo blanco.

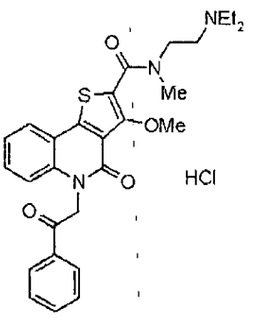
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.88 - 2.20 (4H, amplio), 3.05 - 3.65 (6H, amplio), 3.74 - 3.82 (2H, amplio), 3.90 - 4.15 (4H, amplio), 4.28 (3H, s), 5.30 - 5.45 (1H, m), 5.98 (2H, s), 7.29 -

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7.30 (2H, m), 7.36 - 7.51 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 8.09 - 8.19 (3H, m), 8.37 (1H, d, *J* = 7.5 Hz), 9.75 - 10.10 (1H, amplio).

Ejemplo 112.

Producción de N-[2-(dietilamino)etil]-3-metoxi—N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

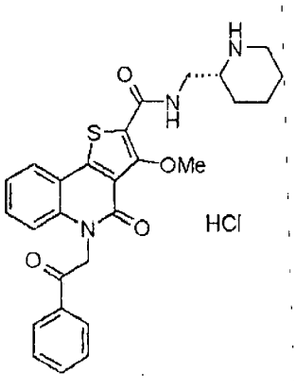


Del mismo modo que en el Ejemplo 30, el compuesto del título (289 mg, 82%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (330 mg, 0.65 mmol) y N,N-dietil-N'-metiletilendiamina (149 mg, 1.14 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.40 (6H, amplio), 3.10 - 3.40 (6H, m), 3.58 (3H, s), 3.84 - 3.90 (5H, m), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.56 (1H, dd, *J* = 7.2, 1.2 Hz), 7.60 - 7.67 (2H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.97 (1H, dd, *J* = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m), 10.35 - 10.60 (1H, amplio).

Ejemplo 113.

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-[(2R)-piperidin-2-ilmetil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



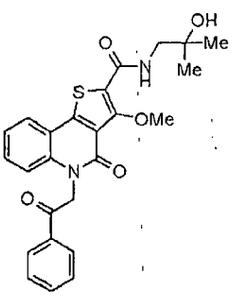
1098

Del mismo modo que en el Ejemplo 73, el compuesto del título (166 mg, 60%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y (R)-2-aminometil-1-N-boc-piperidina (163 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.95 (6H, m), 2.75 - 3.00 (1H, m), 3.25 (2H, d, *J* = 10.8 Hz), 3.49 - 3.57 (1H, m), 3.63 - 3.70 (1H, m), 4.07 (3H, s), 6.01 (2H, s), 7.36 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 8.7 Hz), 7.57-7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.06 (1H, dd, *J* = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m), 8.27 (1H, t, *J* = 6.0 Hz), 8.70 - 8.90 (2H, m).

Ejemplo 114.

Producción de N-(2-hidroxi-2-metilpropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 73, el compuesto del título (108 mg, 47%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 7 (200 mg, 0.51 mmol) y 1-amino-2-metil-2-propanol (68 mg, 0.76 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.16 (6H, s), 3.31 (2H, s), 4.06 (3H, s), 4.77 (1H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 7.57 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.98 (1H, t, *J* = 2.4 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 8.18 (2H, d, *J* = 7.2 Hz).

Ejemplo 115.

Producción de 3-metoxi-N-metil-N-{2-[(1-metiletil)amino]etil}-4-

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oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

A una solución del compuesto del Ejemplo 103 (130 mg, 0.27 mmol), acetona (155 mg, 2.67 mmol) y ácido acético (0.1 ml) en THF (5 ml) se agregó triacetoxiborohidruro de sodio (113 mg, 0.54 mmol), y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo) para dar un aceite sin color (0.09 g). A una solución del aceite sin color obtenido en acetato de etilo (5 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.1 ml). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (73 mg, 52%) como un polvo blanco.

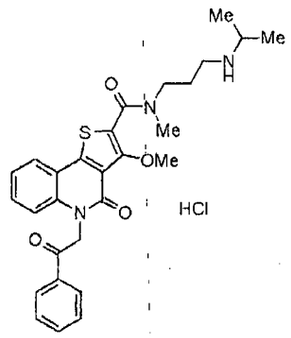
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.35 (6H, amplio), 3.05 - 3.25 (5H, m), 3.30 - 3.40 (1H, m), 3.76 (2H, amplio t, J = 6.6 Hz), 3.90(3H, s), 5.99 (2H, s), 7.35 (1H, t, J = 7.5 Hz), 7.39 (1H, t, J = 8.1 Hz), 7.56 (1H, dd, J =7.2, 1.2 Hz), 7.60 - 7.67 (2H, m), 7.77 (1H, t, J = 7.5 Hz), 7.98 (1H, dd, J = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m), 8.50 - 8.80 (2H, amplio).

Ejemplo 116.

Producción de 3-metoxi-N-metil-N-{3-[(1-metiletil)amino]propil}-4-

1090

oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.

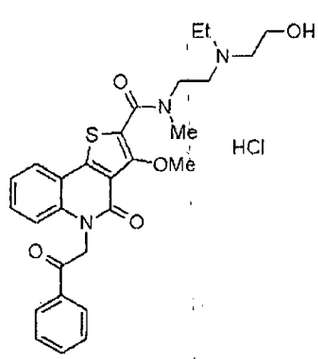


Del mismo modo que en el Ejemplo 115, el compuesto del título (118 mg, 73%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 104 (150 mg, 0.30 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.35 (6H, amplio), 1.85 - 2.05 (2H, amplio), 2.70 - 3.00 (2H, amplio), 3.07 (3H, s), 3.20 - 3.40 (1H, m), 3.45 - 3.60 (2H, m), 3.90 (3H, s), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.56 (1H, dd, *J* = 6.9, 1.2 Hz), 7.62 - 7.67 (2H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.97 (1H, dd, *J* = 7.2, 1.2 Hz), 8.16 - 8.19 (2H, m), 8.65 - 8.80 (2H, amplio).

Ejemplo 117.

Producción de N-{2-[etil(2-hidroxietil)amino]etil}-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una solución del compuesto del Ejemplo 106 (1.0 g, 2.21 mmol) y trietilamina (269 mg, 2.66 mmol) in diclorometano (20 ml) se agregó cloruro de metansulfonilo (279 mg, 2.44 mmol) enfrió

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con hielo, y la mezcla se agitó a temperatura ambiente durante 18 hrs. La mezcla de reacción se diluyó con agua, y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida para dar N-(2-cloroetil)-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (1.01 g) as un sólido no cristalino blanco.

Una solución de la N-(2-cloroetil)-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida obtenida (200 mg, 0.43 mmol), N-etilaminoetanol (228 mg, 2.55 mmol), diisopropiletilamina (330 mg, 2.55 mmol) y yoduro de sodio (64 mg, 0.43 mmol) en 1-butanol (5 ml) se agitó a 11°C durante 18 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo a acetato de etilo/metanol=20/1) para dar N-{2-[etil(2-hidroxietil)amino]etil}-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida (0.08 g) como un sólido no cristalino blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.00 - 1.15 (0.75H, amplio), 1.20 - 1.35 (2.25H, m), 2.20 - 2.9 0 (4H, m), 3.16 (0.75H, s), 3.20 (2.25H, s), 3.50 - 3.95 (6H, m), 4.02 - 4.04 (3H, m), 5.85 (2H, s), 7.03 (1H, d, J = 8.4 Hz), 7.23 - 7.28 (1H, m), 7.35 (1H, t, J = 7.5 Hz), 7.55 (2H, t, J =7.5 Hz), 7.64 - 7.69 (1H, m), 7.80 - 7.84 (1H, m), 8.09 - 8.12 (2H, m).

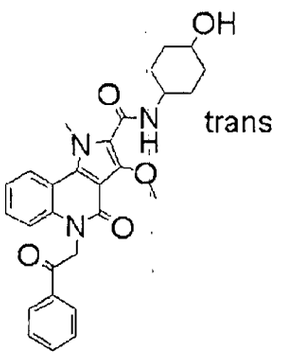
A una solución del sólido no cristalino blanco obtenido en acetato de etilo (5 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0,1 ml). El precipitado se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión

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reducida para dar el compuesto del título (7 mg, 5%) como un polvo blanco.

Ejemplo 118.

Producción de N-(trans-4-hidroxiciclohexil)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

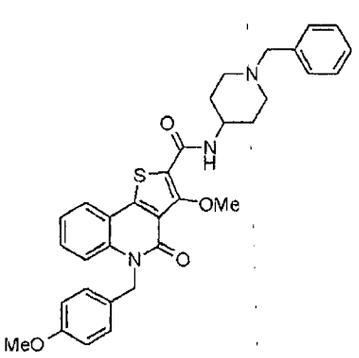


Del mismo modo que en el Ejemplo 25, el compuesto del título (230 mg, 95%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y trans-4-aminociclohexanol (74.2 mg, 0.644 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.22 - 1.44 (4H, m), 1.83 - 1.92 (4H, m), 3.40 - 3.55 (1H, amplio), 3.68 - 3.85 (1H, amplio), 3.96 (3H, s), 4.30 (3H, s), 4.57 (1H, d, *J* = 4.2 Hz), 5.96 (2H, s), 7.28 - 7.38 (2H, m), 7.34 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (2H, m), 8.15 - 8.18 (2H, m), 8.36 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 119.

Producción de N-(1-bencilpiperidin-4-il)-3-metoxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



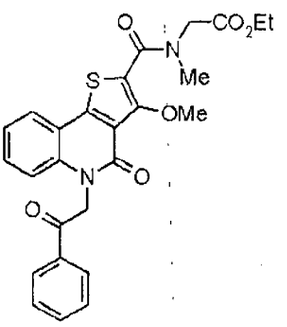
1093

Del mismo modo que en el Ejemplo 25, el compuesto del título (1.17 g, 82%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 13 (1.0 g, 2.52 mmol) y 4-amino-1-bencilpiperidina (720 mg, 3.78 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.55 - 1.75 (2H, m), 1.80 - 1.95 (2H, amplio d), 2.17 (2H, t, *J* = 10.2 Hz), 2.65 - 2.80 (2H, amplio d), 3.50 (2H, s), 3.70 (3H, s), 3.80 - 3.90 (1H, amplio), 4.08 (3H, s), 5.53 (2H, s amplio), 6.85 - 6.88 (2H, m), 7.20 (2H, d, *J* = 8.7 Hz), 7.25 - 7.34 (5H, m), 7.39 - 7.56 (2H, m), 7.74 (1H, d, *J* = 7.8 Hz), 8.00 (1H, dd, *J* = 8.1, 1.2 Hz).

Ejemplo 120.

Producción de etil éster de N-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}-N-metilglicina.

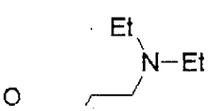


Del mismo modo que en el Ejemplo 25, el compuesto del título (400 mg, 91%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 7 (350 mg, 0.89 mmol) y etil éster de sarcosina, clorhidrato (204 mg, 1.33 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.24 - 1.35 (3H, m), 3.19 (1.2H, s amplio), 3.24 (1,8H, s), 3.98 (1,2H, s amplio), 4.08 (1,8H, s), 4.15 - 4.30 (4H, m), 5.86 (2H, s), 7.03 (1H, d, *J* = 8.7 Hz), 7.24 - 7.29 (1H, m), 7.33 - 7.39 (1H, m), 7.53 - 7.58 (2H, m), 7.65 - 7.70 (1H, m), 7.83 (1H, dd, *J* = 7.8, 1.2 Hz), 8.10 - 8.13 (2H, m).

Ejemplo 121.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-4,5-



1094

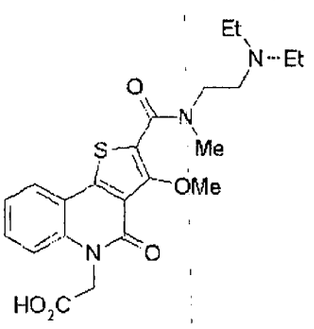
dihidrotieno[3,2-c]quinolin-2-carboxamida.

Una mezcla del compuesto del Ejemplo 48 (4.10 g, 8.08 mol), ácido trifluoroacético (34 ml) y ácido trifluorometansulfónico (6.6 ml) se agitó a temperatura ambiente durante 5 hrs y a 8°C durante 2.5 hrs. Luego de enfriar, la mezcla de reacción se concentró bajo presión reducida, y se agregaron acetato de etilo y solución acuosa 1N de hidróxido de sodio al residuo. La mezcla se extrajo con acetato de etilo y el extracto se lavó en forma consecutiva con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=1/2) para dar el compuesto del título (1.50 g, 48%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.10 (6H, amplio), 2.20 - 2.70 (6H, amplio), 3.05 (3H, s), 3.40 - 3.60 (2H, amplio), 3.91 (3H, s), 7.21 - 7.26 (1H, m), 7.38 - 7.31 (1H, m), 7.39 - 7.55 (1H, m), 7.82 - 7.85 (1H, m), 11.75 (1H, s).

Ejemplo 122.

Producción de ácido [2-{[2-(dietilamino)etil](metil)carbamoil}-3-metoxi-4-oxotieno[3,2-c]quinolin-5(4H)-il]acético.



Una solución del compuesto del Ejemplo 53 (670 mg, 1.41

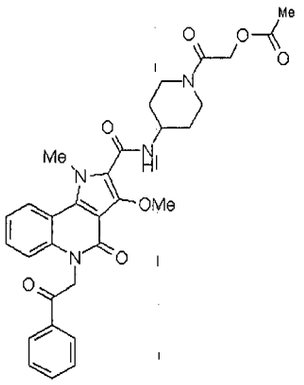
1095

mmol) y solución 8N de hidróxido de sodio (1.0 ml) en etanol (7.0 ml) se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se neutralizó con ácido clorhídrico 1N, y concentró bajo presión reducida. Se agregó THF al residuo y, luego de la filtración, el filtrado se concentró bajo presión reducida para dar el compuesto del título (580 mg, 92%) como un sólido amarillo pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.35 (6H, amplio), 2.70 - 3.30 (9H, m), 3.70 - 3.85 (2H, amplio), 3.91 (3H, s), 5.06 (2H, s), 7.34 (1H, t, *J* = 7.7 Hz), 7.38 (1H, d, *J* = 8.2 Hz), 7.62 (1H, t, *J* = 8.2 Hz), 7.94 (1H, d, *J* = 7.7 Hz).

Ejemplo 123.

Producción de acetato de 2-[4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxo etilo.



A una mezcla del compuesto del Ejemplo 77 (200 mg, 0.423 mmol), trietilamina (122 µl, 0.880 mmol) y THF (10 ml) se agregó cloruro de acetoxiacetilo (47.3 µl, 0.440 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo-THF para dar el compuesto del título (171 mg, 75%) como un polvo blanco.

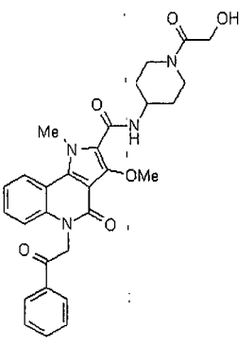
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.70 (2H, m), 1.80 -

1096

2.00 (2H, m), 2.08 (3H, s), 2.80 - 3.00 (1H, m), 3.10 - 3.25 (1H, m), 3.60 - 3.80 (1H, m), 3.97 (3H, s), 4.00 - 4.25 (2H, m), 4.31 (3H, s), 4.80 (2H, d, *J* = 1.8 Hz), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 7.98 (1H, d, *J* = 7.8 Hz), 8.16 - 8.18 (2H, m), 8.37 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 124.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



1) Una solución mixta del compuesto del Ejemplo 123 (125 mg, 0.218 mmol) y solución 8N de hidróxido de sodio (1 ml) en THF (2 ml)-etanol (7 ml) se agitó a temperatura ambiente durante 2 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 6N (1.5 ml), y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo-THF para dar el compuesto del título (59.2 mg, 51%) como cristales blancos.

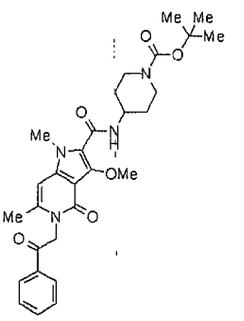
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.65 (2H, m), 1.80 - 2.00 (2H, m), 2.85 - 3.00 (1H, m), 3.05 - 3.25 (1H, m), 3.60 - 3.75 (1H, m), 3.97 (3H, s), 4.00 - 4.30 (4H, m), 4.31 (3H, s), 4.51 (1H, t, *J* = 5.3 Hz), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.38 (1H, t, *J* = 7.6 Hz), 7.63 (2H, t, *J* = 7.6 Hz), 7.76 (1H, t, *J* = 7.3 Hz), 7.95 (1H, d, *J*

= 8.4 Hz), 8.17 (2H, d, *J* = 7.6 Hz), 8.37 (1H, d, *J* = 8.1 Hz).

2) El polvo blanco se recristalizó a partir de etanol-agua para dar el compuesto del título como cristales blancos. Punto de fusión: 224°C

Ejemplo 125.

Producción de *terc*-butil 4-({[3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-il]carbonil}amino)piperidina-1-carboxilato.

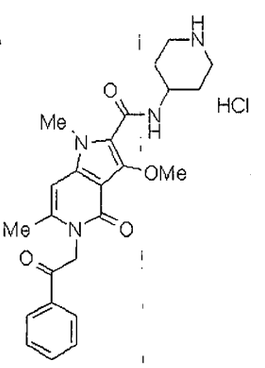


Del mismo modo que en el Ejemplo 25, el compuesto del título (315 mg, 72%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 35 (290 mg, 0.818 mmol) y 4-amino-1-boc-piperidina (212 mg, 1.06 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.29 - 1.51 (11H, m), 1.75 - 1.90 (2H, m), 2.28 (3H, s), 2.86 - 3.05 (2H, m), 3.77 - 3.90 (5H, m), 3.92 - 4.04 (4H, m), 5.62 (2H, s), 6.58 (1H, s), 7.55 - 7.66 (3H, m), 7.73 (1H, d, *J* = 6.6 Hz), 8.11 (2H, d, *J* = 7.7 Hz).

Ejemplo 126.

Producción de 3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida, clorhidrato.



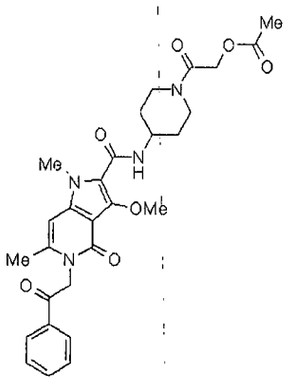
1098

A una mezcla del compuesto del Ejemplo 125 (300 mg, 0.559 mmol) y acetato de etilo (4 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (4 ml), y la mezcla se agitó a temperatura ambiente durante 2 hrs. El sólido precipitado se recolectó por filtración, y se lavó con acetato de etilo para dar el compuesto del título (240 mg, 91%) como un polvo blanco.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.61 - 1.84 (2H, m), 1.95 - 2.11 (2H, m), 2.28 (3H, s), 2.92 - 3,12 (2H, m), 3.20 - 3.32 (2H, m), 3.83 (3H, s), 3.94 - 4.15 (4H, m), 5.62 (2H, s), 6.59 (1H, s), 7.61 (2H, t, *J* = 7.6 Hz), 7.68 - 7.81 (2H, m), 8.04 - 8.19 (2H, m), 8.64 (1H, s amplio.), 8.87 (1H, s amplio).

Ejemplo 127.

Producción de acetato de 2-[4-({[3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-il]carbonil}amino)piperidin-1-il]-2-oxo etilo.



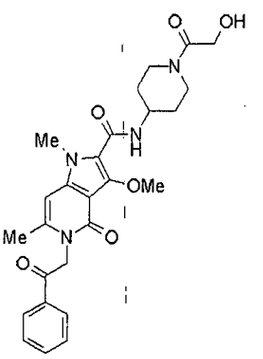
Del mismo modo que en el Ejemplo 123, el compuesto del título (210 mg, 82%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 126 (225 mg, 0.476 mmol) y cloruro de acetoxiacetilo (61.4 µl, 0.571 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.26 - 1.64 (2H, m), 1.78 - 1.97 (2H, m), 2.09 (3 H, s), 2.28 (3 H, s), 2.79 - 2.97 (1 H, m), 3.09 - 3.25 (1 H, m), 3.58 - 3.74 (1 H, m), 3.86 (3 H, s), 3.95 - 4.20 (5 H, m), 4.79 (2 H, s), 5.62 (2 H, s), 6.58 (1 H, s), 7.55 - 7.68 (3 H, m), 7.69 - 7.78 (1 H, m), 8.06 - 8.15 (2 H, m).

1099

Ejemplo 128.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.

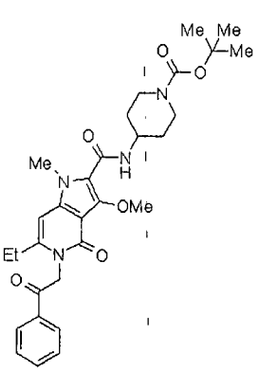


Del mismo modo que en el Ejemplo 124, el compuesto del título (156 mg, 85%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 127 (200 mg, 0.373 mmol), solución 8N de hidróxido de sodio (0.5 ml), THF (2.5 ml) y etanol (5 ml).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.32 - 1.61 (2 H, m), 1.79 - 1.93 (2 H, m), 2.28 (3 H, s), 2.82 - 2.98 (1 H, m), 3.04 - 3.20 (1 H, m), 3.57 - 3.71 (1 H, m), 3.86 (3 H, s), 3.96 - 4.25 (7 H, m), 4.50 (1 H, d, *J* = 5.3 Hz), 5.61 (2 H, s), 6.58 (1 H, s), 7.55 - 7.67 (3 H, m), 7.69 - 7.78 (1 H, m), 8.07 - 8.16 (2 H, m).

Ejemplo 129.

Producción de *terc*-butil 4-({[6-etil-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-il]carbonil}amino)piperidina-1-carboxilato.



Del mismo modo que en el Ejemplo 25, el compuesto del título (126 mg, 84%) se obtuvo como un polvo blanco a partir del

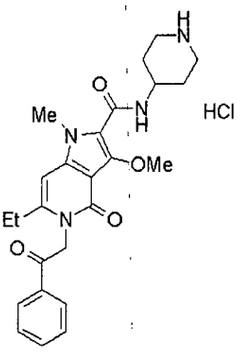
1100

compuesto del Ejemplo de Referencia 42 (100 mg, 0.271 mmol) y 4-amino-1-boc-piperidina (70.7 mg, 0.353 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.32 - 1.51 (11 H, m), 1.74 - 1.89 (2 H, m), 2.58 (2 H, q, *J* = 7.5 Hz), 2.85 - 3.04 (2 H, m), 3.77 - 3.91 (5 H, m), 3.91 - 4.05 (4 H, m), 5.59 (2 H, s), 6.49 (1 H, s), 7.55 - 7.67 (3 H, m), 7.69 - 7.79 (1 H, m), 8.06 - 8.16 (2 H, m).

Ejemplo 130.

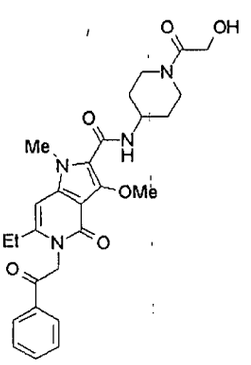
Producción de 6-etil-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida, clorhidrato.



A solución del compuesto del Ejemplo 129 (115 mg, 0.209 mmol) y solución 4N de hidrógeno cloruro de acetato de etilo (4 ml) en acetato de etilo (4 ml) se agitó a temperatura ambiente durante 3 hrs. El sólido precipitado se recolectó por filtración, y se lavó con acetato de etilo para dar el compuesto del título.

Ejemplo 131.

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



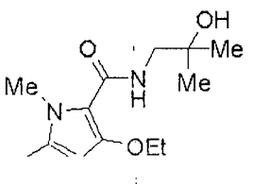
1101

A una mezcla del compuesto del Ejemplo 130 (90.0 mg, 0.185 mmol), trietilamina (76.9 µl, 0.555 mmol) y THF (5 ml) se agregó cloruro de acetoxiacetilo (2 3.8 µl, 0.221 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se disolvió en THF (1.2 ml)-etanol (2.5 ml). Se agregó solución 8N de hidróxido de sodio (250 µl), y la mezcla se agitó a temperatura ambiente durante 2 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 6N (0.5 ml), y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=10/0 - 9/1), y el sólido obtenido se recristalizó a partir de acetato de etilo para dar el compuesto del título (61.2 mg, 65%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.23 (3 H, m), 1.31 - 1.59 (2 H, m,), 1.80 - 1.94 (2 H, m,), 2.58 (2 H, q, *J* = 7.3 Hz), 2.83 - 2.99 (1 H, m), 3.04 - 3.21 (1 H, m), 3.59 - 3.70 (1 H, m,), 3.89 (3 H, s), 3.97 - 4.26 (7 H, m), 4.49 (1 H, t, *J* = 5.4 Hz), 5.59 (2 H, s), 6.49 (1 H, s), 7.56 - 7.67 (3 H, m), 7.70 - 7.78 (1 H, m), 8.06 - 8.15 (2 H, m).

Ejemplo 132.

Producción de 3-etoxi-N-(2-hidroxi-2-metilpropil)- 1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



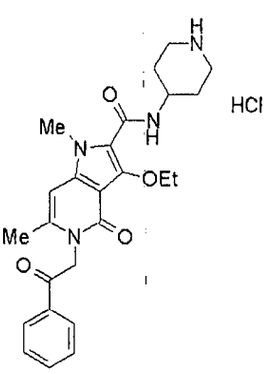
1102

Del mismo modo que en el Ejemplo 25, el compuesto del título (65.8 mg, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 44 (100 mg, 0.271 mmol) y 1-amino-2-metilpropan-2-ol (31.5 mg, 0.353 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 (6 H, s), 1.31 (3 H, t, *J* = 7.0 Hz), 2.28 (3 H, s), 3.24 (2 H, d, *J* = 5.5 Hz), 3.90 (3 H, s), 4.35 (2 H, q, *J* = 7.0 Hz), 4.66 (1 H, s), 5.61 (2 H, s), 6.59 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.79 (1 H, m), 7.93 (1 H, t, *J* = 5.6 Hz), 8.06 - 8.15 (2 H, m).

Ejemplo 133.

Producción de 3-etoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 73, el compuesto del título (303 mg, 95%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 44 (250 mg, 0.679 mmol) y 4-amino-1-boc-piperidina (177 mg, 0.882 mmol).

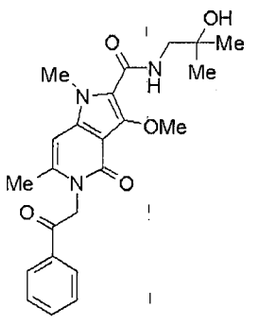
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.28 (3 H, t, *J* = 7.1 Hz), 1.61 - 1.81 (2 H, m), 1.97 - 2.12 (2 H, m), 2.28 (3 H, s), 2.94 -

1103

3.10 (2 H, m), 3.21 - 3.32 (2 H, m), 3.85 (3 H, s), 3.97 - 4.14 (1 H, m), 4.34 (2 H, q, *J* = 7.0 Hz), 5.62 (2 H, s), 6.59 (1 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.69 - 7.81 (2 H, m), 8.04 - 8.17 (2 H, m), 8.85 (2 H, s amplio).

Ejemplo 134.

Producción de N-(2-hidroxi-2-metilpropil)-3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.

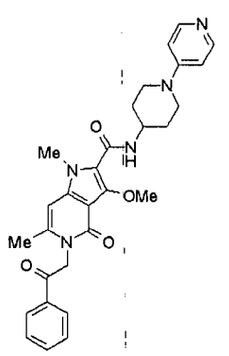


Del mismo modo que en el Ejemplo 25, el compuesto del título (201 mg, 84%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 35 (200 mg, 0.564 mmol) y 1-amino-2-metilpropan-2-ol (65.4 mg, 0.734 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 (6 H, s), 2.29 (3 H, s), 3.24 (2 H, d, *J* = 5.7 Hz), 3.89 (3 H, s), 4.02 (3 H, s), 4.65 (1 H, s), 5.62 (2 H, s), 6.59 (1 H, s), 7.56 - 7.66 (2 H, m), 7.69 - 7.78 (1 H, m), 7.85 (1 H, t, *J* = 5.7 Hz), 8.06 - 8.15 (2 H, m).

Ejemplo 135.

Producción de 3-metoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-piridin-4-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del

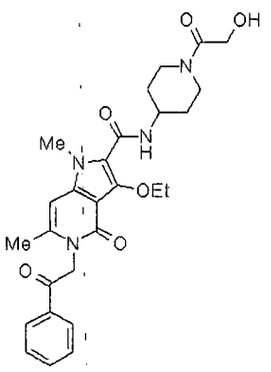
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título (656 mg, 91%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 35 (500 mg, 1.41 mmol) y 1-piridin-4-ilpiperidin-4-amina (388 mg, 1.55 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.48 - 1.65 (2 H, m), 1.85 - 1.97 (2 H, m,), 2.28 (3 H, s), 2.98 - 3,14 (2 H, m), 3.77 - 3.90 (5 H, m), 3.98 (3 H, s), 4.01 - 4.15 (1 H, m), 5.61 (2 H, s), 6.58 (1 H, s), 6.82 (2 H, d, *J* = 1.5 Hz), 7.56 - 7.68 (3 H, m), 7.70 - 7.78 (1 H, m), 8.05 - 8.20 (4 H, m).

Ejemplo 136.

Producción de 3-etoxi-N-[1-(hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



A una mezcla del compuesto del Ejemplo 133 (200 mg, 0.423 mmol), trietilamina (122 µl, 0.880 mmol) y THF (10 ml) se agregó cloruro de acetoxiacetilo (47.3 µl, 0.440 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se disolvió en etanol (7 ml) y THF (2 ml), solución 8N de hidróxido de sodio (1 ml) se agregó, y la mezcla se agitó a temperatura ambiente durante 2 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 6N (1.5 ml), y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato

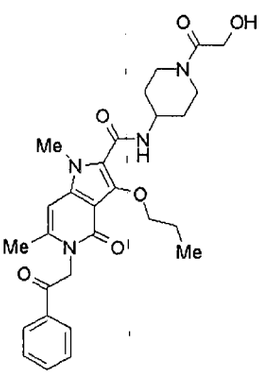
1105

de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (102 mg, 65%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.25 (3 H, t, J = 7.1 Hz), 1.31 - 1.57 (2 H, m), 1.82 - 1.96 (2 H, m), 2.28 (3 H, s), 2.80 - 2.95 (1 H, m), 3.03 - 3.19 (1 H, m), 3.87 (3 H, s), 3.95 - 4.13 (3 H, m), 4.18 - 4.28 (1 H, m), 4.34 (2 H, q, J = 7.0 Hz), 4.50 (1 H, t, J = 5.4 Hz), 5.61 (2 H, s), 6.58 (1 H, s), 7.55 - 7.78 (4 H, m), 8.06 - 8.14 (2 H, m).

Ejemplo 137.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



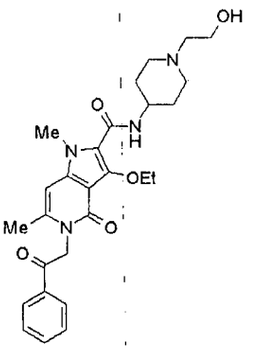
Del mismo modo que en el Ejemplo 25, el compuesto del título (45.2 mg, 33%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 46 (100 mg, 0.262 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (61.1 mg, 0.314 mmol) y trietilamina (43,5 µl, 0.314 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.92 (3 H, t, J = 7.3 Hz), 1.22 - 1.53 (2 H, m), 1.60 - 1.75 (2 H, m), 1.85 - 1.95 (2 H, m), 2.27 (3 H, s), 2.77 - 2.92 (1 H, m), 3.00 - 3.17 (1 H, m), 3.60 - 3.74 (1 H, m), 3.86 (3 H, s), 3.95 - 4.13 (3 H, m), 4.25 (3 H, t, J = 6.7 Hz), 4.50 (1 H, t, J = 5.4 Hz), 5.62 (2 H, s), 6.57 (1 H, s), 7.55 - 7.67 (3 H, m,), 7.69 - 7.78 (1 H, m), 8.05 - 8.16 (2 H, m).

Ejemplo 138.

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Producción de 3-etoxi-N-[1-(2-hidroxietil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.

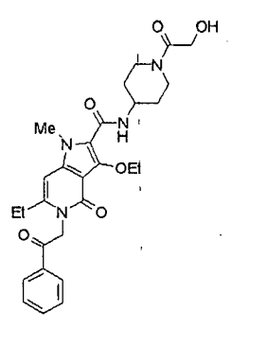


Del mismo modo que en el Ejemplo 79, el compuesto del título (78.5 mg, 57%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 133 (135 mg, 0.277 mmol) y 2-bromoetanol (58.9 µl, 0.832 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.28 (3 H, t, *J* = 7.1 Hz), 1.39 - 1.57 (2 H, m), 1.78 - 1.91 (2 H, m), 2.09 - 2.22 (2 H, m), 2.28 (3 H, s), 2.38 (2 H, t, *J* = 6.3 Hz), 2.67 - 2.81 (2 H, m,), 3.48 (2 H, q, *J* = 6.2 Hz), 3.70 - 3.83 (1 H, m), 3.87 (3 H, s), 4.29 - 4.41 (3 H, m), 5.61 (2 H, s), 6.58 (1 H, s), 7.56 - 7.68 (3 H, m), 7.70 - 7.78 (1 H, m), 8.06 - 8.15 (2 H, m).

Ejemplo 139.

Producción de 3-etoxi-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



1) A una solución del compuesto del Ejemplo de Referencia 48 (74.0 mg, 0.194 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (49.1 mg, 0.252 mmol), HOBt (39.2 mg, 0.290 mmol) y

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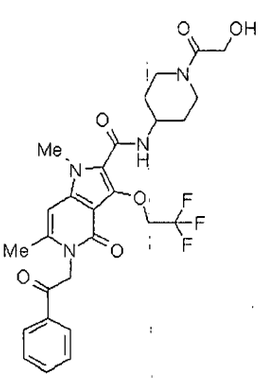
trietilamina (34.9 µl, 0.252 mmol) en DMF (3 ml) se agregó WSCD (55.6 mg, 0.290 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo para dar el compuesto del título (61.2 mg, 60%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.29 (6 H, m), 1.32 - 1.56 (2 H, m), 1.83 - 1.96 (2 H, m), 2.57 (2 H, q, *J* = 7.3 Hz), 2.80 - 2.94 (1 H, m), 3.04 - 3.19 (1 H, m), 3.59 - 3.72 (1 H, m), 3.90 (3 H, s), 3.95 - 4.14 (3 H, m), 4.17 - 4.27 (1 H, m), 4.34 (2 H, q, *J* = 7.2 Hz), 4.51 (1 H, t, *J* = 5.4 Hz), 5.59 (2 H, s), 6.49 (1 H, s), 7.56 - 7.65 (2 H, m), 7.66 - 7.77 (2 H, m), 8.07 - 8.14 (2 H, m).

2) Los cristales blancos se recristalizaron a partir de etanol-agua para dar el compuesto del título como cristales blancos. punto de fusión: 204°C

Ejemplo 140.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



A una solución del compuesto del Ejemplo de Referencia 50

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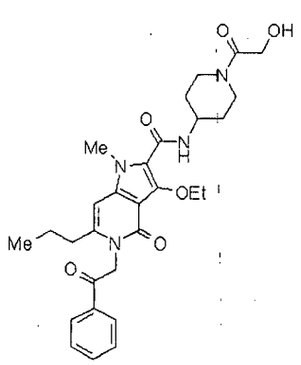
(70.0 mg, 0.166 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (42.0 mg, 0.216 mmol), HOBt (33.6 mg, 0.249 mmol) y trietilamina (29.9 µl, 0.216 mmol) en DMF (3 ml) se agregó WSCD (55.6 mg, 0.290 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de acetato de etilo para dar el compuesto del título (51,3 mg, 55%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.22 - 1.50 (2 H, m), 1.81 - 1.94 (2 H, m), 2.29 (3 H, s), 2.74 - 2.91 (1 H, m), 3.01 - 3.16 (1 H, m), 3.63 - 3.75 (1 H, m), 3.83 (3 H, s), 3.95 - 4.13 (3 H, m), 4.20 - 4.32 (1 H, m), 4.53 (1 H, t, *J* = 5.5 Hz), 5.06 (2 H, q, *J* = 9.3 Hz), 5.65 (2 H, s), 6.64 (1 H, s), 7.51 (1 H, d, *J* = 7.7 Hz), 7.57 - 7.66 (2 H, m), 7.70 - 7.79 (1 H, m), 8.07 - 8.15 (2 H, m).

2) Los cristales blancos se recristalizaron a partir de etanol-agua para dar el compuesto del título como cristales blancos. punto de fusión: 132°C

Ejemplo 141.

Producción de 3-etoxi-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-6-propil-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



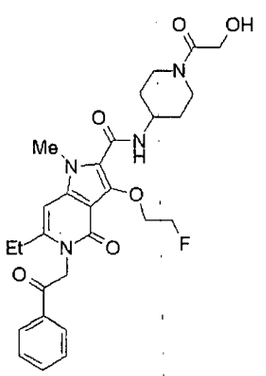
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A una solución del compuesto del Ejemplo de Referencia 57 (200 mg, 0.504 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (128 mg, 0.656 mmol), HOBt (102 mg, 0.757 mmol) y trietilamina (90.8 µl, 0.656 mmol) en DMF (5 ml) se agregó WSCD (145 mg, 0.757 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de THF-acetato de etilo para dar el compuesto del título (224 mg, 83%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.93 (3 H, t, *J* = 7.3 Hz), 1.25 (3 H, t, *J* = 7.1 Hz), 1.31 - 1.66 (4 H, m), 1.84 - 1.95 (2 H, m), 2.51 - 2.59 (2 H, m), 2.81 - 2.95 (1 H, m), 3.04 - 3.18 (1 H, m), 3.61 - 3.71 (1 H, m), 3.89 (3 H, s), 3.96 - 4.14 (3 H, m), 4.18 - 4.27 (1 H, m), 4.33 (2 H, q, *J* = 7.0 Hz), 4.51 (1 H, t, *J* = 5.1 Hz), 5.55 (2 H, s), 6.51 (1 H, s), 7.56 - 7.77 (4 H, m), 8.08 - 8.14 (2 H, m).

Ejemplo 142.

Producción de 6-etil-3-(2-fluoroetoxi)-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-fenilétil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



A una solución del compuesto del Ejemplo de Referencia 59

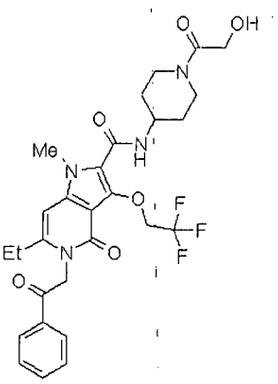
1110

(202 mg, 0.504 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (128 mg, 0.656 mmol), HOBt (102 mg, 0.757 mmol) y trietilamina (90.8 µl, 0.656 mmol) en DMF (5 ml) se agregó WSCD (145 mg, 0.757 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo), y el sólido obtenido se recristalizó a partir de THF-acetato de etilo para dar el compuesto del título (219 mg, 80%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, J = 7.3 Hz), 1.26 - 1.48 (2 H, m), 1.87 (2 H, s), 2.59 (2 H, q, J = 7.3 Hz), 2.76 - 2.91 (1 H, m), 3.01 - 3.17 (1 H, m), 3.57 - 3.73 (1 H, m), 3.92 (3 H, s), 3.97 - 4.13 (3 H, m), 4.18 - 4.32 (1 H, m), 4.45 - 4.81 (5 H, m), 5.59 (2 H, s), 6.49 - 6.56 (1 H, m), 7.55 - 7.66 (3 H, m), 7.69 - 7.78 (1 H, m), 8.06 - 8.16 (2 H, m).

Ejemplo 143.

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



1) A una solución del compuesto del Ejemplo de Referencia 61 (230 mg, 0.527 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (133 mg, 0.685 mmol), HOBt (107 mg, 0.791 mmol) y

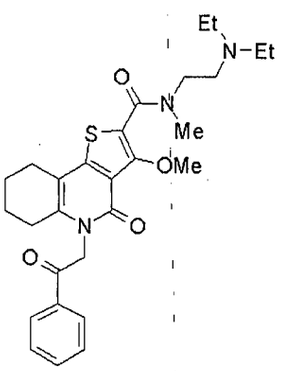
trietilamina (95.0 µl, 0.685 mmol) en DMF (4 ml) se agregó WSCD (152 mg, 0.791 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=1/3 - 1/0), y el sólido obtenido se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (146 mg, 48%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.13 - 1.49 (5 H, m), 1.82 - 1.94 (2 H, m), 2.59 (2 H, q, *J* = 7.2 Hz), 2.76 - 2.88 (1 H, m), 3.02 - 3.15 (1 H, m), 3.64 - 3.75 (1 H, m), 3.86 (3 H, s), 3.96 - 4.16 (3 H, m), 4.20 - 4.33 (1 H, m), 4.53 (1 H, t, *J* = 5.4 Hz), 5.05 (2 H, q, *J* = 9.3 Hz), 5.63 (2 H, s), 6.54 (1 H, s), 7.51 (1 H, d, *J* = 7.7 Hz), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.78 (1 H, m), 8.08 - 8.14 (2 H, m).

2) Los cristales blancos se recristalizaron a partir de etanol-agua para dar el compuesto del título como cristales blancos. Punto de fusión: 159°C

Ejemplo 144.

Producción de N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5,6,7,8,9-hexahidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del

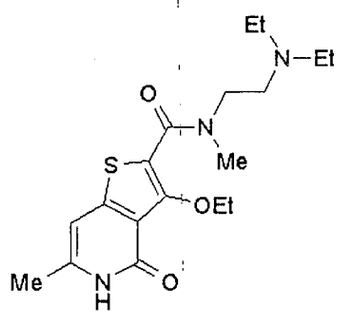
1112

título (54.0 mg, 28%) se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo de Referencia 66 (150 mg, 0.377 mmol) y N,N-dietil-N'-metiletan-1,2-diamina (79.3 µl, 0.490 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.74 - 1.05 (6 H, m), 1.67 - 1.85 (4 H, m), 2.19 - 2.65 (10 H, m), 3.03 (3 H, s), 3.40 - 3.56 (2 H, m), 3.82 (3 H, s), 5.65 (2 H, s), 7.61 (2 H, t, *J* = 7.6 Hz), 7.70 - 7.78 (1 H, m), 8.07 - 8.16 (2 H, m).

Ejemplo 145.

Producción de N-[2-(dietilamino)etil]-3-etoxi-N,6-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.



Una mezcla del compuesto del Ejemplo de Referencia 70 (2.50 g, 6.51 mmol), ácido clorhídrico 6N (15 ml) y DMF (15 ml) se agitó durante 15 hrs en condiciones de reflujo. Luego de enfriar, la mezcla de reacción se concentró bajo presión reducida, y agua (20 ml) se agregó al residuo. La mezcla se neutralizó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se lavó en forma consecutiva con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo) para dar el compuesto del título (568 mg, 24%) como un aceite incoloro.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.05 (6H, m), 1.21 (3H, t, *J* = 7.0 Hz), 2.21 (3H, s), 2.25 - 2.65 (6H, m), 3.01 (3H, s), 3.40 - 3.55 (2H, m), 4.13 (2H, q, *J* = 7.0 Hz), 6.54 (1H, s), 11.41 (1H, s).

Ejemplo 146.

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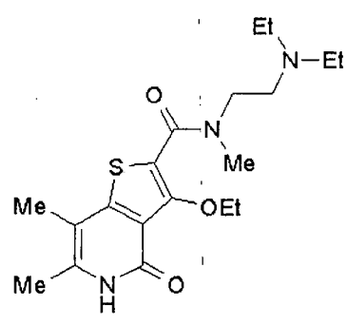
Producción de N-[2-(dietilamino)etil]-3-etoxi-N,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.

Una mezcla del compuesto del Ejemplo 145 (300 mg, 0.821 mmol), bromuro de fenacilo (196 mg, 0.985 mmol), carbonato de potasio (272 mg, 1.97 mmol) y DMF (5 ml) se agitó a 6°C durante 15 hrs. Luego de enfriar, la mezcla se diluyó con agua (10 ml), y se extrajo con acetato de etilo. El extracto se lavó en forma consecutiva con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano = 1/9 a 10/0) para dar el compuesto del título (51.2 mg, 13%) como un aceite incoloro.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.70 - 1.05 (6H, m), 1.15 - 1.20 (3H, m), 2.25 - 2.65 (9H, m), 3.02 (3H, s amplio), 3.40 - 3.55 (2H, m), 4.05 (2H, q, *J* = 6.9 Hz), 5.66 (2H, s), 6.80 - 6.81 (1H, m), 7.62 (2H, t, *J* = 7.7 Hz), 7.72 - 7.78 (1H, m), 8.10 - 8.13 (2H, m).

Ejemplo 147.

Producción de N-[2-(dietilamino)etil]-3-etoxi-N,6,7-trimetil-4-oxo-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.



Del mismo modo que en el Ejemplo 145, el compuesto del

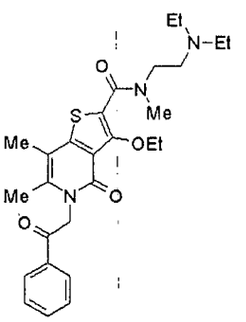
1114

título (60 mg, 29%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 74 (220 mg, 0.55 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 0.80 - 1.10 (6H, m), 1.37 (3H, t, *J* = 6.9 Hz), 2.17 (3H, s), 2.41 (3H, s), 2.48 - 2.73 (6H, m), 3.17 (3H, s), 3.61 (2H, s amplio), 4.27 (2H, q, *J* = 7.1 Hz), 12.31 (1H, s amplio).

Ejemplo 148.

Producción de N-[2-(dietilamino)etil]-3-etoxi-N,6,7-trimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.

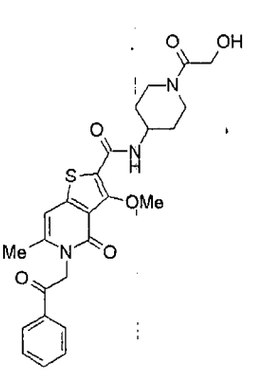


Del mismo modo que en el Ejemplo 146, el compuesto del título (10 mg, 12%) se obtuvo como un aceite amarillo pálido a partir del compuesto del Ejemplo 147 (60 mg, 0.16 mmol) y bromuro de fenacilo (196 mg, 0.985 mmol).

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 0.80 - 1.15 (6 H, m), 1.34 (3 H, t, *J* = 7.1 Hz), 2.21 - 2.80 (12 H, m), 3.16 (3H, s), 3.62 (2 H, s amplio), 4.22 (2 H, q, *J* = 7.1 Hz), 5.67 (2 H, s), 7.54 (2 H, t, *J* = 7.5 Hz), 7.66 (1 H, t, *J* = 7.5 Hz), 8.08 (2 H, dd, *J* = 8.1, 1.5 Hz).

Ejemplo 149.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.



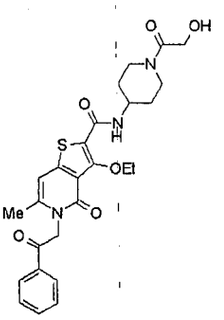
1115

Del mismo modo que en el Ejemplo 25, el compuesto del título (224 mg, 80%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 78 (200 mg, 0.560 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (142 mg, 0.727 mmol) y trietilamina (101 µl, 0.727 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.38 - 1.66 (2 H, m), 1.79 - 1.92 (2 H, m), 2.26 - 2.35 (3 H, m), 2.78 - 2.94 (1 H, m), 3.03 - 3.18 (1 H, m), 3.58 - 3.71 (1 H, m), 3.94 - 4.14 (6 H, m), 4.18 - 4.30 (1 H, m), 4.51 (1 H, t, J = 5.3 Hz), 5.68 (2 H, s), 6.86 (1 H, s), 7.56 - 7.69 (3 H, m), 7.71 - 7.80 (1 H, m), 8.07 - 8.16 (2 H, m).

Ejemplo 150.

Producción de 3-etoxi-N-[1-(hidroxiacetil)piperidin-4-il]- 6-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (178 mg, 65%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 79 (200 mg, 0.538 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (142 mg, 0.727 mmol) y trietilamina (101 µl, 0.727 mmol).

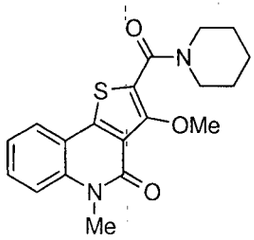
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.30 (3 H, t, J = 7.1 Hz), 1.37 - 1.61 (2 H, m), 1.84 - 1.95 (2 H, m), 2.30 (3 H, s), 2.76 - 2.91 (1 H, m), 3.02 - 3.18 (1 H, m), 3.59 - 3.73 (1 H, m), 3.95 - 4.13 (3 H, m), 4.21 - 4.33 (3 H, m), 4.51 (1 H, t, J = 5.4 Hz), 5.68 (2 H, s), 6.86 (1 H, s), 7.57 - 7.70 (3 H, m), 7.71 - 7.79 (1 H, m),

1116

8.07 - 8.17 (2 H, m).

Ejemplo 151.

Producción de 3-metoxi-5-metil-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

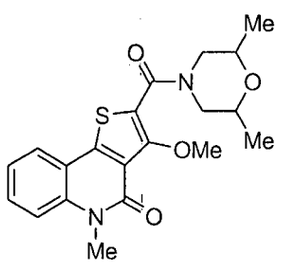


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y piperidina.

LC/EM 357 (M+H).

Ejemplo 152.

Producción de 2-[(2.6-dimetilmorfolin-4-il)carbonil]-3-metoxi-5-metiltieno[3,2-c]quinolin-4(5H)-ona.

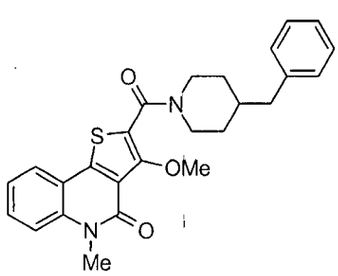


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2.6-dimetilmorfolina.

LC/EM 387 (M+H).

Ejemplo 153.

Producción de 2-[(4-bencilpiperidin-1-il)carbonil]-3-metoxi-5-metiltieno[3,2-c]quinolin-4(5H)-ona.

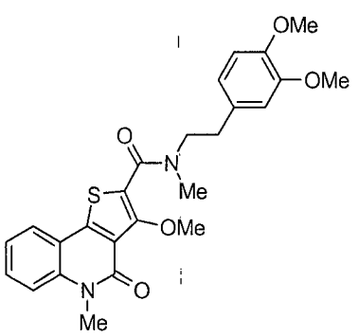


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 4-bencilpiperidina.

LC/EM 447 (M+H).

Ejemplo 154.

Producción de N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

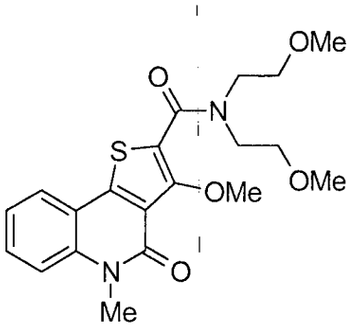


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-(3.4-dimetoxifenil)-N-metiletanamina.

LC/EM 467 (M+H).

Ejemplo 155.

Producción de 3-metoxi-N,N-bis(2-metoxietil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



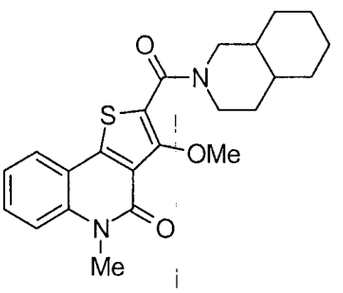
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-metoxi-N-(2-metoxietil)etanamina.

LC/EM 405 (M+H).

1118

Ejemplo 156

Producción de 3-metoxi-5-metil-2-(octahidroisoquinolin-2(1H)-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona

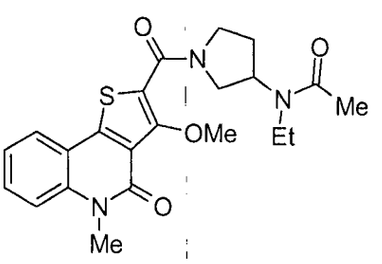


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y decahidroisoquinolina.

LC/EM 411 (M+H).

Ejemplo 157.

Producción de N-etil-N-{1-[(3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-il)carbonil]pirrolidin-3-il}acetamida.

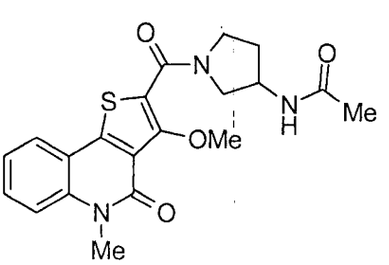


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N-etil-N-pirrolidin-3-ilacetamida.

LC/EM 428 (M+H).

Ejemplo 158.

Producción de N-{1-[(3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-il)carbonil]pirrolidin-3-il}acetamida.



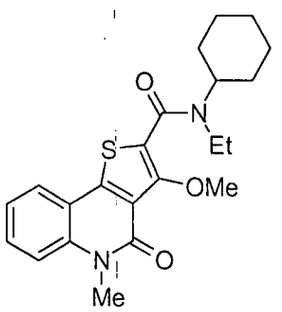
1119

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N-pirrolidin-3-ilacetamida.

LC/EM 400 (M+H).

Ejemplo 159.

Producción de N-ciclohexil-N-etil-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

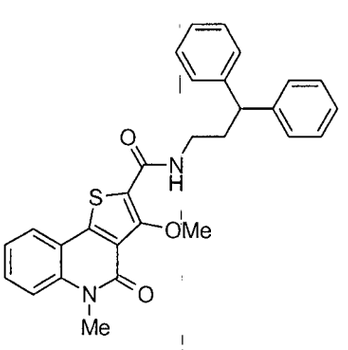


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N-etilciclohexanamina.

LC/EM 399 (M+H).

Ejemplo 160.

Producción de N-(3.3-difenilpropil)-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



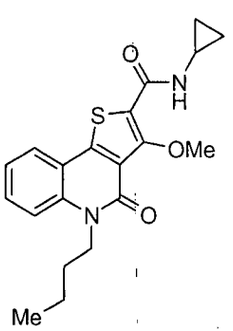
Una solución del compuesto del Ejemplo de Referencia 84 en DMF (0.10 M, 0.601 ml, 60 µmol) se diluyó con DMF (0.200 ml), y una solución de 3.3-difenilpropan-1-amina en DMF (1.0 M,

0.062 ml, 62 µmol) y se agregaron una solución (de HOBt y WSCD en mezcla 1:1 en DMF 0.50 M, 0.134 ml, 67 µmol). La mezcla resultante se agitó a temperatura ambiente durante 16 hrs. Se agregaron diclorometano (2 ml) y agua (1 ml) a la mezcla de reacción. Luego de agitar durante 2.5 hrs, se agregó hidrógeno carbonato de sodio (7 mg) y la mezcla se agitó. La fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (21.9 mg, 76%).

LC/EM 483 (M+H).

Ejemplo 161.

Producción de 5-butil-N-ciclopropil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

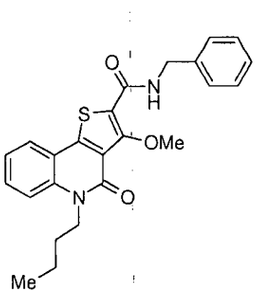


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y ciclopropanamina.

LC/EM 371 (M+H).

Ejemplo 162.

Producción de N-bencil-5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



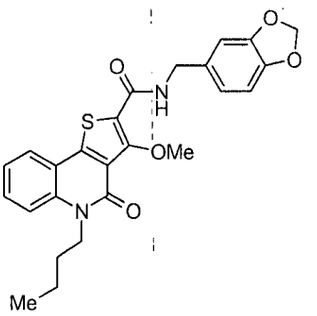
1121

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-fenilmetanamina.

LC/EM 421 (M+H).

Ejemplo 163.

Producción de N-(1,3-benzodioxol-5-ilmetil)-5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

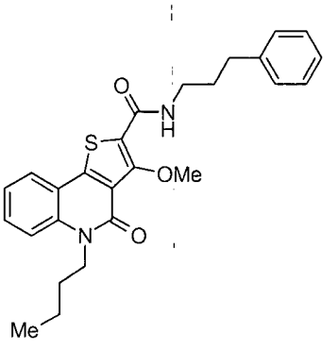


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 465 (M+H).

Ejemplo 164.

Producción de 5-butil-3-metoxi-4-oxo-N-(3-fenilpropil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



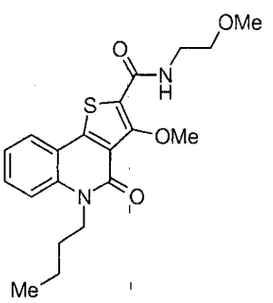
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-fenilpropan-1-amina.

122

LC/EM 449 (M+H).

Ejemplo 165.

Producción de 5-butil-3-metoxi-N-(2-metoxietil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

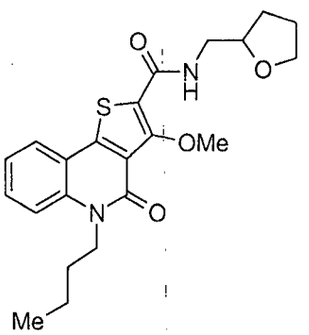


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-metoxietanamina.

LC/EM 389 (M+H).

Ejemplo 166.

Producción de 5-butil-3-metoxi-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

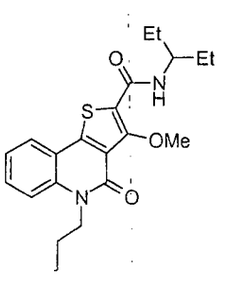


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 415 (M+H).

Ejemplo 167.

Producción de 5-butil-N-(1-etilpropil)-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



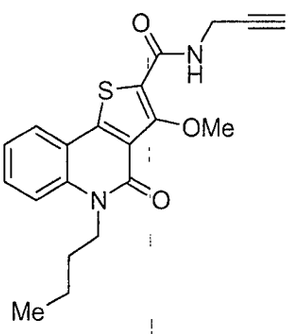
1123

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y pentan-3-amina.

LC/EM 401 (M+H).

Ejemplo 168.

Producción de 5-butil-3-metoxi-4-oxo-N-prop-2-in-1-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

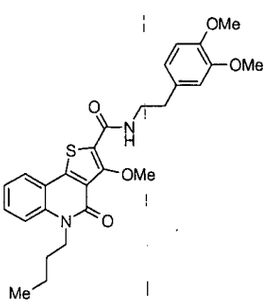


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y prop-2-in-1-amina.

LC/EM 369 (M+H).

Ejemplo 169.

Producción de 5-butil-N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



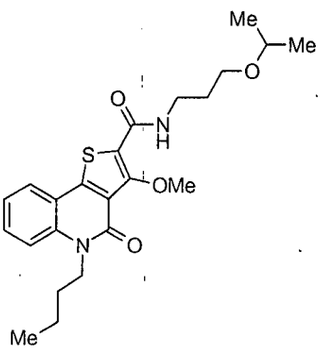
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-(3.4-dimetoxifenil)etanamina.

1124

LC/EM 495 (M+H).

Ejemplo 170.

Producción de 5-butil-3-metoxi-N-[3-(1-metiletoxi)propil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

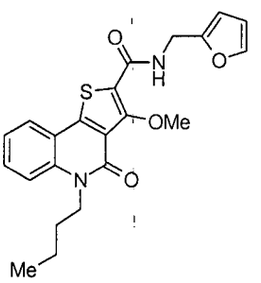


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-(1-metiletoxi)propan-1-amina.

LC/EM 431 (M+H).

Ejemplo 171.

Producción de 5-butil-N-(furan-2-ilmetil)-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

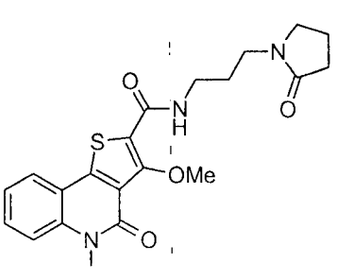


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-furan-2-ilmetanamina.

LC/EM 411 (M+H).

Ejemplo 172.

Producción de 5-butil-3-metoxi-4-oxo-N-[3-(2-oxopirrolidin-1-il)propil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



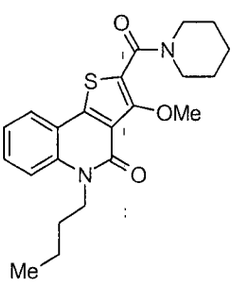
1125

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-(3-aminopropil)pirrolidin-2-ona.

LC/EM 456 (M+H).

Ejemplo 173.

Producción de 5-butil-3-metoxi-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

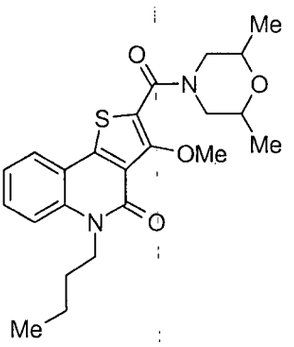


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y piperidina.

LC/EM 399 (M+H).

Ejemplo 174.

Producción de 5-butil-2-[(2.6-dimetilmorfolin-4-il)carbonil]-3-metoxitieno[3,2-c]quinolin-4(5H)-ona.



Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

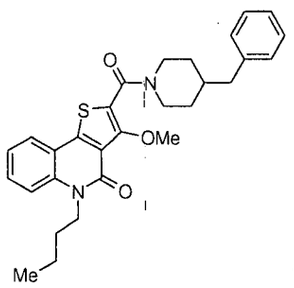
1126

103 y 2.6-dimetilmorfolina.

LC/EM 429 (M+H).

Ejemplo 175.

Producción de 2-[(4-bencilpiperidin-1-il)carbonil]-5-butil-3-metoxitieno[3,2-c]quinolin-4(5H)-ona.

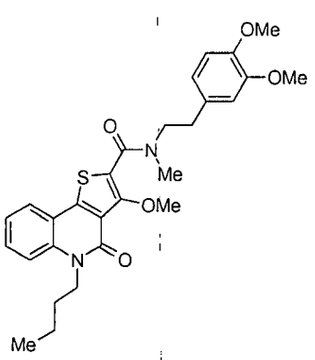


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 4-bencilpiperidina.

LC/EM 489 (M+H).

Ejemplo 176.

Producción de 5-butil-N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

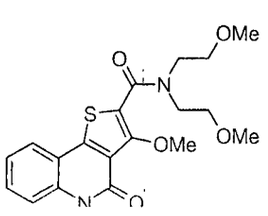


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-(3.4-dimetoxifenil)-N-metiletanamina.

LC/EM 509 (M+H).

Ejemplo 177.

Producción de 5-butil-3-metoxi-N,N-bis(2-metoxietil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



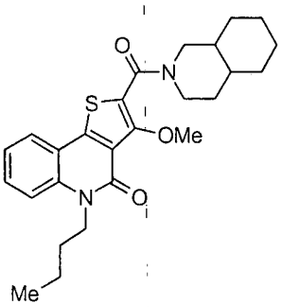
1127

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-metoxi-N-(2-metoxietil)etanamina.

LC/EM 447 (M+H).

Ejemplo 178.

Producción de 5-butil-3-metoxi-2-(octahidroisoquinolin-2(1H)-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

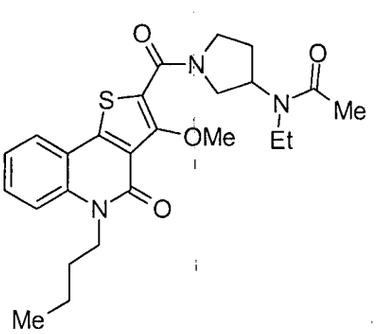


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y decahidroisoquinolina.

LC/EM 453 (M+H).

Ejemplo 179.

Producción de N-{1-[(5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-il)carbonil]pirrolidin-3-il}-N-etilacetamida.



Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

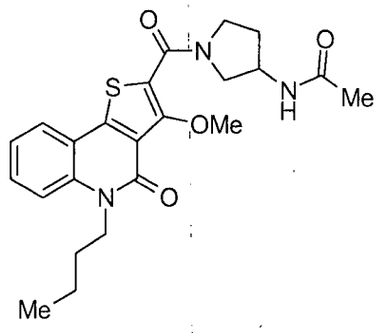
1128

103 y N-etil-N-pirrolidin-3-ilacetamida.

LC/EM 470 (M+H).

Ejemplo 180.

Producción de N-{1-[(5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-il)carbonil]pirrolidin-3-il}acetamida.

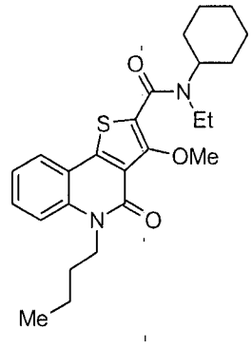


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N-pirrolidin-3-ilacetamida.

LC/EM 442 (M+H).

Ejemplo 181.

Producción de 5-butil-N-ciclohexil-N-etil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



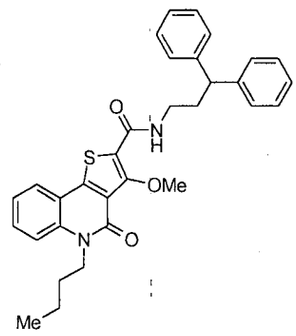
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N-etilciclohexanamina.

LC/EM 441 (M+H).

Ejemplo 182.

Producción de 5-butil-N-(3.3-difenilpropil)-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

1129

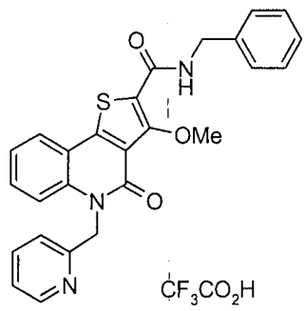


Del mismo modo que en el Ejemplo 160, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3.3-difenilpropan-1-amina.

LC/EM 525 (M+H).

Ejemplo 183.

Producción de N-bencil-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

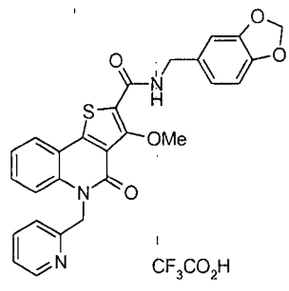


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-fenilmetanamina.

LC/EM 456 (M+H).

Ejemplo 184.

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

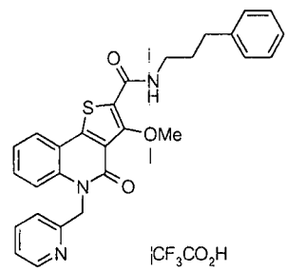


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 500 (M+H).

Ejemplo 185.

Producción de 3-metoxi-4-oxo-N-(3-fenilpropil)-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

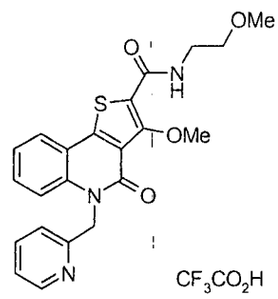


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-fenilpropan-1-amina.

LC/EM 484 (M+H).

Ejemplo 186.

Producción de 3-metoxi-N-(2-metoxietil)-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



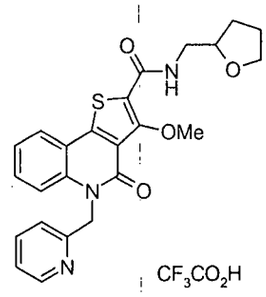
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-metoxietanamina.

LC/EM 424 (M+H).

1131

Ejemplo 187.

Producción de 3-metoxi-4-oxo-5-(piridin-2-ilmetil)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

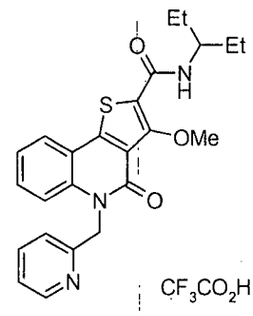


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 450 (M+H).

Ejemplo 188.

Producción de N-(1-etilpropil)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

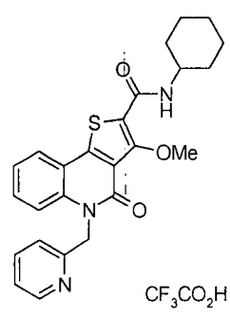


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y pentan-3-amina.

LC/EM 436 (M+H).

Ejemplo 189.

Producción de N-ciclohexil-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



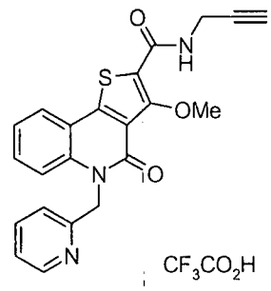
1132

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y ciclohexanamina.

LC/EM 448 (M+H).

Ejemplo 190.

Producción de 3-metoxi-4-oxo-N-prop-2-in-1-il-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

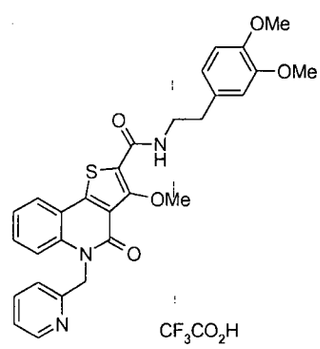


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y prop-2-in-1-amina.

LC/EM 404 (M+H).

Ejemplo 191.

Producción de N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



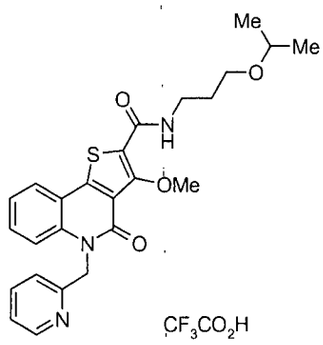
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-(3.4-dimetoxifenil)etanamina.

1133

LC/EM 530 (M+H).

Ejemplo 192.

Producción de 3-metoxi-N-[3-(1-metiletoxi)propil]-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

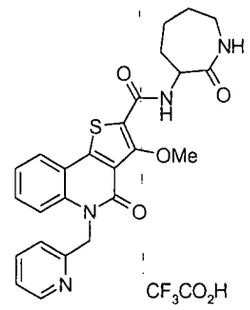


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-(1-metiletoxi)propan-1-amina.

LC/EM 466 (M+H).

Ejemplo 193.

Producción de 3-metoxi-4-oxo-N-(2-oxoazepan-3-il)-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

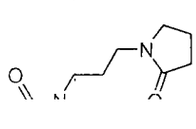


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-aminoazepan-2-ona.

LC/EM 477 (M+H).

Ejemplo 194

Producción de 3-metoxi-4-oxo-N-[3-(2-oxopirrolidin-1-il)propil]-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida,



1134

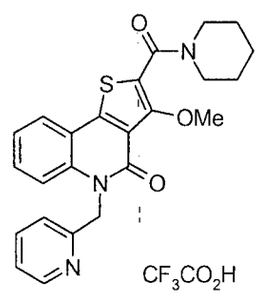
trifluoroacetato

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-(3-aminopropil)pirrolidin-2-ona.

LC/EM 491 (M+H).

Ejemplo 195

Producción de 3-metoxi-2-(piperidin-1-ilcarbonil)-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

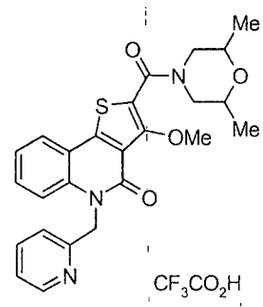


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y piperidina.

LC/EM 434 (M+H).

Ejemplo 196

Producción de 2-[(2.6-dimetilmorfolin-4-il)carbonil]-3-metoxi-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



Del mismo modo que en el Ejemplo 1, el compuesto del

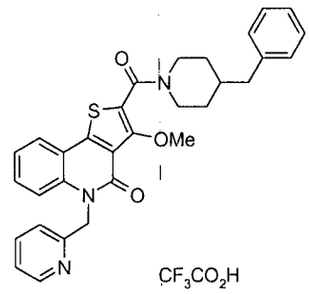
1735

título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2.6-dimetilmorfolina.

LC/EM 464 (M+H).

Ejemplo 197

Producción de 2-[(4-bencilpiperidin-1-il)carbonil]-3-metoxi-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

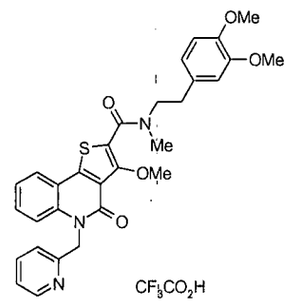


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 4-bencilpiperidina.

LC/EM 524 (M+H).

Ejemplo 198

Producción de N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-N-metil-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

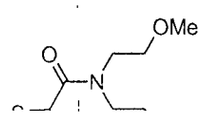


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-(3.4-dimetoxifenil)-N-metiletanamina.

LC/EM 544 (M+H).

Ejemplo 199

Producción de 3-metoxi-N,N-bis(2-metoxietil)-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida,



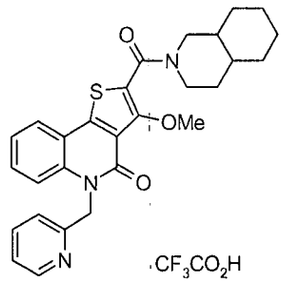
trifluoroacetato

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-metoxi-N-(2-metoxietil)etanamina.

LC/EM 482 (M+H).

Ejemplo 200

Producción de 3-metoxi-2-(octahidroisoquinolin-2(1H)-ilcarbonil)-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

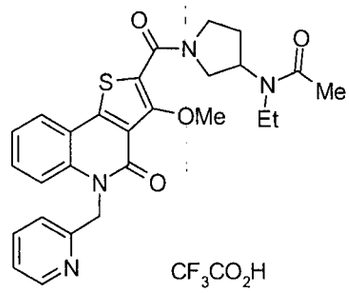


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y decahidroisoquinolina.

LC/EM 488 (M+H).

Ejemplo 201

Producción de N-etil-N-(1-{[3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}pirrolidin-3-il)acetamida, trifluoroacetato

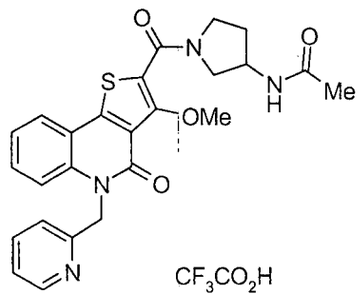


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N-etil-N-pirrolidin-3-ilacetamida.

LC/EM 505 (M+H).

Ejemplo 202

Producción de N-(1-{[3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}pirrolidin-3-il)acetamida, trifluoroacetato

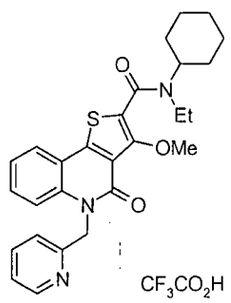


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N-pirrolidin-3-ilacetamida.

LC/EM 477 (M+H).

Ejemplo 203

Producción de N-ciclohexil-N-etil-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N-etilciclohexanamina.

LC/EM 476 (M+H).

Ejemplo 204

1138

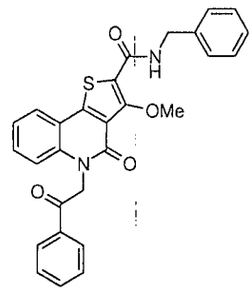
Producción de N-(3.3-difenilpropil)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

Del mismo modo que en el Ejemplo 160, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3.3-difenilpropan-1-amina.

LC/EM 560 (M+H).

Ejemplo 205

Producción de N-bencil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

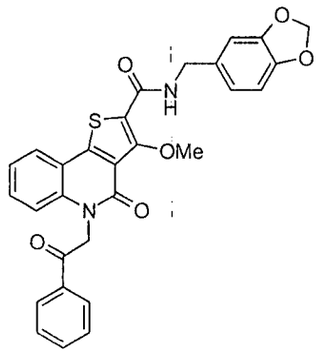


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-fenilmetanamina.

LC/EM 483 (M+H).

Ejemplo 206

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



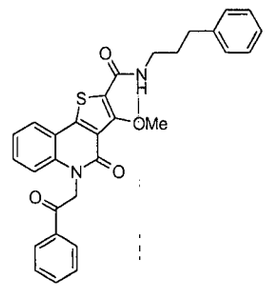
1139

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 527 (M+H).

Ejemplo 207

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(3-fenilpropil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

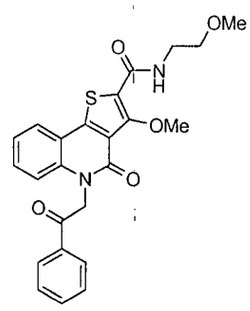


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-fenilpropan-1-amina.

LC/EM 511 (M+H).

Ejemplo 208

Producción de 3-metoxi-N-(2-metoxietil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-metoxietanamina.

LC/EM 451 (M+H).

Ejemplo 209

1140

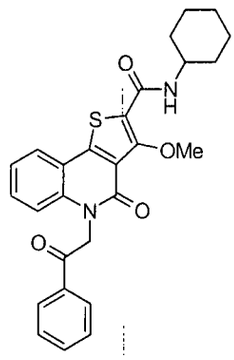
Producción de N-(1-etilpropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y pentan-3-amina.

LC/EM 463 (M+H).

Ejemplo 210

Producción de N-ciclohexil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

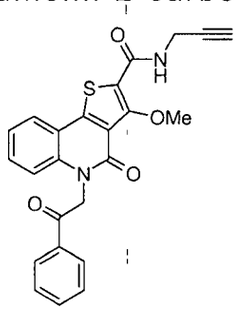


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y ciclohexanamina.

LC/EM 475 (M+H).

Ejemplo 211

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-prop-2-in-1-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



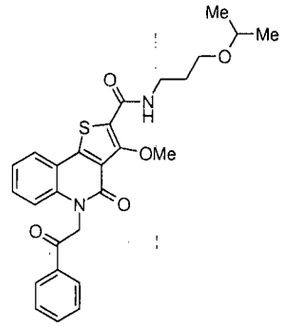
1141

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y prop-2-in-1-amina.

LC/EM 431 (M+H).

Ejemplo 212

Producción de 3-metoxi-N-[3-(1-metiletoxi)propil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

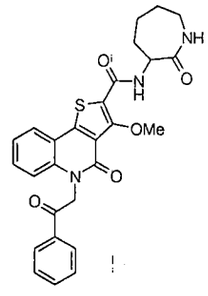


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-(1-metiletoxi)propan-1-amina.

LC/EM 493 (M+H).

Ejemplo 213

Producción de 3-metoxi-4-oxo-N-(2-oxoazepan-3-il)-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3-aminoazepan-2-ona.

LC/EM 504 (M+H).

Ejemplo 214

1142

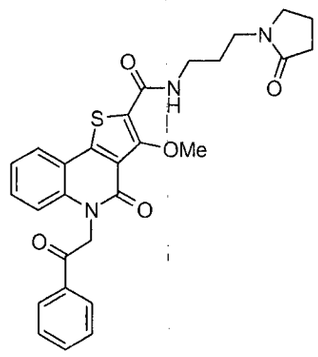
Producción de N-(furan-2-ilmetil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-furan-2-ilmetanamina.

LC/EM 473 (M+H).

Ejemplo 215

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-[3-(2-oxopirrolidin-1-il)propil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

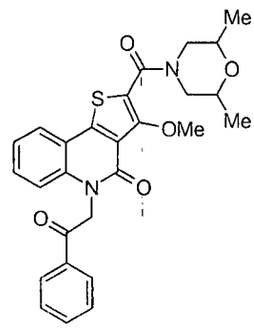


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-(3-aminopropil)pirrolidin-2-ona.

LC/EM 518 (M+H).

Ejemplo 216

Producción de 2-[(2.6-dimetilmorfolin-4-il)carbonil]-3-metoxi-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona



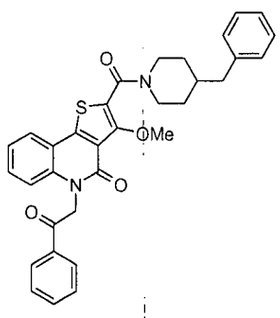
1143

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2.6-dimetilmorfolina.

LC/EM 491 (M+H).

Ejemplo 217

Producción de 2-[(4-bencilpiperidin-1-il)carbonil]-3-metoxi-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona

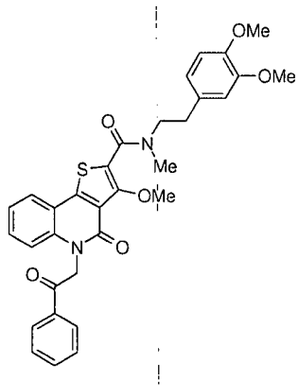


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 4-bencilpiperidina.

LC/EM 551 (M+H).

Ejemplo 218

Producción de N-[2-(3.4-dimetoxifenil)etil]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



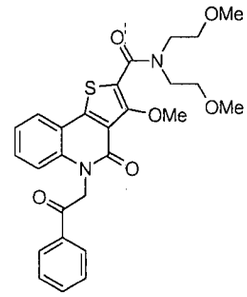
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-(3.4-dimetoxifenil)-N-metiletanamina.

1144

LC/EM 571 (M+H).

Ejemplo 219

Producción de 3-metoxi-N,N-bis(2-metoxietil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

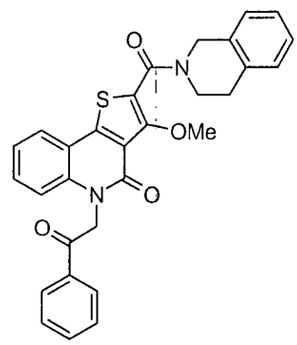


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-metoxi-N-(2-metoxietil)etanamina.

LC/EM 509 (M+H).

Ejemplo 220

Producción de 2-(3.4-dihidroisoquinolin-2(1H)-ilcarbonil)-3-metoxi-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona

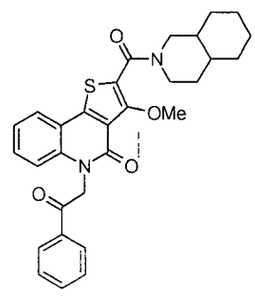


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1.2,3.4-tetrahidroisoquinolina.

LC/EM 509 (M+H).

Ejemplo 221

Producción de 3-metoxi-2-(octahidroisoquinolin-2(1H)-ilcarbonil)-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona



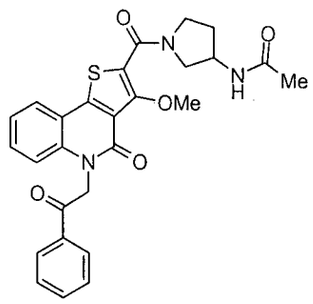
1145

Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y decahidroisoquinolina.

LC/EM 515 (M+H).

Ejemplo 222

Producción de N-(1-{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}pirrolidin-3-il)acetamida

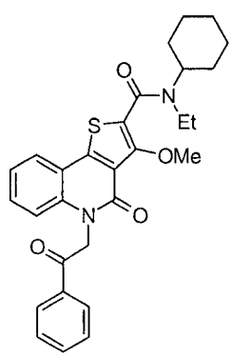


Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N-pirrolidin-3-ilacetamida.

LC/EM 504 (M+H).

Ejemplo 223

Producción de N-ciclohexil-N-etil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



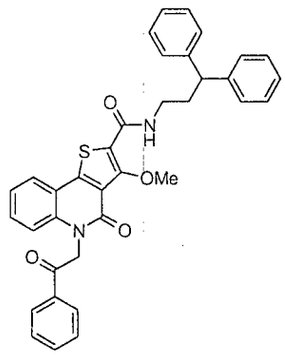
Del mismo modo que en el Ejemplo 1, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y N-etilciclohexanamina.

1146

LC/EM 503 (M+H).

Ejemplo 224

Producción de N-(3.3-difenilpropil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

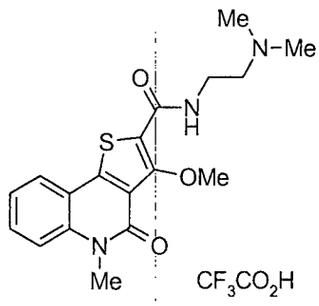


Del mismo modo que en el Ejemplo 160, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 3.3-difenilpropan-1-amina.

LC/EM 587 (M+H).

Ejemplo 225

Producción de N-[2-(dimetilamino)etil]-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

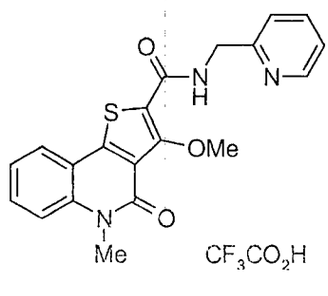


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N,N-dimetiletan-1,2-diamina.

LC/EM 360 (M+H).

Ejemplo 226

Producción de 3-metoxi-5-metil-4-oxo-N-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



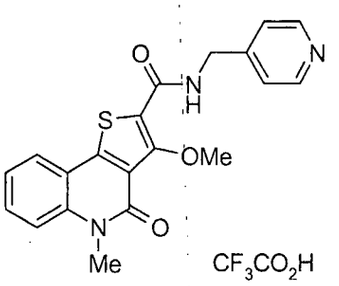
1147

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-piridin-2-ilmetanamina.

LC/EM 380 (M+H).

Ejemplo 227

Producción de 3-metoxi-5-metil-4-oxo-N-(piridin-4-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

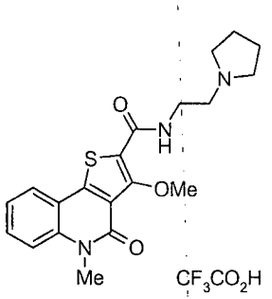


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-piridin-4-ilmetanamina.

LC/EM 380 (M+H).

Ejemplo 228

Producción de 3-metoxi-5-metil-4-oxo-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



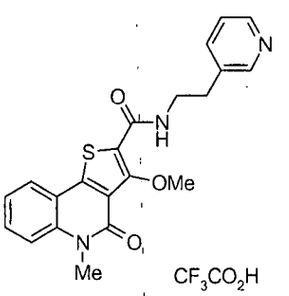
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-pirrolidin-1-iletanamina.

LC/EM 386 (M+H).

1148

Ejemplo 229

Producción de 3-metoxi-5-metil-4-oxo-N-(2-piridin-3-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

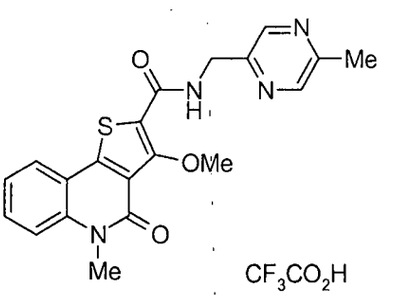


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-piridin-3-iletanamina.

LC/EM 394 (M+H).

Ejemplo 230

Producción de 3-metoxi-5-metil-N-[(5-metilpirazin-2-il)metil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

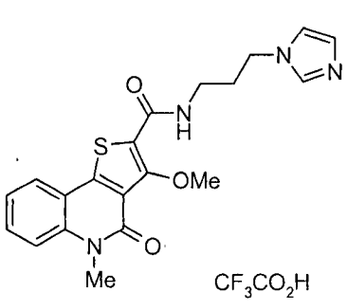


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-(5-metilpirazin-2-il)metanamina.

LC/EM 395 (M+H).

Ejemplo 231

Producción de N-[3-(1H-imidazol-1-il)propil]-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



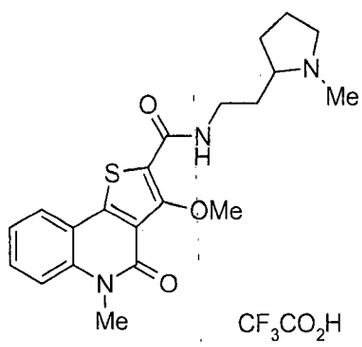
1169

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 397 (M+H).

Ejemplo 232

Producción de 3-metoxi-5-metil-N-[2-(1-metilpirrolidin-2-il)etil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

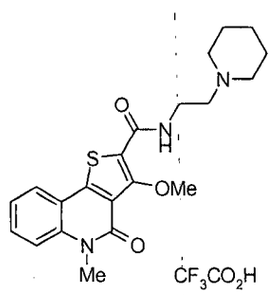


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-(1-metilpirrolidin-2-il)etanamina.

LC/EM 400 (M+H).

Ejemplo 233

Producción de 3-metoxi-5-metil-4-oxo-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 2-piperidin-1-iletanamina.

LC/EM 400 (M+H).

Ejemplo 234

1150

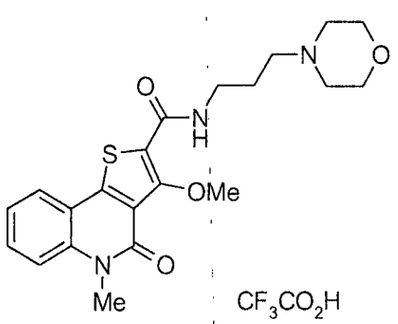
Producción de N-[3-(dietilamino)propil]-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N,N-dietilpropano-1,3-diamina.

LC/EM 402 (M+H).

Ejemplo 235

Producción de 3-metoxi-5-metil-N-(3-morfolin-4-ilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

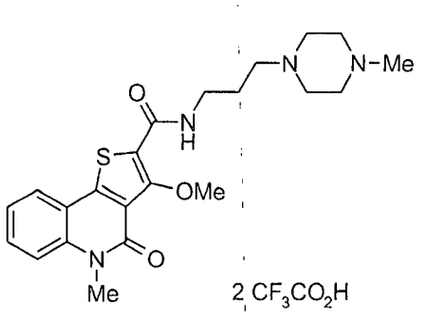


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-morfolin-4-ilpropan-1-amina.

LC/EM 416 (M+H).

Ejemplo 236

Producción de 3-metoxi-5-metil-N-[3-(4-metilpiperazin-1-il)propil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



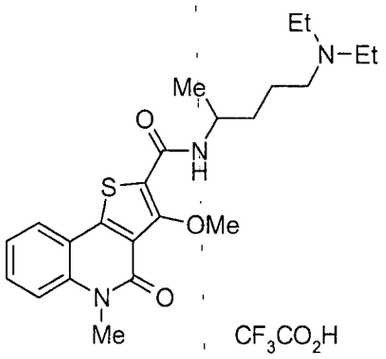
1151

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-(4-metilpiperazin-1-il)propan-1-amina.

LC/EM 429 (M+H).

Ejemplo 237

Producción de N-[4-(dietilamino)-1-metilbutil]-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

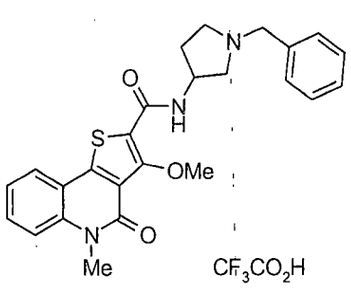


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N1,N1-dietilpentano-1,4-diamina.

LC/EM 430 (M+H).

Ejemplo 238

Producción de N-(1-bencilpirrolidin-3-il)-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



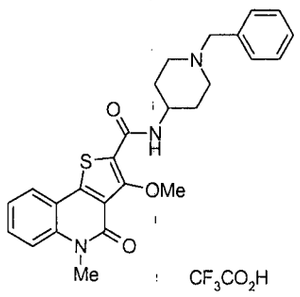
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-bencilpirrolidin-3-amina.

LC/EM 448 (M+H).

Ejemplo 239

1152

Producción de N-(1-bencilpiperidin-4-il)-3-metoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

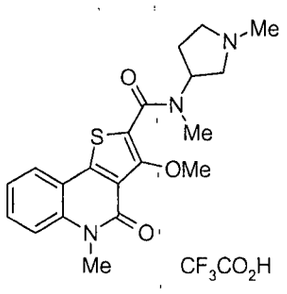


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-bencilpiperidin-4-amina.

LC/EM 462 (M+H).

Ejemplo 240

Producción de 3-metoxi-N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

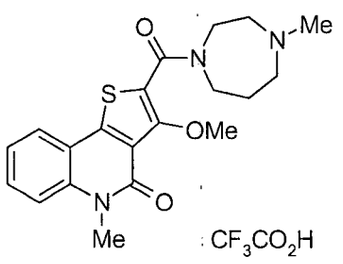


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N,1-dimetilpirrolidin-3-amina.

LC/EM 386 (M+H).

Ejemplo 241

Producción de 3-metoxi-5-metil-2-[(4-metil-1,4-diazepan-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



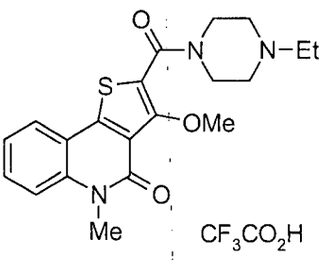
1153

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-metil-1,4-diazepano.

LC/EM 386 (M+H).

Ejemplo 242

Producción de 2-[(4-etilpiperazin-1-il)carbonil]-3-metoxi-5-metiltieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

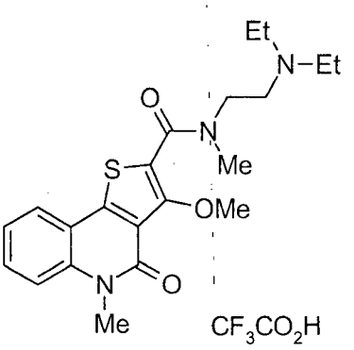


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-etilpiperazina.

LC/EM 386 (M+H).

Ejemplo 243

Producción de N-[2-(dietilamino)etil]-3-metoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y N,N-dietil-N'-metiletan-1,2-diamina.

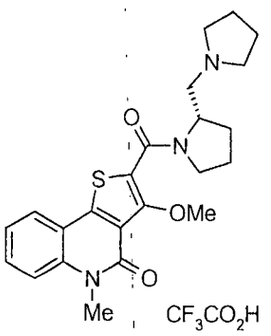
LC/EM 402 (M+H).

Ejemplo 244

Producción de 3-metoxi-5-metil-2-{[(2S)-2-(pirrolidin-1-

1154

ilmetil)pirrolidin-1-il]carbonil}tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

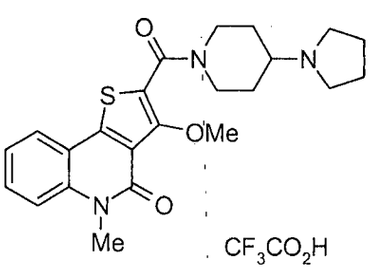


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-[(2S)-pirrolidin-2-ilmetil]pirrolidina.

LC/EM 426 (M+H).

Ejemplo 245

Producción de 3-metoxi-5-metil-2-[(4-pirrolidin-1-ilpiperidin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

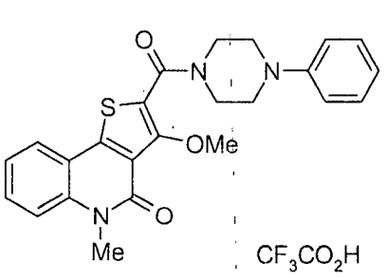


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 4-pirrolidin-1-ilpiperidina.

LC/EM 426 (M+H).

Ejemplo 246

Producción de 3-metoxi-5-metil-2-[(4-fenilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



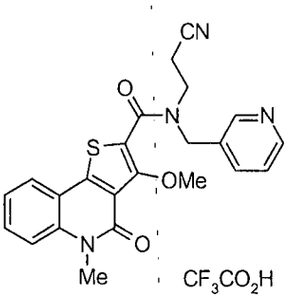
1155

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-fenilpiperazina.

LC/EM 434 (M+H).

Ejemplo 247

Producción de N-(2-cianoetil)-3-metoxi-5-metil-4-oxo-N-(piridin-3-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

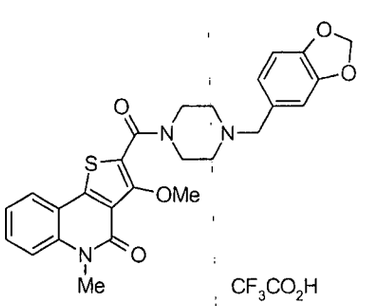


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 3-[(piridin-3-ilmetil)amino]propanonitrilo.

LC/EM 433 (M+H).

Ejemplo 248

Producción de 2-{[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]carbonil}-3-metoxi-5-metiltieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 84 y 1-(1,3-benzodioxol-5-ilmetil)piperazina.

LC/EM 492 (M+H).

Ejemplo 249

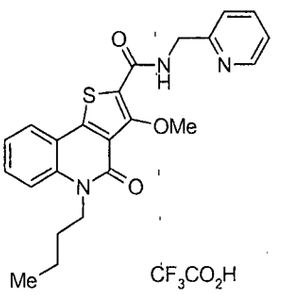
Producción de 5-butil-N-[2-(dimetilamino)etil]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N,N-dimetiletan-1,2-diamina.

LC/EM 402 (M+H).

Ejemplo 250

Producción de 5-butil-3-metoxi-4-oxo-N-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

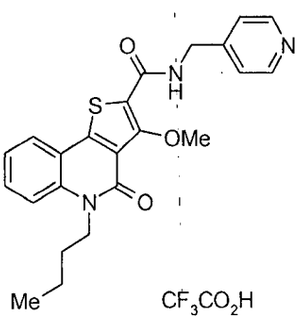


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-piridin-2-ilmetanamina.

LC/EM 422 (M+H).

Ejemplo 251

Producción de 5-butil-3-metoxi-4-oxo-N-(piridin-4-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



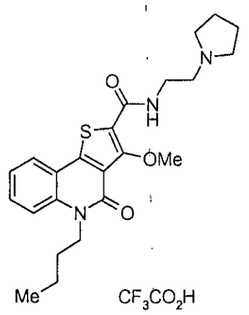
1157

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-piridin-4-ilmetanamina.

LC/EM 422 (M+H).

Ejemplo 252

Producción de 5-butil-3-metoxi-4-oxo-N-(2-pirrolidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

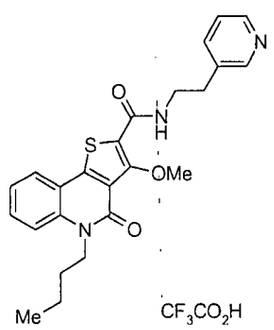


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-pirrolidin-1-iletanamina.

LC/EM 428 (M+H).

Ejemplo 253

Producción de 5-butil-3-metoxi-4-oxo-N-(2-piridin-3-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



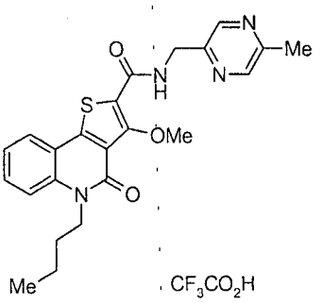
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-piridin-3-iletanamina.

LC/EM 436 (M+H).

Ejemplo 254

1158

Producción de 5-butil-3-metoxi-N-[(5-metilpirazin-2-il)metil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

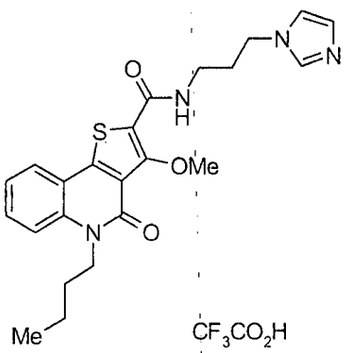


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-(5-metilpirazin-2-il)metanamina.

LC/EM 437 (M+H).

Ejemplo 255

Producción de 5-butil-N-[3-(1H-imidazol-1-il)propil]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

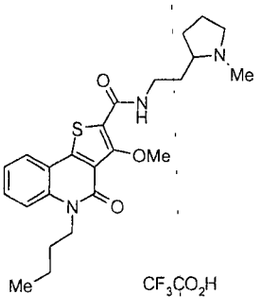


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 439 (M+H).

Ejemplo 256

Producción de 5-butil-3-metoxi-N-[2-(1-metilpirrolidin-2-il)etil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

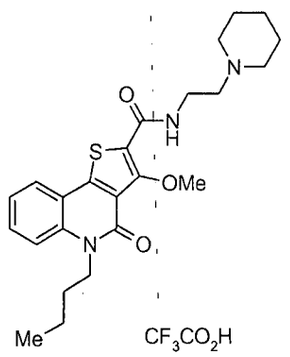


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-(1-metilpirrolidin-2-il)etanamina.

LC/EM 442 (M+H).

Ejemplo 257

Producción de 5-butil-3-metoxi-4-oxo-N-(2-piperidin-1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

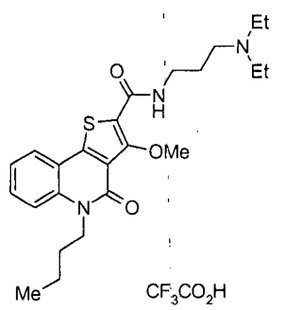


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 2-piperidin-1-iletanamina.

LC/EM 442 (M+H).

Ejemplo 258

Producción de 5-butil-N-[3-(dietilamino)propil]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N,N-dietilpropano-1,3-diamina.

LC/EM 444 (M+H).

Ejemplo 259

1160

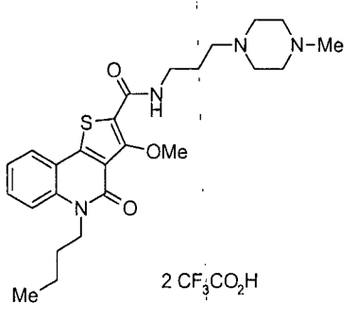
Producción de 5-butil-3-metoxi-N-(3-morfolin-4-ilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-morfolin-4-ilpropan-1-amina.

LC/EM 458 (M+H).

Ejemplo 260

Producción de 5-butil-3-metoxi-N-[3-(4-metilpiperazin-1-il)propil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

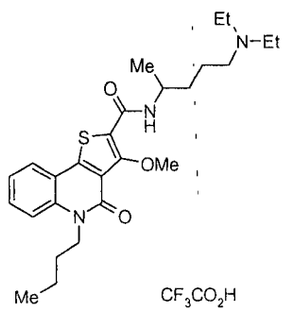


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-(4-metilpiperazin-1-il)propan-1-amina.

LC/EM 471 (M+H).

Ejemplo 261

Producción de 5-butil-N-[4-(dietilamino)-1-metilbutil]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



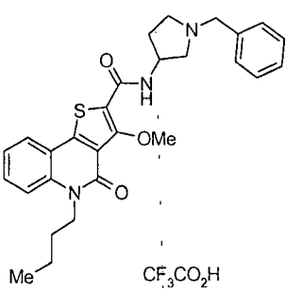
1161

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N^1,N^1-dietilpentano-1,4-diamina.

LC/EM 472 (M+H).

Ejemplo 262

Producción de N-(1-bencilpirrolidin-3-il)-5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

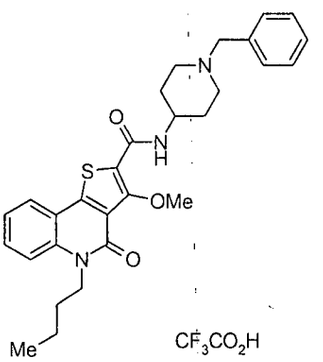


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-bencilpirrolidin-3-amina.

LC/EM 490 (M+H).

Ejemplo 263

Producción de N-(1-bencilpiperidin-4-il)-5-butil-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



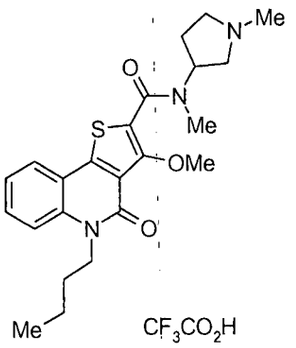
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-bencilpiperidin-4-amina.

LC/EM 504 (M+H).

1162

Ejemplo 264

Producción de 5-butil-3-metoxi-N-metil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

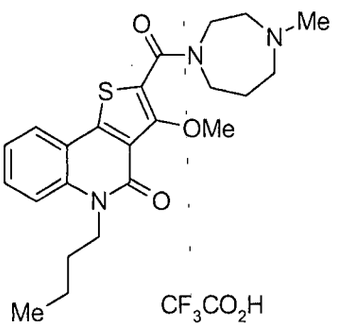


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N,1-dimetilpirrolidin-3-amina.

LC/EM 428 (M+H).

Ejemplo 265

Producción de 5-butil-3-metoxi-2-[(4-metil-1,4-diazepan-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

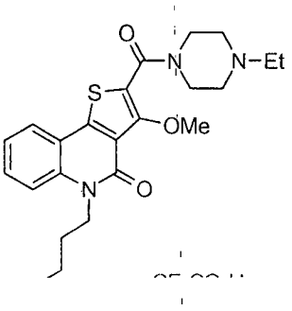


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-metil-1,4-diazepano.

LC/EM 428 (M+H).

Ejemplo 266

Producción de 5-butil-2-[(4-etilpiperazin-1-il)carbonil]-3-metoxitieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

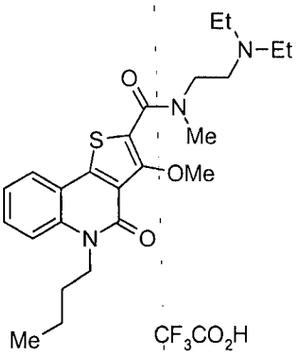


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-etilpiperazina.

LC/EM 428 (M+H).

Ejemplo 267

Producción de 5-butil-N-[2-(dietilamino)etil]-3-metoxi-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

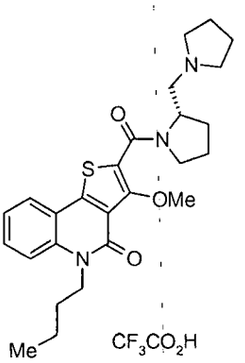


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 444 (M+H).

Ejemplo 268

Producción de 5-butil-3-metoxi-2-{[(2S)-2-(pirrolidin-1-ilmetil)pirrolidin-1-il]carbonil}tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



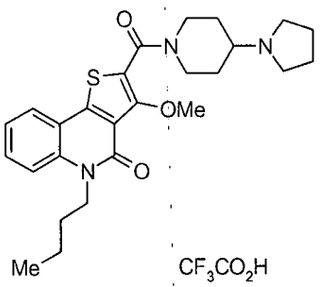
Del mismo modo que en el Ejemplo 5, el compuesto del

título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-[(2S)-pirrolidin-2-ilmetil]pirrolidina.

LC/EM 468 (M+H).

Ejemplo 269

Producción de 5-butil-3-metoxi-2-[(4-pirrolidin-1-ilpiperidin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

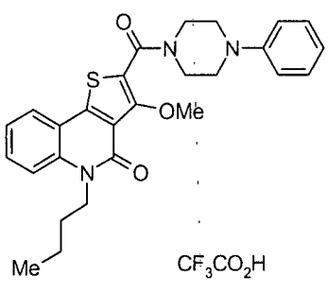


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 4-pirrolidin-1-ilpiperidina.

LC/EM 468 (M+H).

Ejemplo 270

Producción de 5-butil-3-metoxi-2-[(4-fenilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

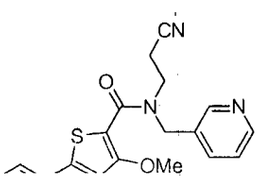


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-fenilpiperazina.

LC/EM 476 (M+H).

Ejemplo 271

Producción de 5-butil-N-(2-cianoetil)-3-metoxi-4-oxo-N-(piridin-3-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

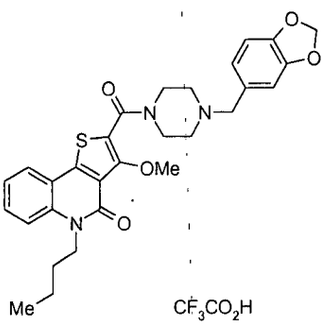


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 3-[(piridin-3-ilmetil)amino]propanonitrilo.

LC/EM 475 (M+H).

Ejemplo 272

Producción de 2-{[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]carbonil}-5-butil-3-metoxitieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

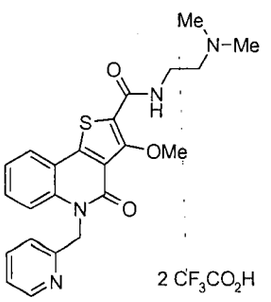


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 103 y 1-(1,3-benzodioxol-5-ilmetil)piperazina.

LC/EM 534 (M+H).

Ejemplo 273

Producción de N-[2-(dimetilamino)etil]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

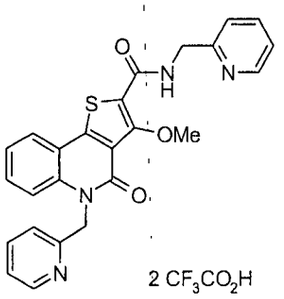


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N,N-dimetiletan-1,2-diamina.

LC/EM 437 (M+H).

Ejemplo 274

Producción de 3-metoxi-4-oxo-N,5-bis(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

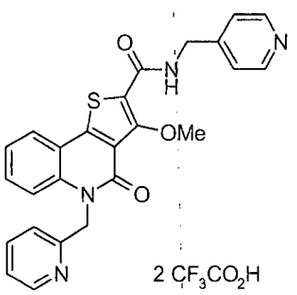


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-piridin-2-ilmetanamina.

LC/EM 457 (M+H).

Ejemplo 275

Producción de 3-metoxi-4-oxo-5-(piridin-2-ilmetil)-N-(piridin-4-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-piridin-4-ilmetanamina.

LC/EM 457 (M+H).

Ejemplo 276

Producción de 3-metoxi-4-oxo-5-(piridin-2-ilmetil)-N-(2-pirrolidin-

1167

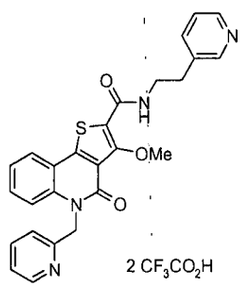
1-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-pirrolidin-1-iletanamina.

LC/EM 463 (M+H).

Ejemplo 277

Producción de 3-metoxi-4-oxo-N-(2-piridin-3-iletil)-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

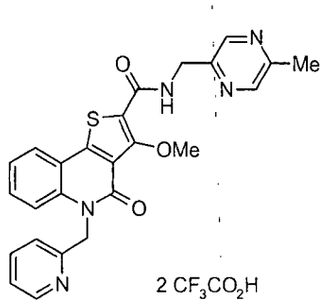


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-piridin-3-iletanamina.

LC/EM 471 (M+H).

Ejemplo 278

Producción de 3-metoxi-N-[(5-metilpirazin-2-il)metil]-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



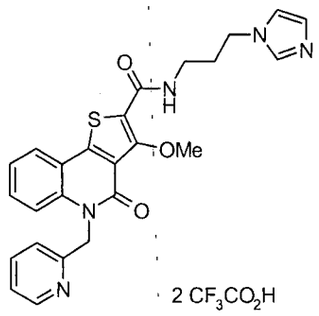
1168

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-(5-metilpirazin-2-il)metanamina.

LC/EM 472 (M+H).

Ejemplo 279

Producción de N-[3-(1H-imidazol-1-il)propil]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

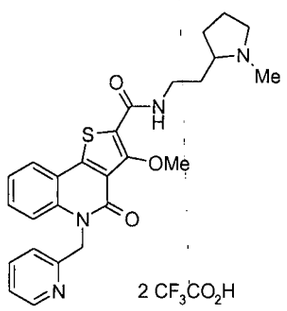


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 474 (M+H).

Ejemplo 280

Producción de 3-metoxi-N-[2-(1-metilpirrolidin-2-il)etil]-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



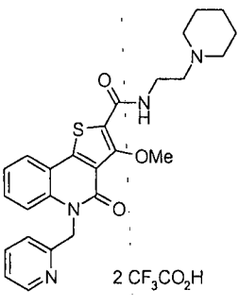
Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-(1-metilpirrolidin-2-il)etanamina.

LC/EM 477 (M+H).

1169

Ejemplo 281

Producción de 3-metoxi-4-oxo-N-(2-piperidin-1-iletil)-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

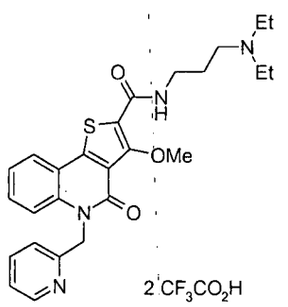


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 2-piperidin-1-iletanamina.

LC/EM 477 (M+H).

Ejemplo 282

Producción de N-[3-(dietilamino)propil]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

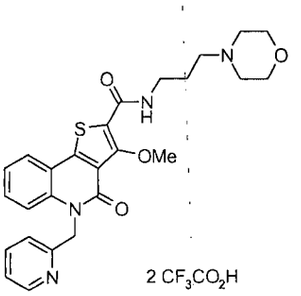


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N,N-dietilpropano-1,3-diamina.

LC/EM 479 (M+H).

Ejemplo 283

Producción de 3-metoxi-N-(3-morfolin-4-ilpropil)-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



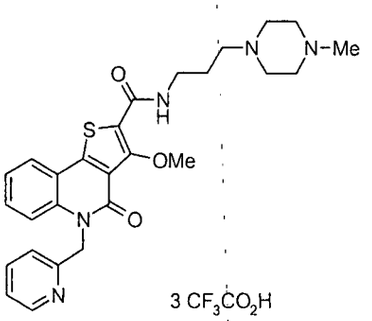
1170

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-morfolin-4-ilpropan-1-amina.

LC/EM 493 (M+H).

Ejemplo 284

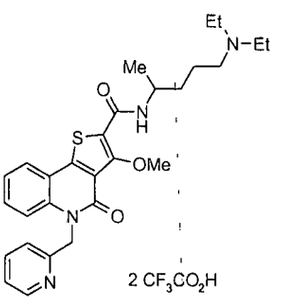
Producción de 3-metoxi-N-[3-(4-metilpiperazin-1-il)propil]-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida tri trifluoroacetato



Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-(4-metilpiperazin-1-il)propan-1-amina.

Ejemplo 285

Producción de N-[4-(dietilamino)-1-metilbutil]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



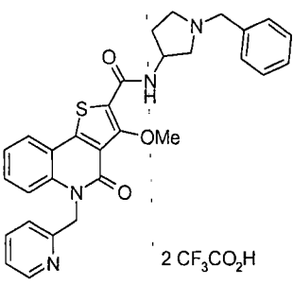
Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N1,N1-dietilpentano-1,4-diamina.

LC/EM 507 (M+H).

1171

Ejemplo 286

Producción de N-(1-bencilpirrolidin-3-il)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

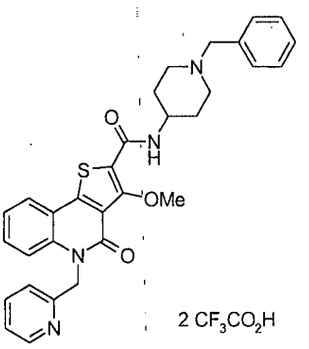


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-bencilpirrolidin-3-amina.

LC/EM 525 (M+H).

Ejemplo 287

Producción de N-(1-bencilpiperidin-4-il)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

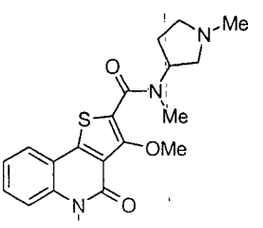


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-bencilpiperidin-4-amina.

LC/EM 539 (M+H).

Ejemplo 288

Producción de 3-metoxi-N-metil-N-(1-metilpirrolidin-3-il)-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

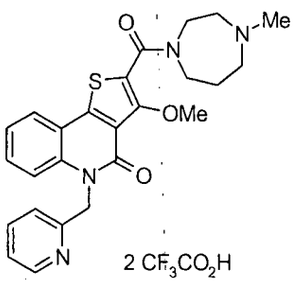


1172

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y N,1-dimetilpirrolidin-3-amina.

Ejemplo 289

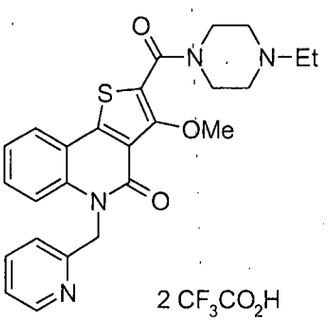
Producción de 3-metoxi-2-[(4-metil-1,4-diazepan-1-il)carbonil]-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato



Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-metil-1,4-diazepano.

Ejemplo 290

Producción de 2-[(4-etilpiperazin-1-il)carbonil]-3-metoxi-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato



Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-etilpiperazina.

Ejemplo 291

Producción de 3-metoxi-5-(piridin-2-ilmetil)-2-{[(2S)-2-(pirrolidin-

1173

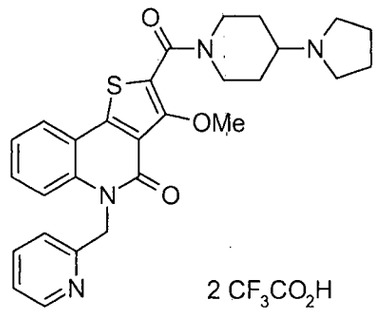
1-ilmetil)pirrolidin-1-il]carbonil}tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-[(2S)-pirrolidin-2-ilmetil]pirrolidina.

LC/EM 503 (M+H).

Ejemplo 292

Producción de 3-metoxi-5-(piridin-2-ilmetil)-2-[(4-pirrolidin-1-ilpiperidin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato

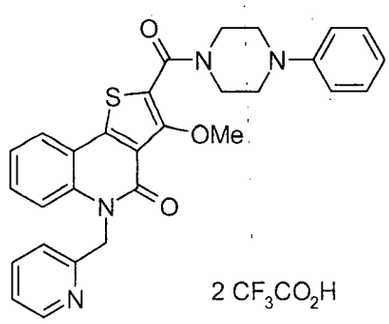


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 4-pirrolidin-1-ilpiperidina.

LC/EM 503 (M+H).

Ejemplo 293

Producción de 3-metoxi-2-[(4-fenilpiperazin-1-il)carbonil]-5-(piridin-2-ilmetil)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato



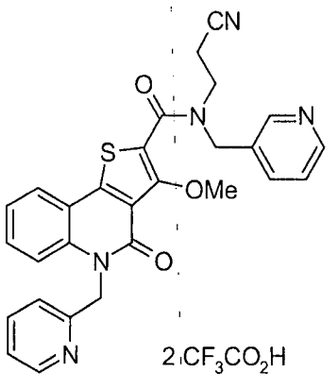
1174

Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 1-fenilpiperazina.

LC/EM 511 (M+H).

Ejemplo 294

Producción de N-(2-cianoetil)-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-N-(piridin-3-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

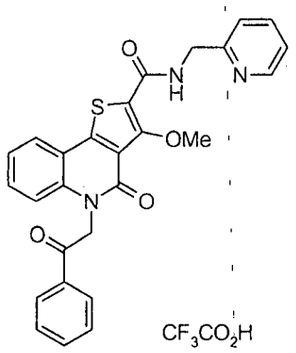


Del mismo modo que en el Ejemplo 3. el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 19 y 3-[(piridin-3-ilmetil)amino]propanonitrilo.

LC/EM 510 (M+H).

Ejemplo 295

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



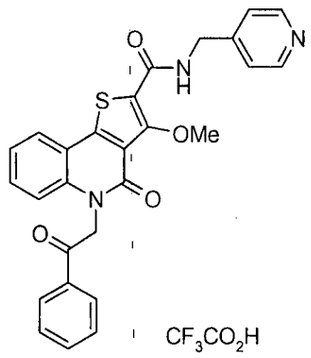
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-piridin-2-ilmetanamina.

1175

LC/EM 484 (M+H).

Ejemplo 296

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(piridin-4-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

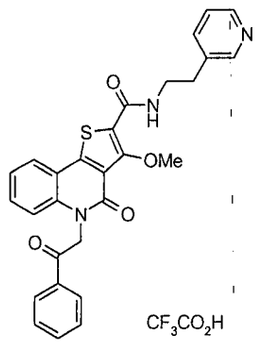


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-piridin-4-ilmetanamina.

LC/EM 484 (M+H).

Ejemplo 297

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(2-piridin-3-iletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

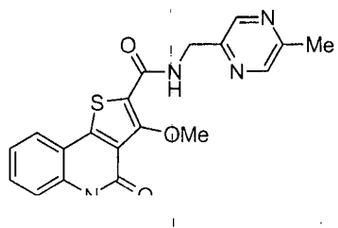


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 2-piridin-3-iletanamina.

LC/EM 498 (M+H).

Ejemplo 298

Producción de 3-metoxi-N-[(5-metilpirazin-2-il)metil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



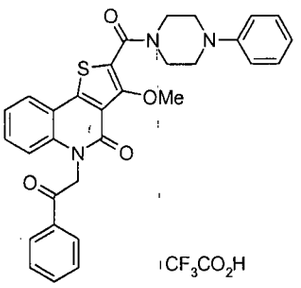
1176

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-(5-metilpirazin-2-il)metanamina.

LC/EM 499 (M+H).

Ejemplo 299

Producción de 3-metoxi-5-(2-oxo-2-feniletil)-2-[(4-fenilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

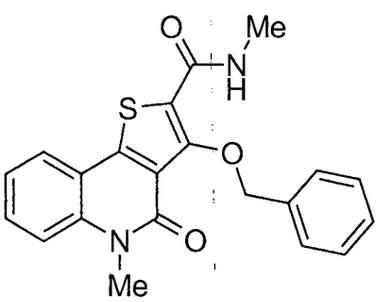


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 7 y 1-fenilpiperazina.

LC/EM 538 (M+H).

Ejemplo 300

Producción de 3-(benciloxi)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



A una solución (0,15 M, 0.40 ml, 60 μmol) del compuesto del Ejemplo de Referencia 91 en DMF se agregaron una solución

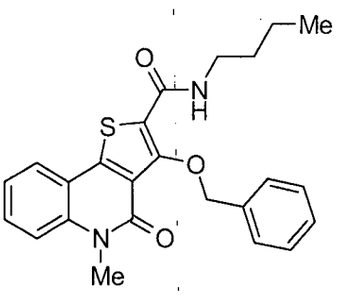
1177

(0.66 M, 0.10 ml, 66 µmol) de metanamina (solución 2.0 M de THF) en DMF y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y clorhidrato de WSC en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) se agregaron a la mezcla de reacción, la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (12.4 mg, 55%).

LC/EM 379 (M+H).

Ejemplo 301

Producción de 3-(benciloxi)-N-butil-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

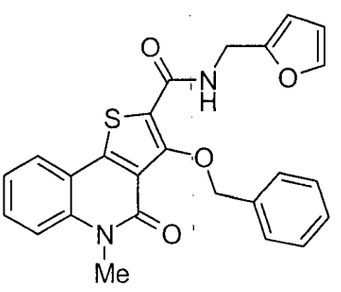


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y butan-1-amina.

LC/EM 421 (M+H).

Ejemplo 302

Producción de 3-(benciloxi)-N-(furan-2-ilmetil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

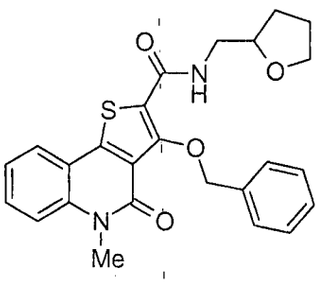


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-furan-2-ilmetanamina.

LC/EM 445 (M+H).

Ejemplo 303

Producción de 3-(benciloxi)-5-metil-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

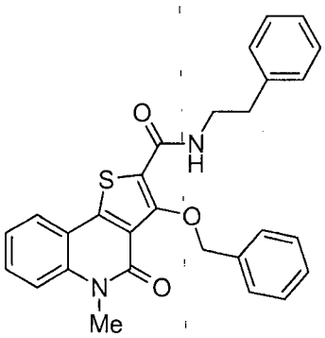


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 449 (M+H).

Ejemplo 304

Producción de 3-(benciloxi)-5-metil-4-oxo-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 2-feniletanamina.

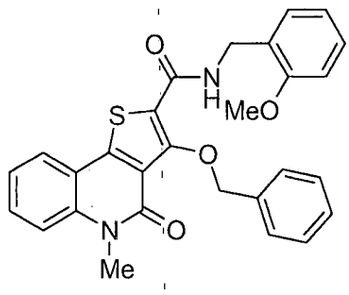
LC/EM 469 (M+H).

Ejemplo 305

Producción de 3-(benciloxi)-N-(2-metoxibencil)-5-metil-4-oxo-4,5-

1179

dihidrotieno[3,2-c]quinolin-2-carboxamida

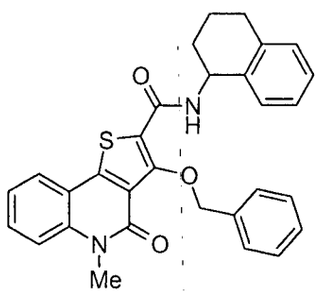


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-(2-metoxifenil)metanamina.

LC/EM 485 (M+H).

Ejemplo 306

Producción de 3-(benciloxi)-5-metil-4-oxo-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

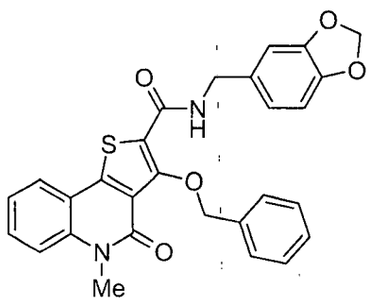


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1,2,3,4-tetrahidronaftalen-1-amina.

LC/EM 495 (M+H).

Ejemplo 307

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-(benciloxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

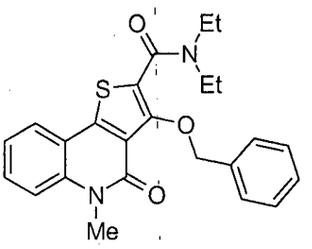


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 499 (M+H).

Ejemplo 308

Producción de 3-(benciloxi)-N,N-dietil-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

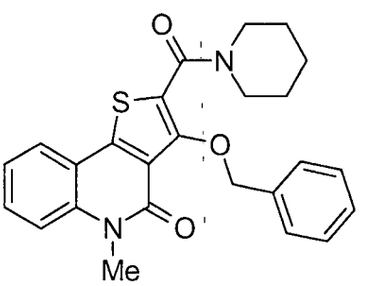


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N-etiletanamina.

LC/EM 421 (M+H).

Ejemplo 309

Producción de 3-(benciloxi)-5-metil-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona



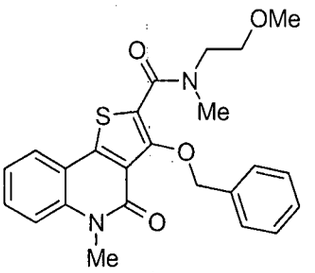
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y piperidina.

LC/EM 433 (M+H).

Ejemplo 310

Producción de 3-(benciloxi)-N-(2-metoxietil)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

1181

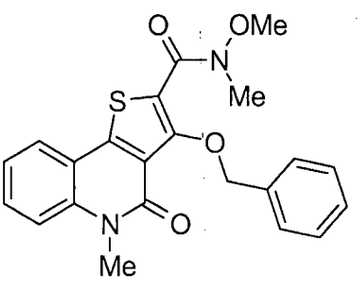


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 2-metoxi-N-metiletanamina.

LC/EM 437 (M+H).

Ejemplo 311

Producción de 3-(benciloxi)-N-metoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

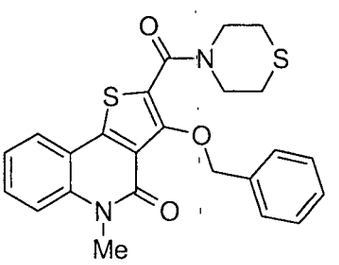


Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N-metoximetanamina, clorhidrato.

LC/EM 409 (M+H).

Ejemplo 312

Producción de 3-(benciloxi)-5-metil-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona



Del mismo modo que en el Ejemplo 5, el compuesto del

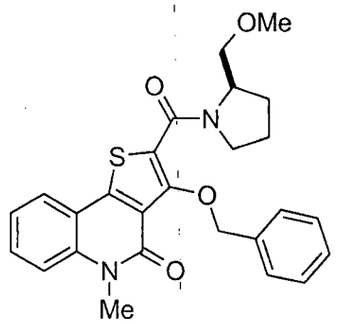
1182

título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y tiomorfolina.

LC/EM 451 (M+H).

Ejemplo 313

Producción de 3-(benciloxi)-2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metiltieno[3,2-c]quinolin-4(5H)-ona

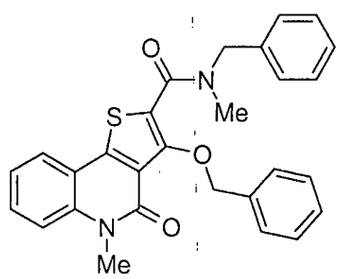


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 463 (M+H).

Ejemplo 314

Producción de N-bencil-3-(benciloxi)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



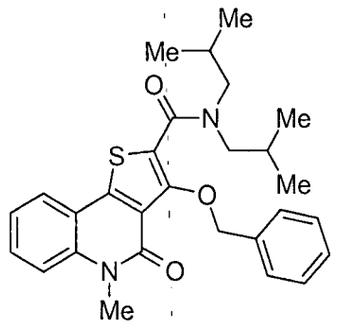
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N-metil-1-fenilmetanamina.

LC/EM 469 (M+H).

Ejemplo 315

Producción de 3-(benciloxi)-5-metil-N,N-bis(2-metilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

1183

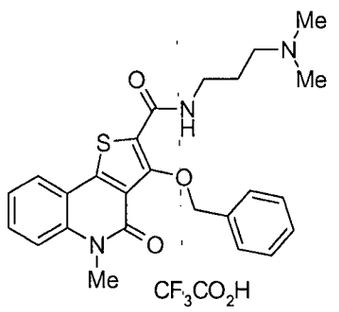


Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 477 (M+H).

Ejemplo 316

Producción de 3-(benciloxi)-N-[3-(dimetilamino)propil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

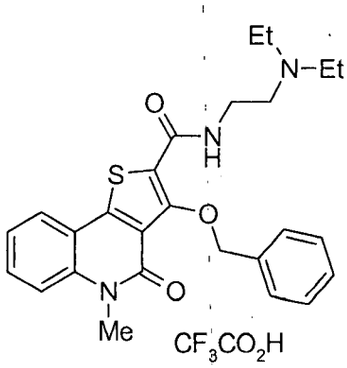


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N,N-dimetilpropano-1,3-diamina.

LC/EM 450 (M+H).

Ejemplo 317

Producción de 3-(benciloxi)-N-[2-(dietilamino)etil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



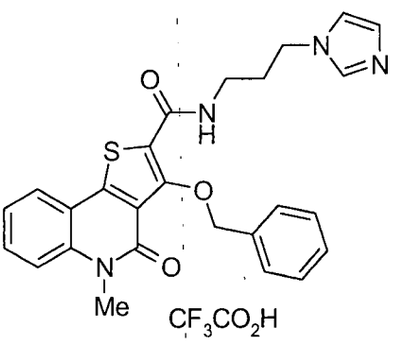
1184

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N,N-dietiletan-1,2-diamina.

LC/EM 464 (M+H).

Ejemplo 318

Producción de 3-(benciloxi)-N-[3-(1H-imidazol-1-il)propil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

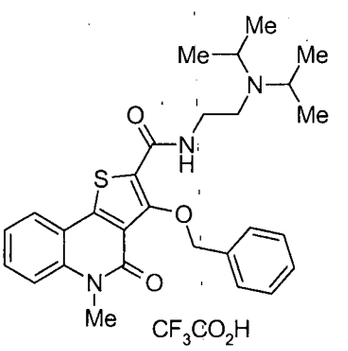


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 473 (M+H).

Ejemplo 319

Producción de 3-(benciloxi)-N-{2-[bis(1-metiletil)amino]etil}-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



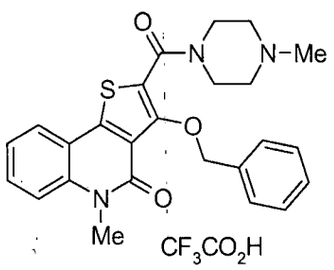
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N,N-bis(1-metiletil)etan-1,2-diamina.

1185

LC/EM 492 (M+H).

Ejemplo 320

Producción de 3-(benciloxi)-5-metil-2-[(4-metilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

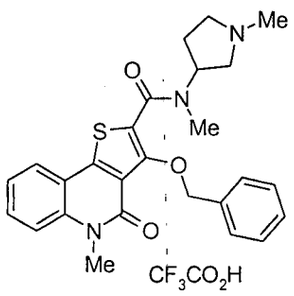


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-metilpiperazina.

LC/EM 448 (M+H).

Ejemplo 321

Producción de 3-(benciloxi)-N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

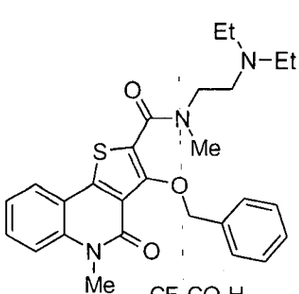


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N,1-dimetilpirrolidin-3-amina.

LC/EM 462 (M+H).

Ejemplo 322

Producción de 3-(benciloxi)-N-[2-(dietilamino)etil]-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



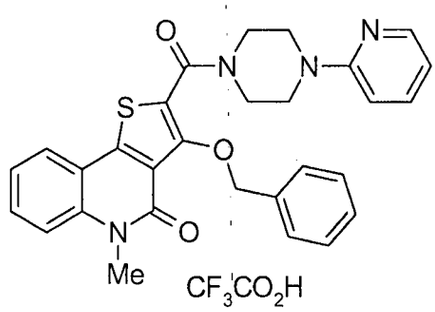
1186

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 478 (M+H).

Ejemplo 323

Producción de 3-(benciloxi)-5-metil-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

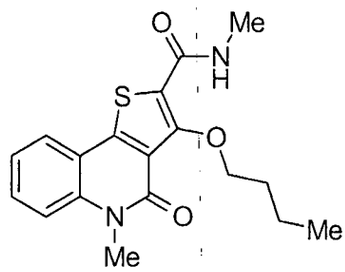


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 91 y 1-piridin-2-ilpiperazina.

LC/EM 511 (M+H).

Ejemplo 324

Producción de 3-butoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



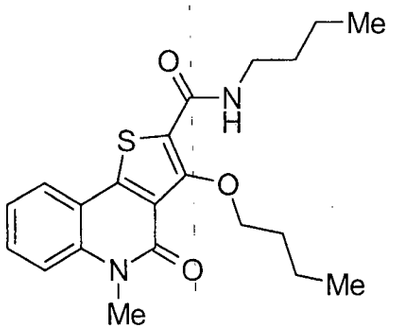
Del mismo modo que en el Ejemplo 300, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y metanamina (solución 2.0 M de THF).

LC/EM 345 (M+H).

1187

Ejemplo 325

Producción de 3-butoxi-N-butil-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

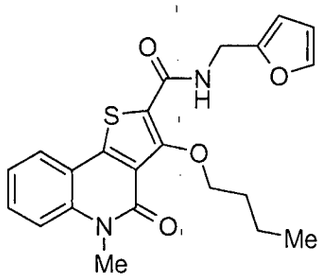


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y butan-1-amina.

LC/EM 387 (M+H).

Ejemplo 326

Producción de 3-butoxi-N-(furan-2-ilmetil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

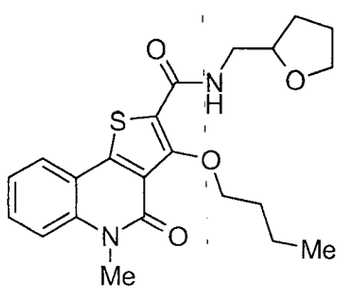


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-furan-2-ilmetanamina.

LC/EM 411 (M+H).

Ejemplo 327

Producción de 3-butoxi-5-metil-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



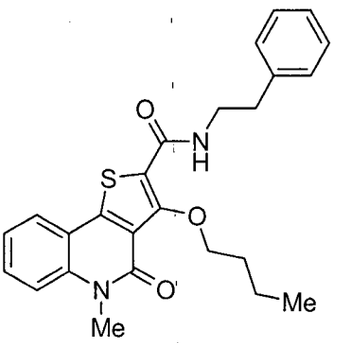
1188

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 415 (M+H).

Ejemplo 328

Producción de 3-butoxi-5-metil-4-oxo-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

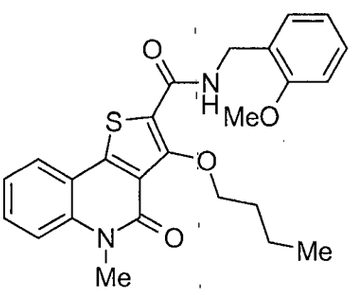


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 2-feniletanamina.

LC/EM 435 (M+H).

Ejemplo 329

Producción de 3-butoxi-N-(2-metoxibencil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



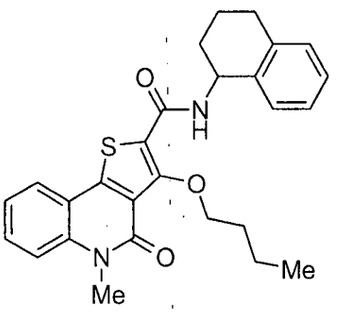
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-(2-metoxifenil)metanamina.

LC/EM 451 (M+H).

1189

Ejemplo 330

Producción de 3-butoxi-5-metil-4-oxo-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

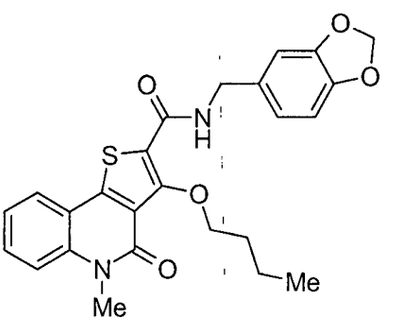


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1,2,3,4-tetrahidronaftalen-1-amina.

LC/EM 461 (M+H).

Ejemplo 331

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-butoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

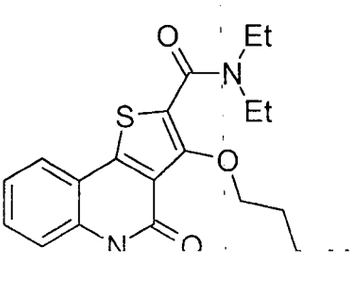


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 465 (M+H).

Ejemplo 332

Producción de 3-butoxi-N,N-dietil-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



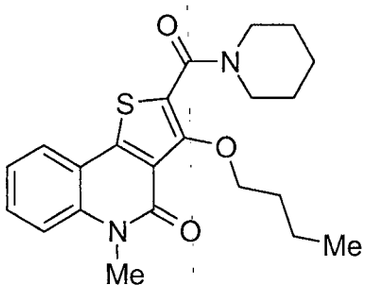
1190

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N-etiletanamina.

LC/EM 387 (M+H).

Ejemplo 333

Producción de 3-butoxi-5-metil-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona

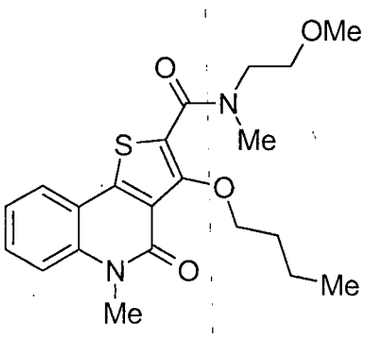


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y piperidina.

LC/EM 399 (M+H).

Ejemplo 334

Producción de 3-butoxi-N-(2-metoxietil)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

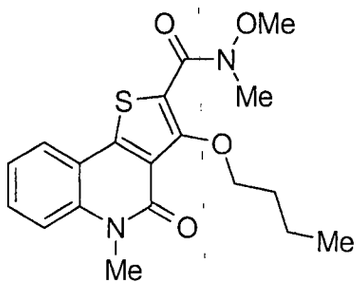
1191

92 y 2-metoxi-N-metiletanamina.

LC/EM 403 (M+H).

Ejemplo 335

Producción de 3-butoxi-N-metoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

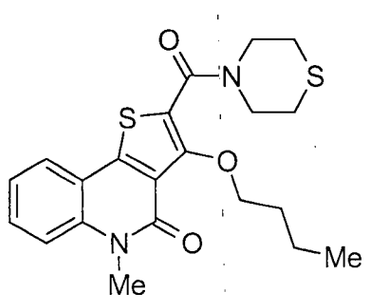


A una solución (0.15 M, 0.40 ml, 60 µmol) del compuesto del Ejemplo de Referencia 92 en DMF se agregaron una mezcla de una suspensión (0.66 M, 0.111 ml, 73 µmol) de N-metoximetanamina, clorhidrato en DMF y trietilamina (10.9 µml, 78 µmol), y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y clorhidrato de WSC en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) se agregaron a la mezcla de reacción, la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (16.6 mg, 74%).

LC/EM 375 (M+H).

Ejemplo 336

Producción de 3-butoxi-5-metil-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona



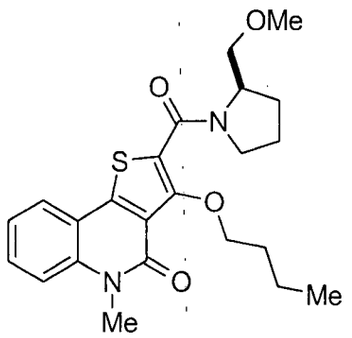
1192

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y tiomorfolina.

LC/EM 417 (M+H).

Ejemplo 337

Producción de 3-butoxi-2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metiltieno[3,2-c]quinolin-4(5H)-ona

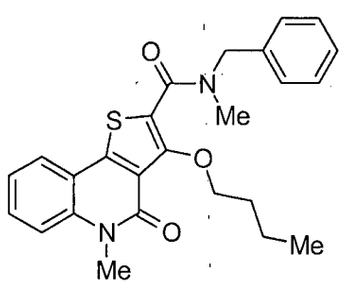


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 429 (M+H).

Ejemplo 338

Producción de N-bencil-3-butoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N-metil-1-fenilmetanamina.

LC/EM 435 (M+H).

Ejemplo 339

1193

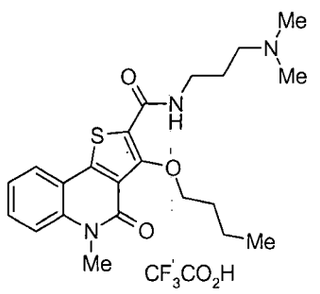
Producción de 3-butoxi-5-metil-N,N-bis(2-metilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 443 (M+H).

Ejemplo 340

Producción de 3-butoxi-N-[3-(dimetilamino)propil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

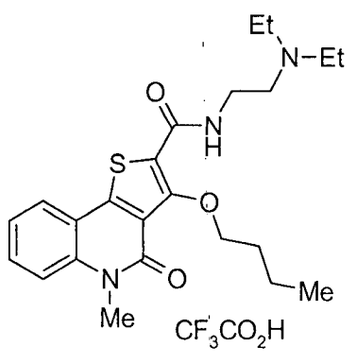


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N,N-dimetilpropano-1,3-diamina.

LC/EM 416 (M+H).

Ejemplo 341

Producción de 3-butoxi-N-[2-(dietilamino)etil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



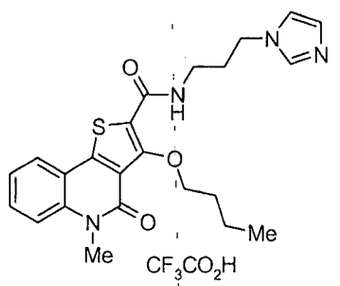
1194

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N,N-dietiletan-1,2-diamina.

LC/EM 430 (M+H).

Ejemplo 342

Producción de 3-butoxi-N-[3-(1H-imidazol-1-il)propil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

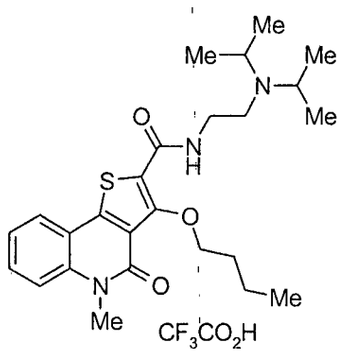


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 439 (M+H).

Ejemplo 343

Producción de N-{2-[bis(1-metiletil)amino]etil}-3-butoxi-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



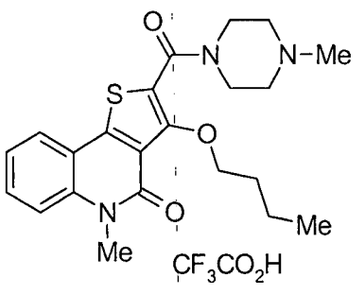
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 458 (M+H).

1795

Ejemplo 344

Producción de 3-butoxi-5-metil-2-[(4-metilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

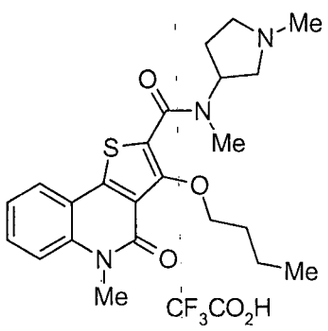


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-metilpiperazina.

LC/EM 414 (M+H).

Ejemplo 345

Producción de 3-butoxi-N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

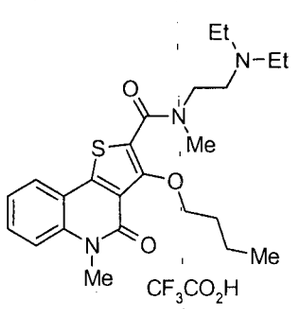


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N,1-dimetilpirrolidin-3-amina.

LC/EM 428 (M+H).

Ejemplo 346

Producción de 3-butoxi-N-[2-(dietilamino)etil]-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



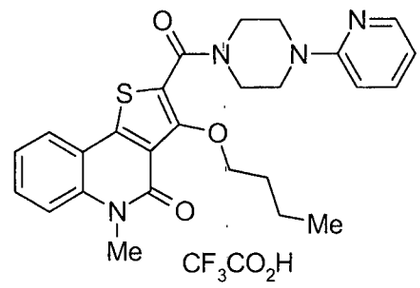
1196

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 444 (M+H).

Ejemplo 347

Producción de 3-butoxi-5-metil-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

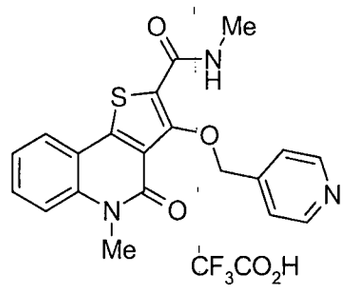


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 92 y 1-piridin-2-ilpiperazina.

LC/EM 477 (M+H).

Ejemplo 348

Producción de N,5-dimetil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



A una solución (0.10 M, 0.40 ml, 40 µmol) del compuesto del Ejemplo de Referencia 93 en DMF se agregaron una solución (0.66 M, 0.10 ml, 66 µmol) de metanamina (solución 2.0 M de THF) en DMF y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y

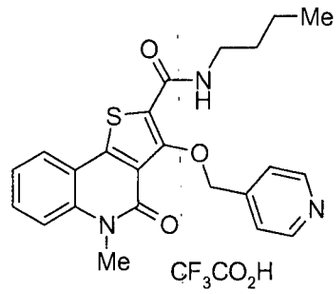
1197

WSCD en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) se agregaron a la mezcla de reacción, la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (13.2 mg, 67%).

LC/EM 380 (M+H).

Ejemplo 349

Producción de N-butil-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

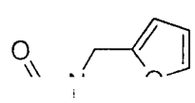


A una solución (0.10 M, 0.40 ml, 40 µmol) del compuesto del Ejemplo de Referencia 93 en DMF se agregaron una solución (0.66 M, 0.10 ml, 66 µmol) de butan-1-amina en DMF y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y WSC-D en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Se agregaron diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) a la mezcla de reacción, la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (13.5 mg, 63%).

LC/EM 422 (M+H).

Ejemplo 350

Producción de N-(furan-2-ilmetil)-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida,



1198

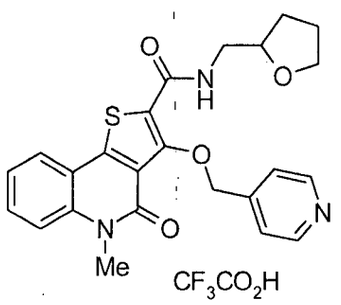
trifluoroacetato

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-furan-2-ilmetanamina.

LC/EM 446 (M+H).

Ejemplo 351

Producción de 5-metil-4-oxo-3-(piridin-4-ilmetoxi)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

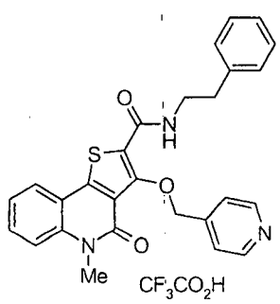


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 450 (M+H).

Ejemplo 352

Producción de 5-metil-4-oxo-N-(2-feniletil)-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



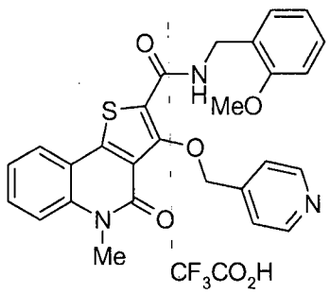
1199

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 2-feniletanamina.

LC/EM 470 (M+H).

Ejemplo 353

Producción de N-(2-metoxibencil)-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

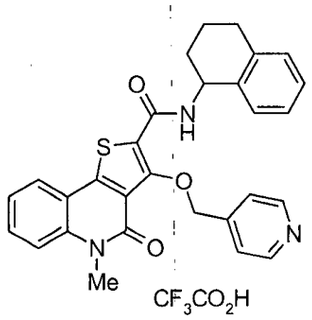


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-(2-metoxifenil)metanamina.

LC/EM 486 (M+H).

Ejemplo 354

Producción de 5-metil-4-oxo-3-(piridin-4-ilmetoxi)-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1,2,3,4-tetrahidronaftalen-1-amina.

LC/EM 496 (M+H).

Ejemplo 355

1200

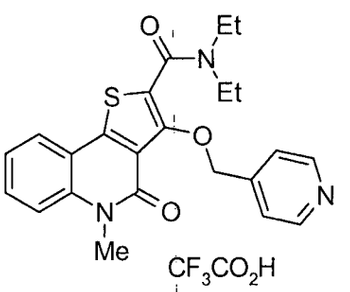
Producción de N-(1,3-benzodioxol-5-ilmetil)-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 500 (M+H).

Ejemplo 356

Producción de N,N-dietil-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

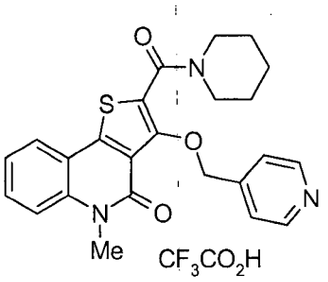


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N-etiletanamina.

LC/EM 422 (M+H).

Ejemplo 357

Producción de 5-metil-2-(piperidin-1-ilcarbonil)-3-(piridin-4-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



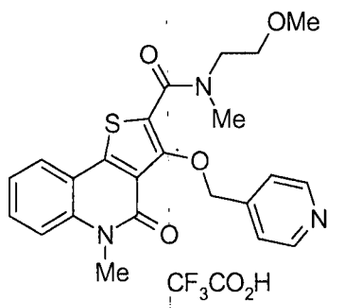
1201

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y piperidina.

LC/EM 434 (M+H).

Ejemplo 358

Producción de N-(2-metoxietil)-N,5-dimetil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

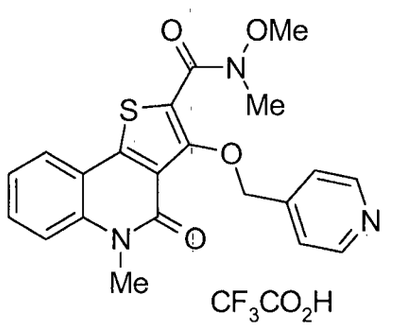


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 2-metoxi-N-metiletanamina.

LC/EM 438 (M+H).

Ejemplo 359

Producción de N-metoxi-N,5-dimetil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



A una solución (0.10 M, 0.40 ml, 40 µmol) del compuesto del Ejemplo de Referencia 93 en DMF se agregaron una mezcla de una suspensión (0.66 M, 0.111 ml, 73 µmol) de N-metoximetanamina, clorhidrato en DMF y trietilamina (10.9 µml,

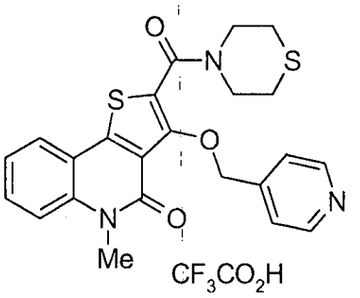
1702

78 µmol), y una solución (0.39 M, 0.20 ml, 78 µmol) de HOBt y WSC-D en mezcla 1:1 en DMF. La mezcla resultante se agitó a temperatura ambiente durante 14 hrs. Diclorometano (2 ml) y solución de hidrógeno carbonato de sodio (1 ml) se agregaron a la mezcla de reacción, la fase orgánica se filtró a través de un filtro de Teflón (marca registrada) para separar la fase acuosa, y el filtrado se concentró bajo presión reducida. El residuo se purificó por HPLC preparativa para dar el compuesto del título (12.3 mg, 59%).

LC/EM 410 (M+H).

Ejemplo 360

Producción de 5-metil-3-(piridin-4-ilmetoxi)-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

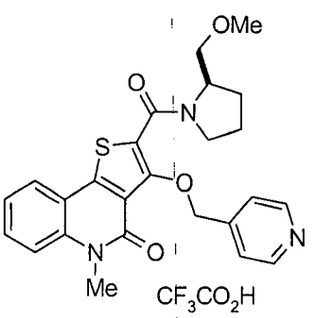


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y tiomorfolina.

LC/EM 452 (M+H).

Ejemplo 361

Producción de 2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metil-3-(piridin-4-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



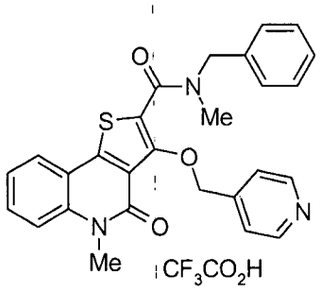
1203

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 464 (M+H).

Ejemplo 362

Producción de N-bencil-N,5-dimetil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

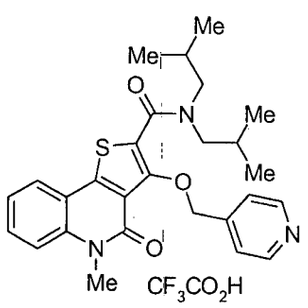


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N-metil-1-fenilmetanamina.

LC/EM 470 (M+H).

Ejemplo 363

Producción de 5-metil-N,N-bis(2-metilpropil)-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 359, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

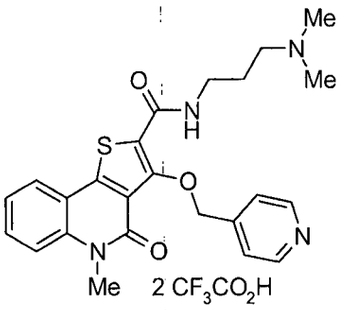
LC/EM 478 (M+H).

Ejemplo 364

Producción de N-[3-(dimetilamino)propil]-5-metil-4-oxo-3-(piridin-

1204

4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

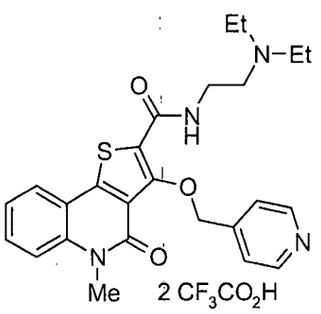


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N,N-dimetilpropano-1,3-diamina.

LC/EM 451 (M+H).

Ejemplo 365

Producción de N-[2-(dietilamino)etil]-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

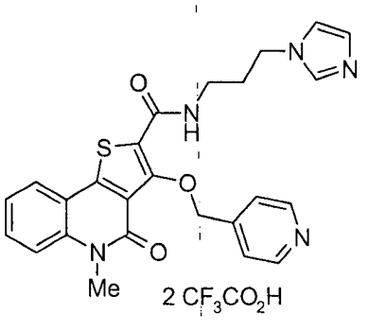


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N,N-dietiletan-1,2-diamina.

LC/EM 465 (M+H).

Ejemplo 366

Producción de N-[3-(1H-imidazol-1-il)propil]-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



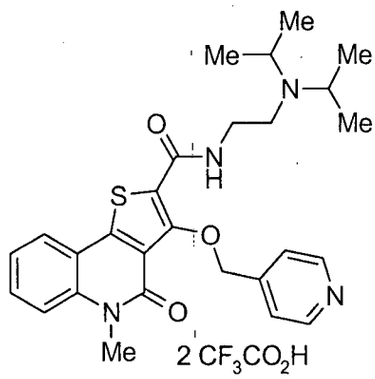
1205

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 474 (M+H).

Ejemplo 367

Producción de N-{2-[bis(1-metiletil)amino]etil}-5-metil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

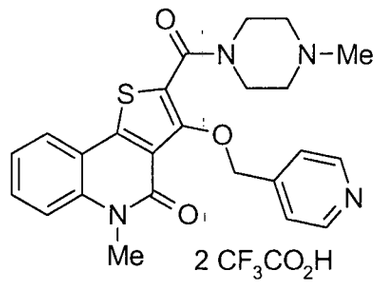


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 493 (M+H).

Ejemplo 368

Producción de 5-metil-2-[(4-metilpiperazin-1-il)carbonil]-3-(piridin-4-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato

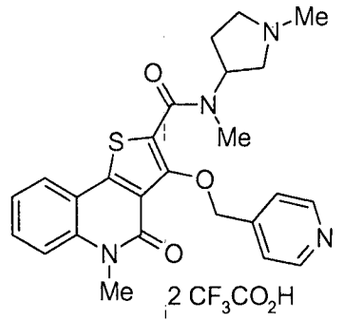


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-metilpiperazina.

1206

Ejemplo 369

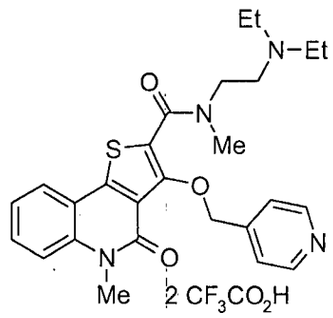
Producción de N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N,1-dimetilpirrolidin-3-amina.

Ejemplo 370

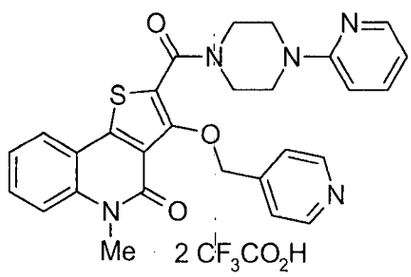
Producción de N-[2-(dietilamino)etil]-N,5-dimetil-4-oxo-3-(piridin-4-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y N,N-dietil-N'-metiletan-1,2-diamina.

Ejemplo 371

Producción de 5-metil-3-(piridin-4-ilmetoxi)-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato



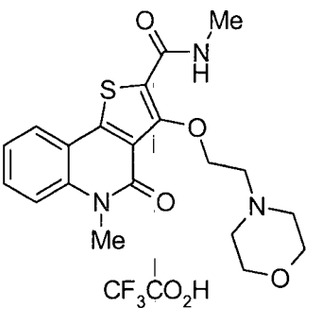
1207

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 93 y 1-piridin-2-ilpiperazina.

LC/EM 512 (M+H).

Ejemplo 372

Producción de N,5-dimetil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

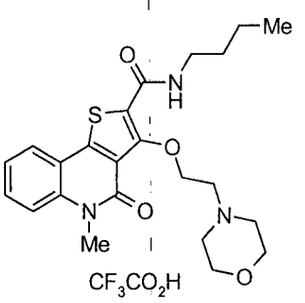


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y metanamina (solución 2.0 M de THF).

LC/EM 402 (M+H).

Ejemplo 373

Producción de N-butil-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



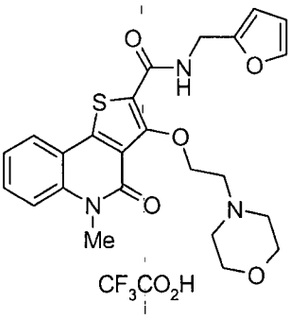
Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y butan-1-amina.

LC/EM 444 (M+H).

Ejemplo 374

1208

Producción de N-(furan-2-ilmetil)-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

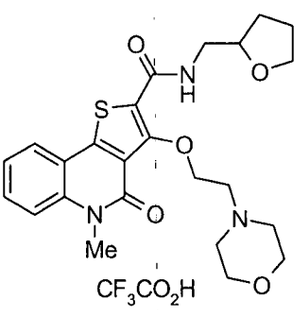


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-furan-2-ilmetanamina.

LC/EM 468 (M+H).

Ejemplo 375

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

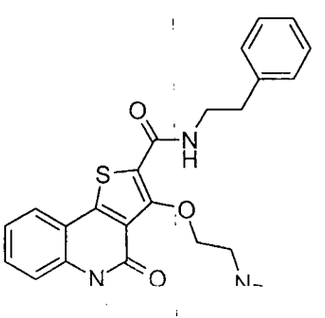


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 472 (M+H).

Ejemplo 376

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



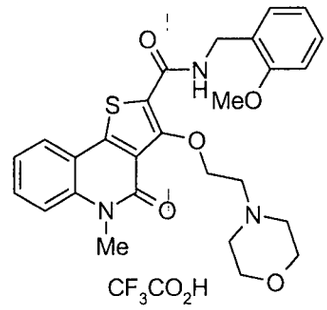
1209

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 2-feniletanamina.

LC/EM 492 (M+H).

Ejemplo 377

Producción de N-(2-metoxibencil)-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

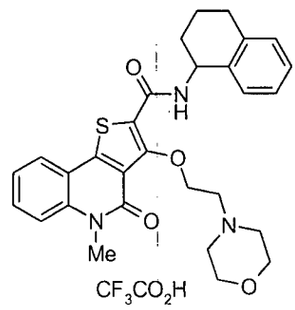


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-(2-metoxifenil)metanamina.

LC/EM 508 (M+H).

Ejemplo 378

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del

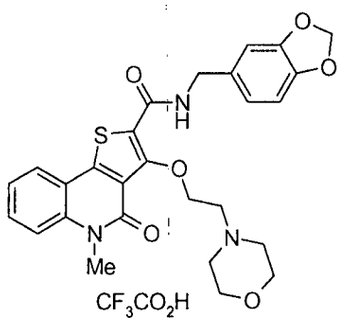
1210

título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1,2,3,4-tetrahidronaftalen-1-amina.

LC/EM 518 (M+H).

Ejemplo 379

Producción de N-(1,3-benzodioxol-5-ilmetil)-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

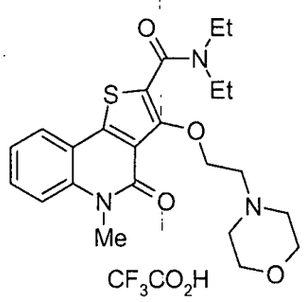


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 522 (M+H).

Ejemplo 380

Producción de N,N-dietil-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

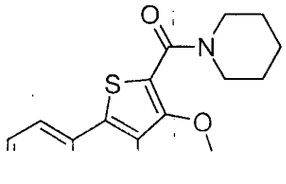


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N-etiletanamina.

LC/EM 444 (M+H).

Ejemplo 381

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato



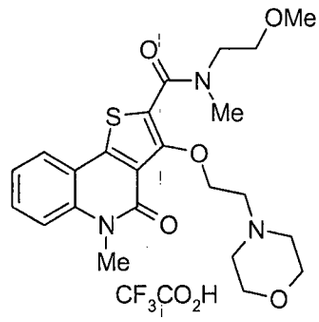
1211

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y piperidina.

LC/EM 456 (M+H).

Ejemplo 382

Producción de N-(2-metoxietil)-N,5-dimetil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

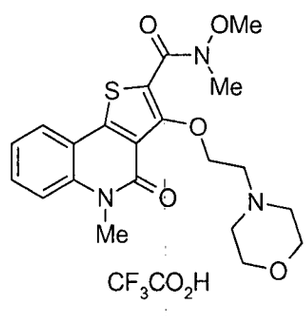


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 2-metoxi-N-metiletanamina.

LC/EM 460 (M+H).

Ejemplo 383

Producción de N-metoxi-N,5-dimetil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



Del mismo modo que en el Ejemplo 359, el compuesto del

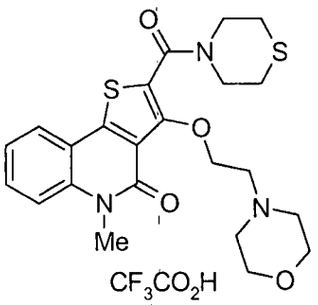
1212

título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N-metoximetanamina, clorhidrato.

LC/EM 432 (M+H).

Ejemplo 384

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

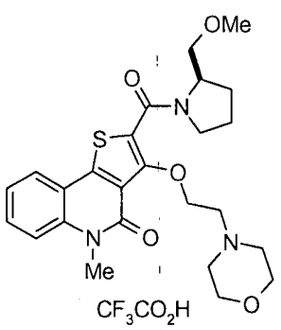


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y tiomorfolina.

LC/EM 474 (M+H).

Ejemplo 385

Producción de 2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metil-3-(2-morfolin-4-iletoxi)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato

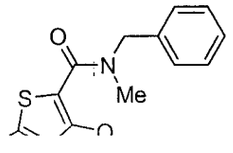


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 486 (M+H).

Ejemplo 386

Producción de N-bencil-N,5-dimetil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



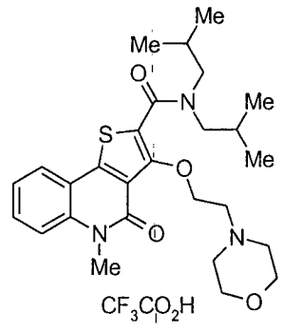
1213

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N-metil-1-fenilmetanamina.

LC/EM 492 (M+H).

Ejemplo 387

Producción de 5-metil-N,N-bis(2-metilpropil)-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

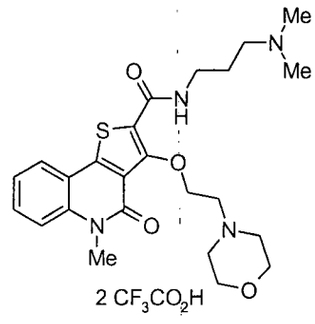


Del mismo modo que en el Ejemplo 359, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 2-metil-N-(2-metilpropil)propán-1-amina, clorhidrato.

LC/EM 500 (M+H).

Ejemplo 388

Producción de N-[3-(dimetilamino)propil]-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



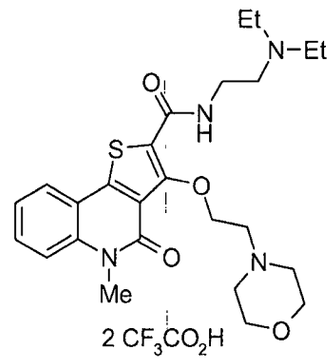
1214

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N,N-dimetilpropano-1,3-diamina.

LC/EM 473 (M+H).

Ejemplo 389

Producción de N-[2-(dietilamino)etil]-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

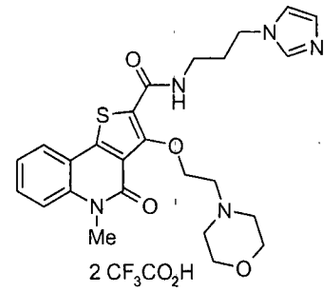


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N,N-dietiletan-1,2-diamina.

LC/EM 487 (M+H).

Ejemplo 390

Producción de N-[3-(1H-imidazol-1-il)propil]-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 496 (M+H).

Ejemplo 391

1215

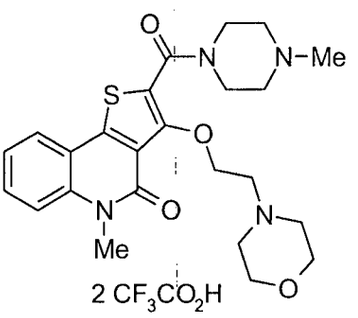
Producción de N-{2-[bis(1-metiletil)amino]etil}-5-metil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 515 (M+H).

Ejemplo 392

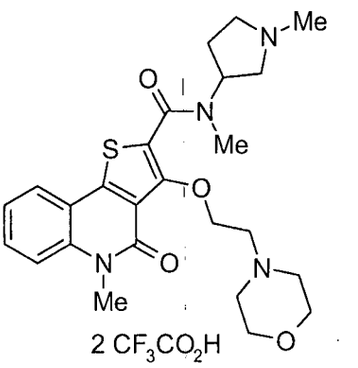
Producción de 5-metil-2-[(4-metilpiperazin-1-il)carbonil]-3-(2-morfolin-4-iletoxi)tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato



Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-metilpiperazina.

Ejemplo 393

Producción de N,5-dimetil-N-(1-metilpirrolidin-3-il)-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato



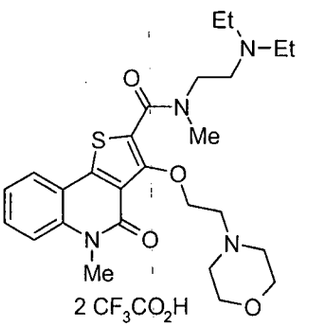
1216

Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N,1-dimetilpirrolidin-3-amina.

LC/EM 485 (M+H).

Ejemplo 394.

Producción de N-[2-(dietilamino)etil]-N,5-dimetil-3-(2-morfolin-4-iletoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, ditrifluoroacetato.

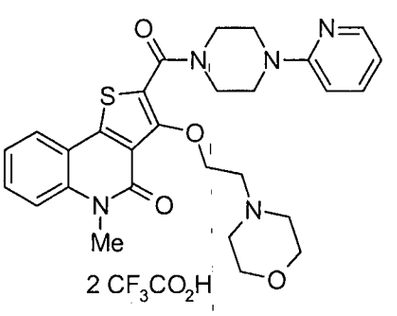


Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 501 (M+H).

Ejemplo 395.

Producción de 5-metil-3-(2-morfolin-4-iletoxi)-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona ditrifluoroacetato.



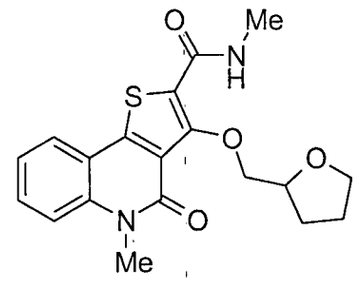
Del mismo modo que en el Ejemplo 349, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 94 y 1-piridin-2-ilpiperazina.

LC/EM 534 (M+H).

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Ejemplo 396.

Producción de N,5-dimetil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

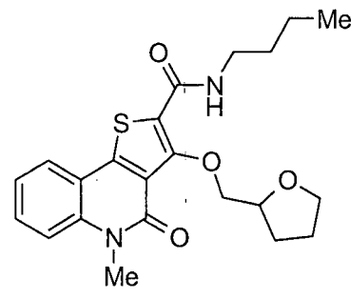


Del mismo modo que en el Ejemplo 300, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y metanamina (solución 2.0 M de THF).

LC/EM 373 (M+H).

Ejemplo 397.

Producción de N-butil-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

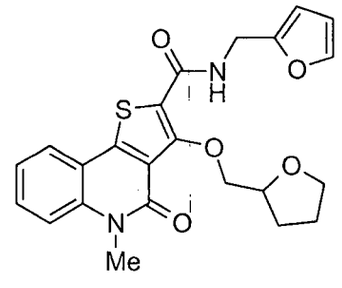


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y butan-1-amina.

LC/EM 415 (M+H).

Ejemplo 398.

Producción de N-(furan-2-ilmetil)-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



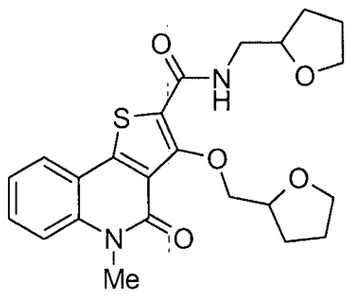
1218

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-furan-2-ilmetanamina.

LC/EM 439 (M+H).

Ejemplo 399.

Producción de 5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

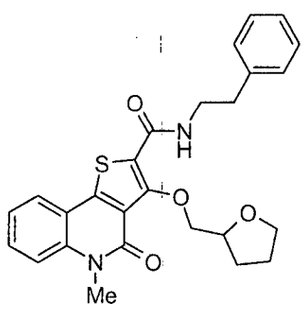


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 443 (M+H).

Ejemplo 400.

Producción de 5-metil-4-oxo-N-(2-feniletil)-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



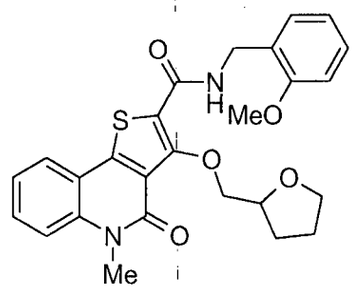
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 2-feniletanamina.

LC/EM 463 (M+H).

Ejemplo 401.

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Producción de N-(2-metoxibencil)-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

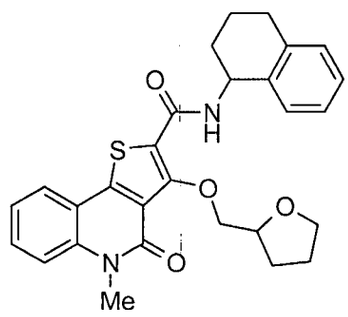


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-(2-metoxifenil)metanamina.

LC/EM 479 (M+H).

Ejemplo 402.

Producción de 5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-N-(1,2,3,4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

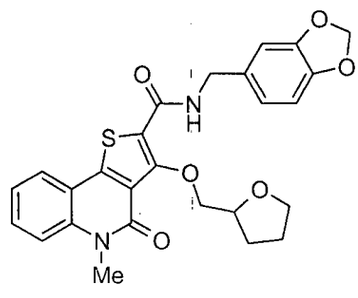


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1,2,3,4-tetrahidronaftalen-1-amina.

LC/EM 489 (M+H).

Ejemplo 403.

Producción de N-(1,3-benzodioxol-5-ilmetil)-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



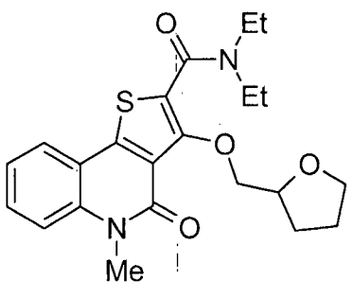
1220

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 493 (M+H).

Ejemplo 404.

Producción de N,N-dietil-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

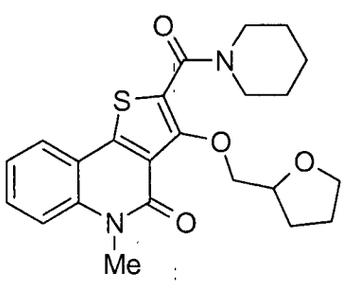


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N-etiletanamina.

LC/EM 415 (M+H).

Ejemplo 405.

Producción de 5-metil-2-(piperidin-1-ilcarbonil)-3-(tetrahidrofuran-2-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona.



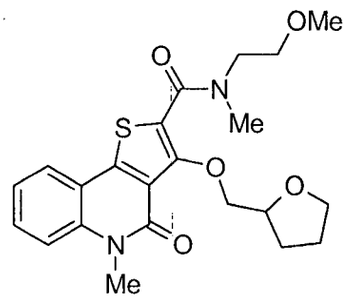
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y piperidina.

LC/EM 427 (M+H).

1221

Ejemplo 406.

Producción de N-(2-metoxietil)-N,5-dimetil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

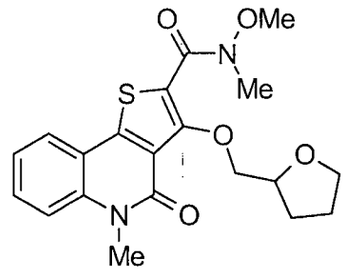


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 2-metoxi-N-metiletanamina.

LC/EM 461 (M+H).

Ejemplo 407.

Producción de N-metoxi-N,5-dimetil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

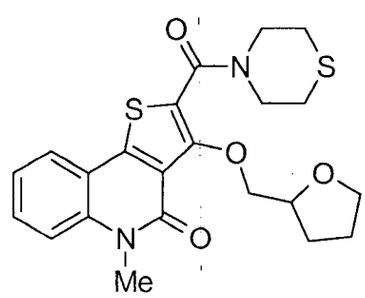


Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N-metoximetanamina, clorhidrato.

LC/EM 403 (M+H).

Ejemplo 408.

Producción de 5-metil-3-(tetrahidrofuran-2-ilmetoxi)-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.



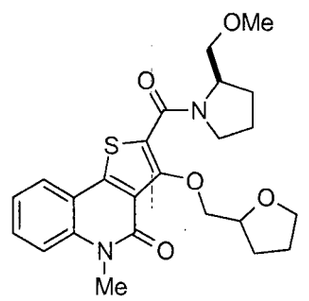
1222

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y tiomorfolina.

LC/EM 445 (M+H).

Ejemplo 409.

Producción de 2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metil-3-(tetrahidrofuran-2-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona.

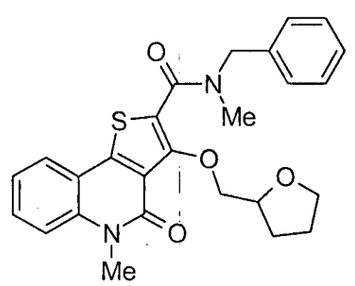


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 457 (M+H).

Ejemplo 410.

Producción de N-bencil-N,5-dimetil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N-metil-1-fenilmetanamina.

LC/EM 463 (M+H).

Ejemplo 411.

1223

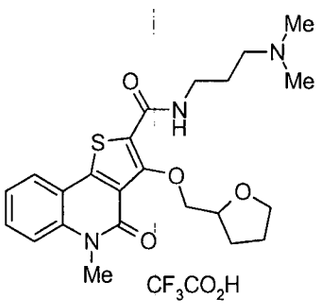
Producción de 5-metil-N,N-bis(2-metilpropil)-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 471 (M+H).

Ejemplo 412.

Producción de N-[3-(dimetilamino)propil]-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

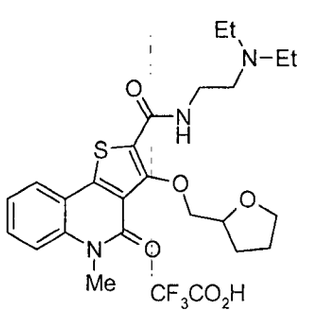


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N,N-dimetilpropano-1,3-diamina.

LC/EM 444 (M+H).

Ejemplo 413.

Producción de N-[2-(dietilamino)etil]-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



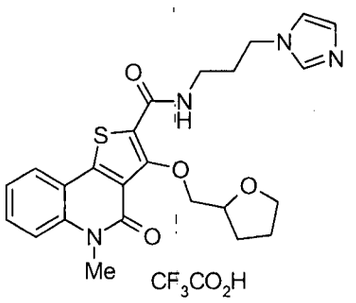
1224

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N,N-dietiletan-1,2-diamina.

LC/EM 458 (M+H).

Ejemplo 414.

Producción de N-[3-(1H-imidazol-1-il)propil]-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

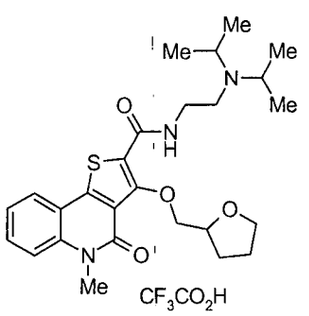


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 467 (M+H).

Ejemplo 415.

Producción de N-{2-[bis(1-metiletil)amino]etil}-5-metil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



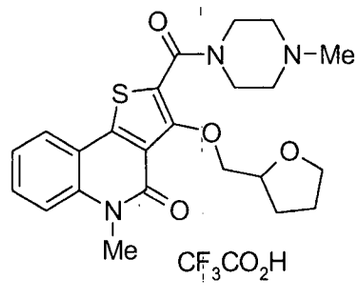
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N,N-bis(1-metiletil)etan-1,2-diamina.

1225

LC/EM 486 (M+H).

Ejemplo 416.

Producción de 5-metil-2-[(4-metilpiperazin-1-il)carbonil]-3-(tetrahidrofuran-2-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

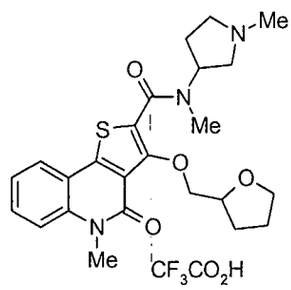


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-metilpiperazina.

LC/EM 442 (M+H).

Ejemplo 417.

Producción de N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

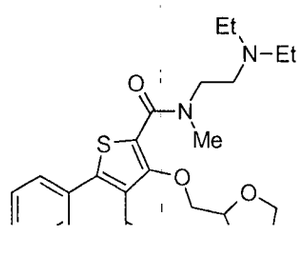


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N,1-dimetilpirrolidin-3-amina.

LC/EM 456 (M+H).

Ejemplo 418.

Producción de N-[2-(dietilamino)etil]-N,5-dimetil-4-oxo-3-(tetrahidrofuran-2-ilmetoxi)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

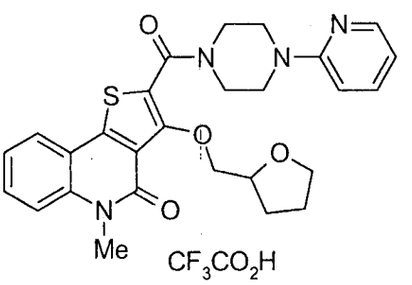


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 472 (M+H).

Ejemplo 419.

Producción de 5-metil-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]-3-(tetrahidrofuran-2-ilmetoxi)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

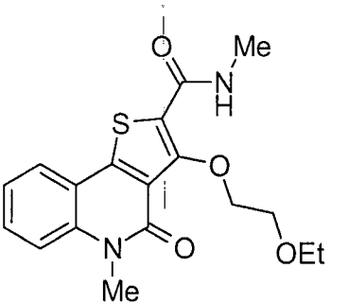


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 95 y 1-piridin-2-ilpiperazina.

LC/EM 505 (M+H).

Ejemplo 420.

Producción de 3-(2-etoxietoxi)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 300, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

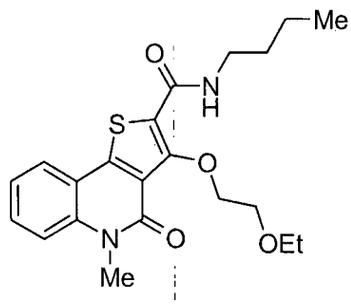
1227

96 y metanamina (solución 2.0 M de THF).

LC/EM 361 (M+H).

Ejemplo 421.

Producción de N-butil-3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

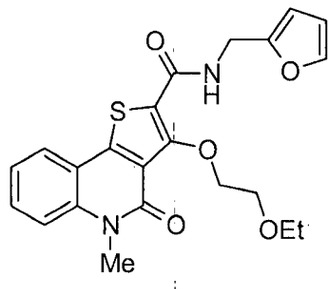


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y butan-1-amina.

LC/EM 403 (M+H).

Ejemplo 422.

Producción de 3-(2-etoxietoxi)-N-(furan-2-ilmetil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

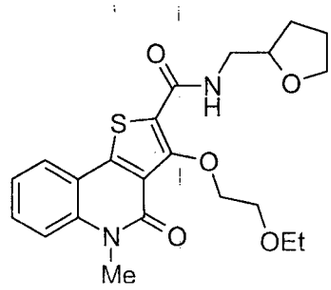


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-furan-2-ilmetanamina.

LC/EM 427 (M+H).

Ejemplo 423.

Producción de 3-(2-etoxietoxi)-5-metil-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



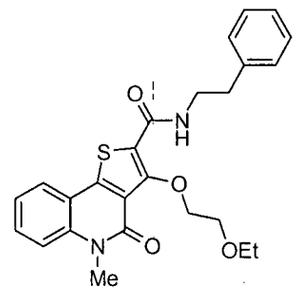
1228

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 431 (M+H).

Ejemplo 424.

Producción de 3-(2-etoxietoxi)-5-metil-4-oxo-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

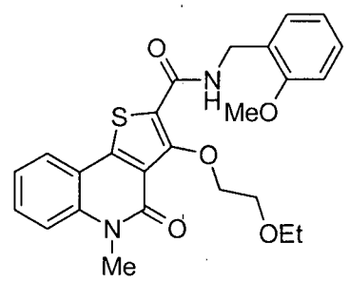


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 2-feniletanamina.

LC/EM 451 (M+H).

Ejemplo 425.

Producción de 3-(2-etoxietoxi)-N-(2-metoxibencil)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



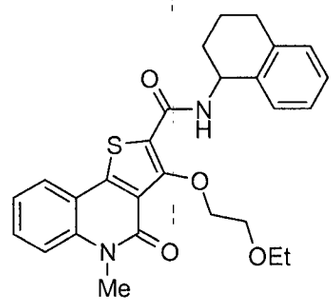
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-(2-metoxifenil)metanamina.

LC/EM 467 (M+H).

1229

Ejemplo 426.

Producción de 3-(2-etoxietoxi)-5-metil-4-oxo-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

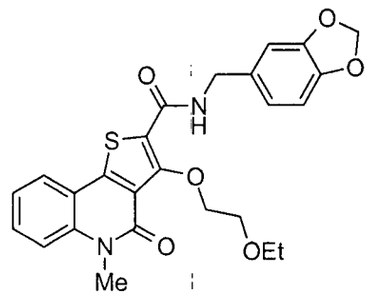


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1.2,3.4-tetrahidronaftalen-1-amina.

LC/EM 477 (M+H).

Ejemplo 427.

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

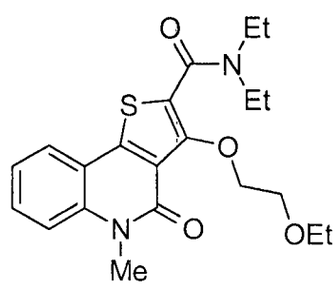


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 481 (M+H).

Ejemplo 428.

Producción de 3-(2-etoxietoxi)-N,N-dietil-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



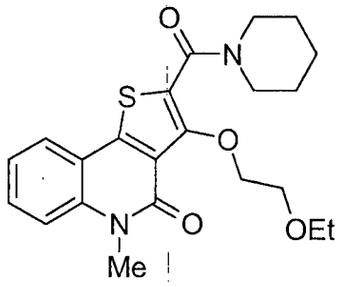
1230

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N-etiletanamina.

LC/EM 403 (M+H).

Ejemplo 429.

Producción de 3-(2-etoxietoxi)-5-metil-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

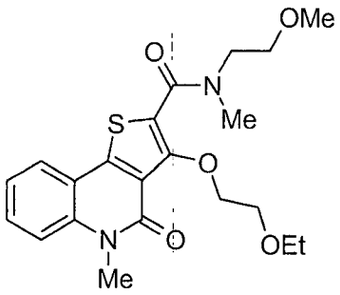


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y piperidina.

LC/EM 415 (M+H).

Ejemplo 430.

Producción de 3-(2-etoxietoxi)-N-(2-metoxietil)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 2-metoxi-N-metiletanamina.

LC/EM 419 (M+H).

Ejemplo 431.



1231

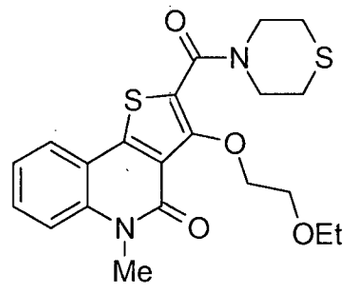
Producción de 3-(2-etoxietoxi)-N-metoxi-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N-metoximetanamina, clorhidrato.

LC/EM 391 (M+H).

Ejemplo 432:

Producción de 3-(2-etoxietoxi)-5-metil-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

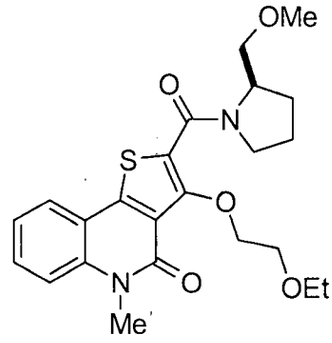


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y tiomorfolina.

LC/EM 433 (M+H).

Ejemplo 433.

Producción de 3-(2-etoxietoxi)-2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-metiltieno[3,2-c]quinolin-4(5H)-ona.



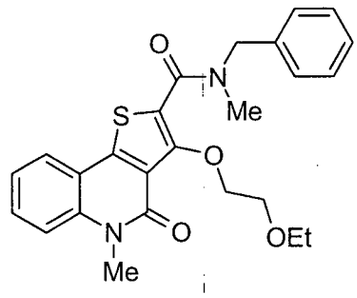
1232

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 445 (M+H).

Ejemplo 434.

Producción de N-bencil-3-(2-etoxietoxi)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

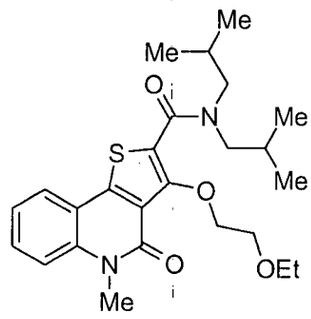


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N-metil-1-fenilmetanamina.

LC/EM 451 (M+H).

Ejemplo 435.

Producción de 3-(2-etoxietoxi)-5-metil-N,N-bis(2-metilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



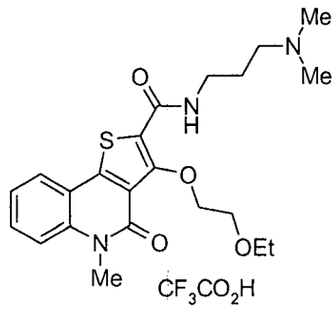
Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 459 (M+H).

Ejemplo 436.

1233

Producción de N-[3-(dimetilamino)propil]-3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

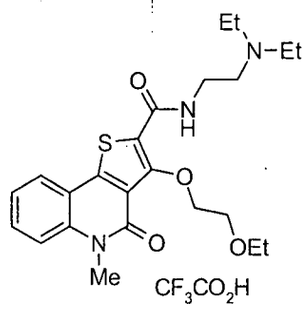


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N,N-dimetilpropano-1,3-diamina.

LC/EM 432 (M+H).

Ejemplo 437.

Producción de N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

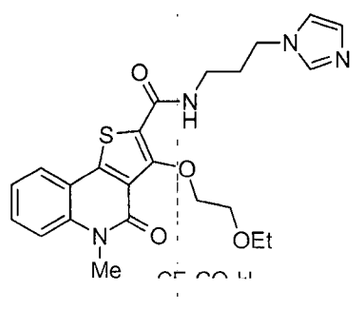


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N,N-dietiletan-1,2-diamina.

LC/EM 446 (M+H).

Ejemplo 438.

Producción de 3-(2-etoxietoxi)-N-[3-(1H-imidazol-1-il)propil]-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



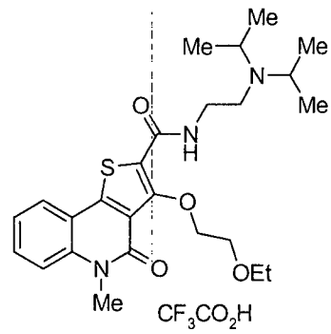
1234

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 455 (M+H).

Ejemplo 439.

Producción de N-{2-[bis(1-metiletil)amino]etil}-3-(2-etoxietoxi)-5-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

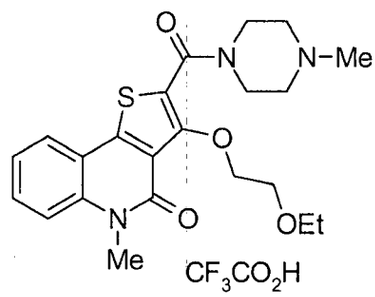


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 474 (M+H).

Ejemplo 440.

Producción de 3-(2-etoxietoxi)-5-metil-2-[(4-metilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.



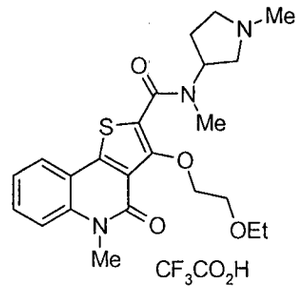
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-metilpiperazina.

1235

LC/EM 430 (M+H).

Ejemplo 441.

Producción de 3-(2-etoxietoxi)-N,5-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

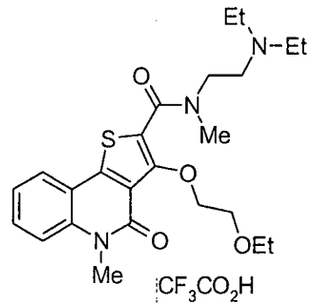


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N,1-dimetilpirrolidin-3-amina.

LC/EM 444 (M+H).

Ejemplo 442.

Producción de N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-N,5-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

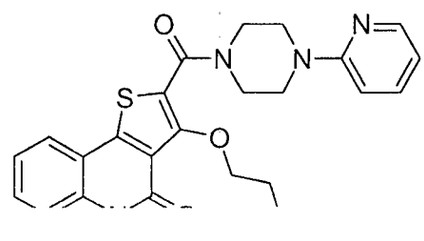


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 460 (M+H).

Ejemplo 443.

Producción de 3-(2-etoxietoxi)-5-metil-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.



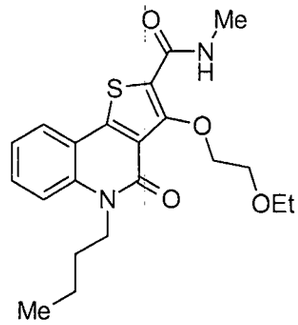
1236

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 96 y 1-piridin-2-ilpiperazina.

LC/EM 493 (M+H).

Ejemplo 444.

Producción de 5-butil-3-(2-etoxietoxi)-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

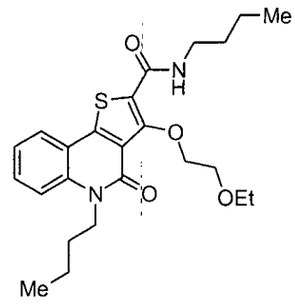


Del mismo modo que en el Ejemplo 300, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y metanamina (solución 2.0 M de THF).

LC/EM 403 (M+H).

Ejemplo 445.

Producción de N,5-dibutil-3-(2-etoxietoxi)-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



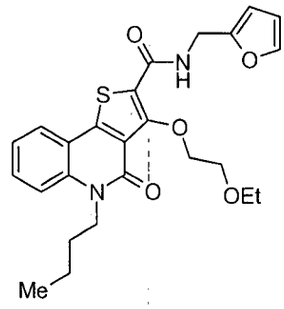
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y butan-1-amina.

1237

LC/EM 445 (M+H).

Ejemplo 446.

Producción de 5-butil-3-(2-etoxietoxi)-N-(furan-2-ilmetil)- 4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

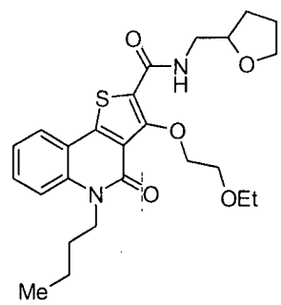


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-furan-2-ilmetanamina.

LC/EM 469 (M+H).

Ejemplo 447.

Producción de 5-butil-3-(2-etoxietoxi)-4-oxo-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

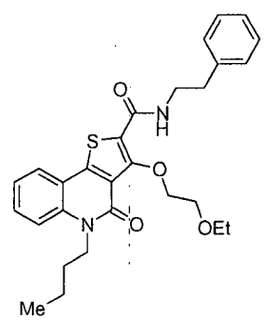


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 473 (M+H).

Ejemplo 448.

Producción de 5-butil-3-(2-etoxietoxi)-4-oxo-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



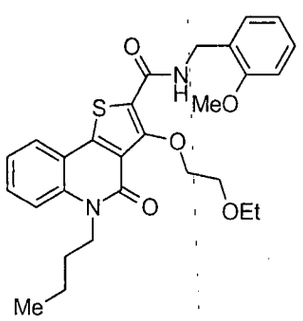
1238

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 2-feniletanamina.

LC/EM 493 (M+H).

Ejemplo 449.

Producción de 5-butil-3-(2-etoxietoxi)-N-(2-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

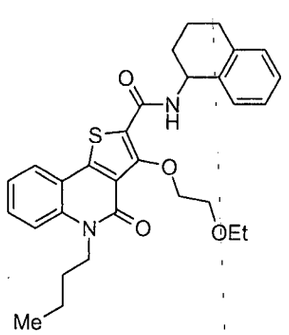


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-(2-metoxifenil)metanamina.

LC/EM 509 (M+H).

Ejemplo 450.

Producción de 5-butil-3-(2-etoxietoxi)-4-oxo-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



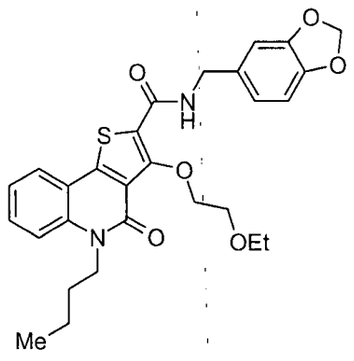
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1.2,3.4-tetrahidronaftalen-1-amina.

LC/EM 519 (M+H).

1239

Ejemplo 451.

Producción de 5-butil-N-(1,3-benzodioxol-5-ilmetil)-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

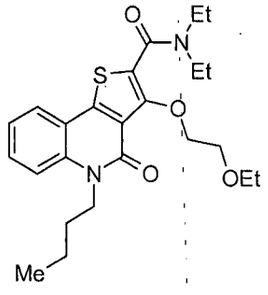


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 523 (M+H).

Ejemplo 452.

Producción de 5-butil-3-(2-etoxietoxi)-N,N-dietil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

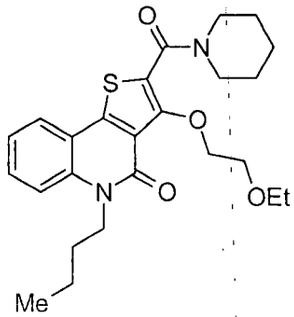


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N-etiletanamina.

LC/EM 445 (M+H).

Ejemplo 453.

Producción de 5-butil-3-(2-etoxietoxi)-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.



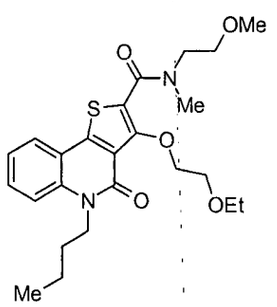
1240

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y piperidina.

LC/EM 457 (M+H).

Ejemplo 454.

Producción de 5-butil-3-(2-etoxietoxi)-N-(2-metoxietil)-N-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

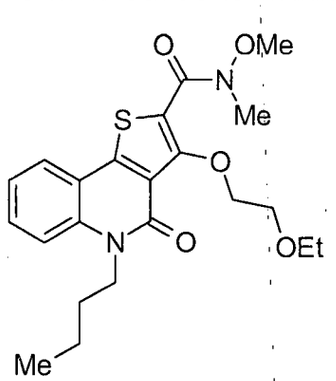


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 2-metoxi-N-metiletanamina.

LC/EM 461 (M+H).

Ejemplo 455.

Producción de 5-butil-3-(2-etoxietoxi)-N-metoxi-N-metil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



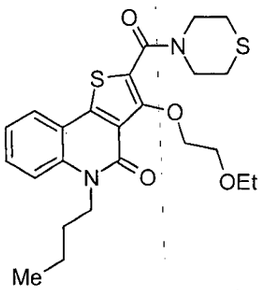
Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N-metoximetanamina, clorhidrato.

1241

LC/EM 433 (M+H).

Ejemplo 456.

Producción de 5-butil-3-(2-etoxietoxi)-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.

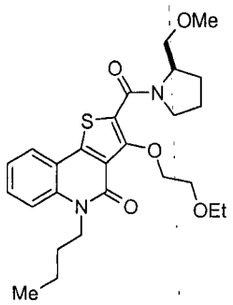


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y tiomorfolina.

LC/EM 475 (M+H).

Ejemplo 457.

Producción de 5-butil-3-(2-etoxietoxi)-2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-tieno[3,2-c]quinolin-4(5H)-ona.

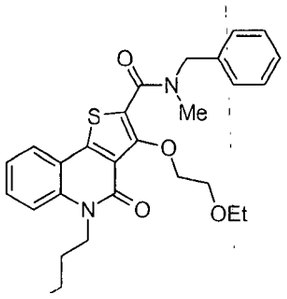


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 487 (M+H).

Ejemplo 458.

Producción de N-bencil-5-butil-3-(2-etoxietoxi)-N -4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

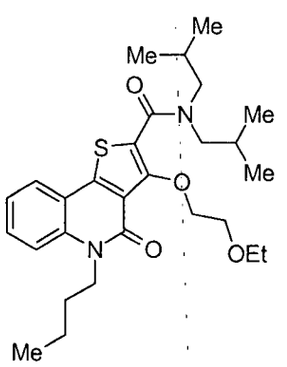


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N-metil-1-fenilmetanamina.

LC/EM 493 (M+H).

Ejemplo 459.

Producción de 5-butil-3-(2-etoxietoxi)-N,N-bis(2-metilpropil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

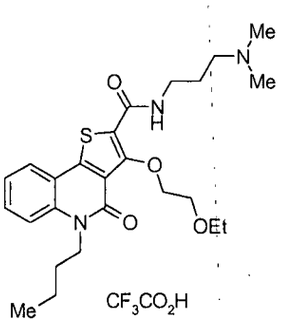


Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 501 (M+H).

Ejemplo 460.

Producción de 5-butil-N-[3-(dimetilamino)propil]-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

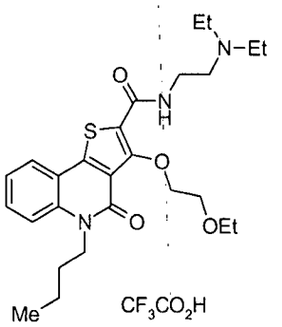
1243

104 y N,N-dimetilpropano-1,3-diamina.

LC/EM 474 (M+H).

Ejemplo 461.

Producción de 5-butil-N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato

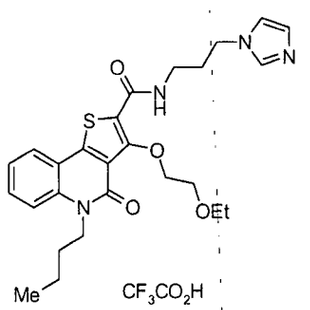


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N,N-dietiletan-1,2-diamina.

LC/EM 488 (M+H).

Ejemplo 462.

Producción de 5-butil-3-(2-etoxietoxi)-N-[3-(1H-imidazol-1-il)propil]-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

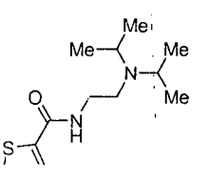


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 497 (M+H).

Ejemplo 463.

Producción de N-{2-[bis(1-metiletil)amino]etil}-5-butil-3-(2-etoxietoxi)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



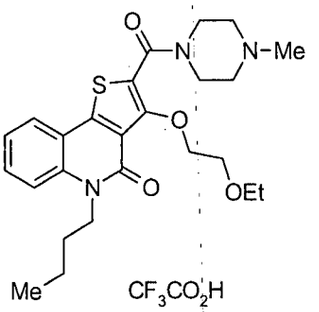
1244

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 516 (M+H).

Ejemplo 464.

Producción de 5-butil-3-(2-etoxietoxi)-2-[(4-metilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.

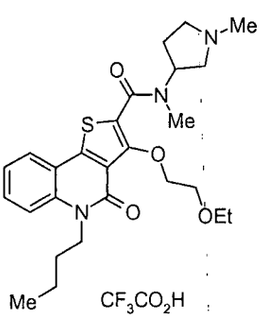


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-metilpiperazina.

LC/EM 472 (M+H).

Ejemplo 465.

Producción de 5-butil-3-(2-etoxietoxi)-N-dimetil-N-(1-metilpirrolidin-3-il)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



Del mismo modo que en el Ejemplo 5, el compuesto del

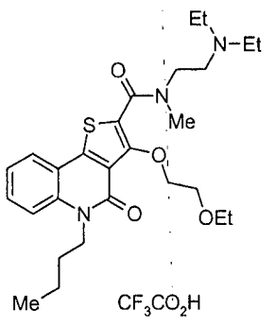
1245

título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N,1-dimetilpirrolidin-3-amina.

LC/EM 486 (M+H).

Ejemplo 466.

Producción de 5-butil-N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-N-dimetil-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

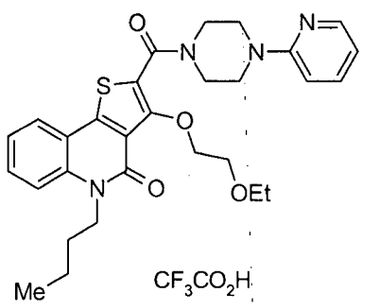


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 502 (M+H).

Ejemplo 467.

Producción de 5-butil-3-(2-etoxietoxi)-2-[(4-piridin-2-ilpiperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona trifluoroacetato.

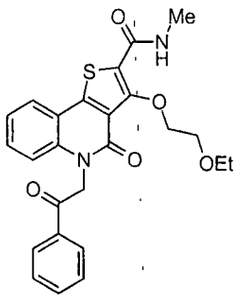


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 104 y 1-piridin-2-ilpiperazina.

LC/EM 535 (M+H).

Ejemplo 468.

Producción de 3-(2-etoxietoxi)-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

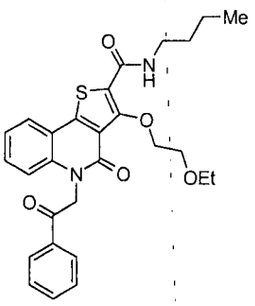


Del mismo modo que en el Ejemplo 300, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y metanamina (solución 2.0 M de THF).

LC/EM 465 (M+H).

Ejemplo 469.

Producción de N-butil-3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

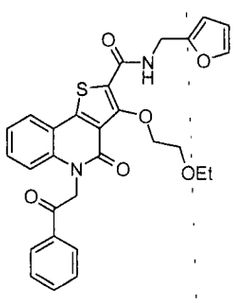


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y butan-1-amina.

LC/EM 507 (M+H).

Ejemplo 470.

Producción de 3-(2-etoxietoxi)-N-(furan-2-ilmetil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

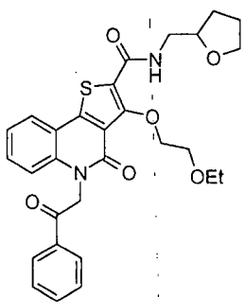
1247

21 y 1-furan-2-ilmetanamina.

LC/EM 531 (M+H).

Ejemplo 471.

Producción de 3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

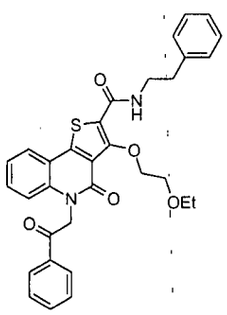


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 1-(tetrahidrofuran-2-il)metanamina.

LC/EM 535 (M+H).

Ejemplo 472.

Producción de 3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-N-(2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

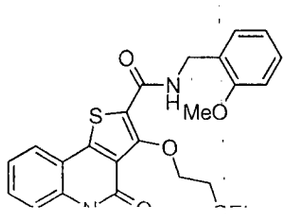


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 2-feniletanamina.

LC/EM 555 (M+H).

Ejemplo 473.

Producción de 3-(2-etoxietoxi)-N-(2-metoxibencil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

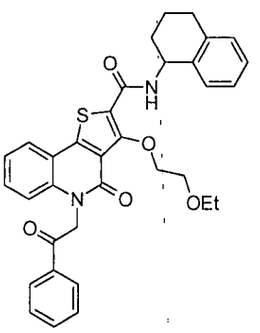


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 1-(2-metoxifenil)metanamina.

LC/EM 571 (M+H).

Ejemplo 474.

Producción de 3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-N-(1,2,3.4-tetrahidronaftalen-1-il)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

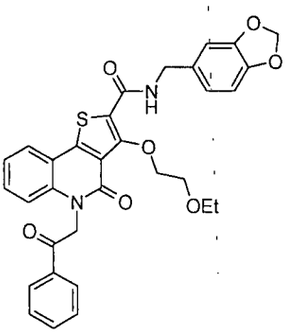


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 1.2,3.4-tetrahidronaftalen-1-amina.

LC/EM 581 (M+H).

Ejemplo 475.

Producción de N-(1,3-benzodioxol-5-ilmetil)-3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



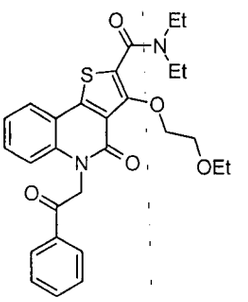
1249

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 1-(1,3-benzodioxol-5-il)metanamina.

LC/EM 585 (M+H).

Ejemplo 476.

Producción de 3-(2-etoxietoxi)-N,N-dietil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

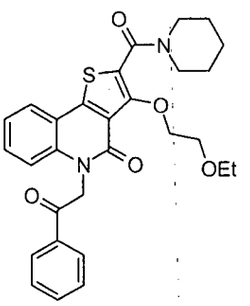


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N-etiletanamina.

LC/EM 507 (M+H).

Ejemplo 477.

Producción de 3-(2-etoxietoxi)-5-(2-oxo-2-feniletil)-2-(piperidin-1-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.



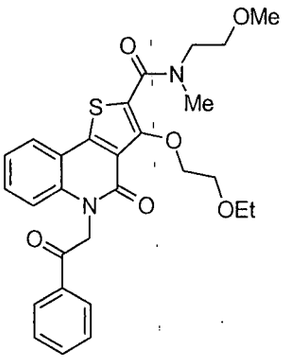
Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y piperidina.

LC/EM 519 (M+H).

Ejemplo 478.

Producción de 3-(2-etoxietoxi)-N-(2-metoxietil)-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

1250

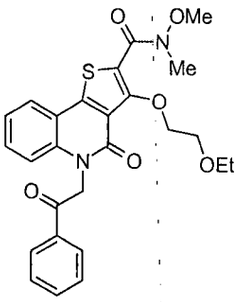


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 2-metoxi-N-metiletanamina.

LC/EM 523 (M+H).

Ejemplo 479.

Producción de 3-(2-etoxietoxi)-N-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

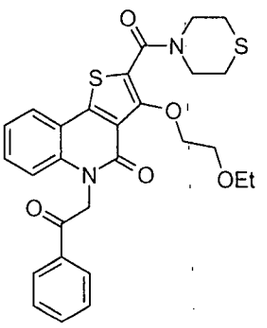


Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N-metoximetanamina, clorhidrato.

LC/EM 495 (M+H).

Ejemplo 480.

Producción de 3-(2-etoxietoxi)-5-(2-oxo-2-feniletil)-2-(tiomorfolin-4-ilcarbonil)tieno[3,2-c]quinolin-4(5H)-ona.



Del mismo modo que en el Ejemplo 5, el compuesto del

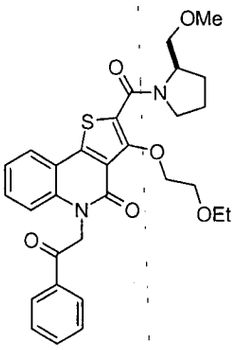
1251

título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y tiomorfolina.

LC/EM 537 (M+H).

Ejemplo 481.

Producción de 3-(2-etoxietoxi)-2-{[(2R)-2-(metoximetil)pirrolidin-1-il]carbonil}-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona.

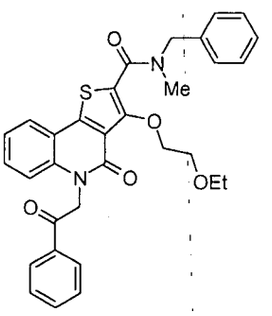


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y (2R)-2-(metoximetil)pirrolidina.

LC/EM 549 (M+H).

Ejemplo 482.

Producción de N-bencil-3-(2-etoxietoxi)-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

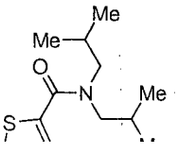


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N-metil-1-fenilmetanamina.

LC/EM 555 (M+H).

Ejemplo 483.

Producción de 3-(2-etoxietoxi)-N,N-bis(2-metilpropil)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



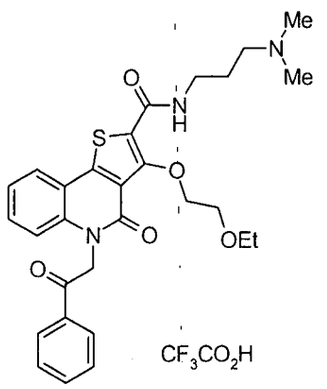
1252

Del mismo modo que en el Ejemplo 335, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 2-metil-N-(2-metilpropil)propan-1-amina, clorhidrato.

LC/EM 563 (M+H).

Ejemplo 484.

Producción de N-[3-(dimetilamino)propil]-3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

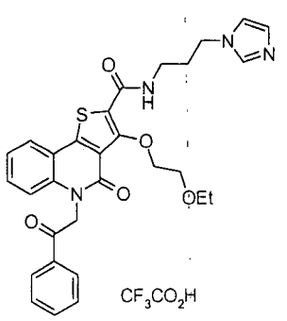


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N,N-dimetilpropano-1,3-diamina.

LC/EM 536 (M+H).

Ejemplo 485.

Producción de 3-(2-etoxietoxi)-N-[3-(1H-imidazol-1-il)propil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.



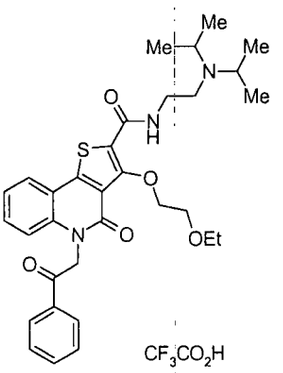
1253

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 3-(1H-imidazol-1-il)propan-1-amina.

LC/EM 559 (M+H).

Ejemplo 486.

Producción de N-{2-[bis(1-metiletil)amino]etil}-3-(2-etoxietoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

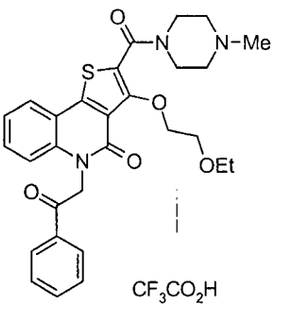


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N,N-bis(1-metiletil)etan-1,2-diamina.

LC/EM 578 (M+H).

Ejemplo 487.

Producción de 3-(2-etoxietoxi)-2-[(4-metilpiperazin-1-il)carbonil]-5-(2-oxo-2-feniletil)tieno[3,2-c]quinolin-4(5H)-ona, trifluoroacetato.



Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia

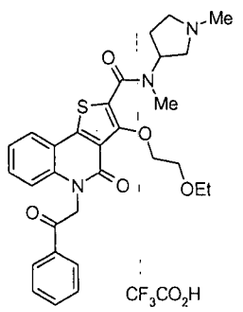
1254

21 y 1-metilpiperazina.

LC/EM 534 (M+H).

Ejemplo 488.

Producción de 3-(2-etoxietoxi)-N-metil-N-(1-metilpirrolidin-3-il)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

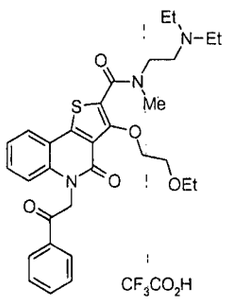


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N,1-dimetilpirrolidin-3-amina.

LC/EM 548 (M+H).

Ejemplo 489.

Producción de N-[2-(dietilamino)etil]-3-(2-etoxietoxi)-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato.

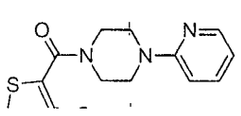


Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y N,N-dietil-N'-metiletan-1,2-diamina.

LC/EM 564 (M+H).

Ejemplo 490.

Producción de 3-(2-etoxietoxi)-5-(2-oxo-2-feniletil)-2-[(4-(piridin-2-il)piperazin-1-il)carbonil]tieno[3,2-c]quinolin-4(5H)-ona,



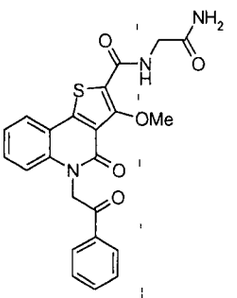
trifluoroacetato.

Del mismo modo que en el Ejemplo 5, el compuesto del título se obtuvo a partir del compuesto del Ejemplo de Referencia 21 y 1-(piridin-2-il)piperazina.

LC/EM 597 (M+H).

Ejemplo 491.

Producción de N-(2-amino-2-oxoetil)-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



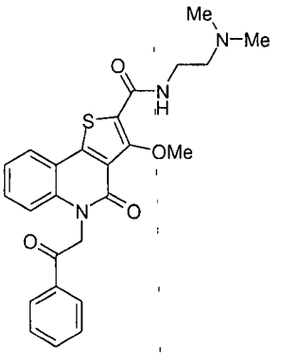
A una solución del compuesto del Ejemplo de Referencia 7 (175 mg, 0.44 mmol), glicina amida (56 mg, 0.51 mmol), HOBt (89 mg, 0.66 mmol) y WSCD (126 mg, 0.66 mmol) en DMF (5.0 ml) se agregó trietilamina (0.16 ml, 1.2 mmol), y la mezcla se agitó a temperatura ambiente durante 25 hrs. Se agregó agua a la mezcla de reacción, y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, etanol y dietil éter, y se recristalizó a partir de DMF para dar el compuesto del título (124 mg, 54%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.95 (2H, d, J = 5.3 Hz), 4.06 (3H, s), 6.00 (2H, s), 7.19 (1H, s), 7.30 - 7.30 (1H, m), 7.35 - 7.69 (5H, m), 7.73 - 7.82 (1H, m), 8.06 (1H, dd, J = 7.9, 1.3 Hz), 8.13 - 8.22 (2H, m), 8.28 (1H, t, J = 5.3 Hz).

1256

Ejemplo 492.

Producción de N-[2-(dimetilamino)etil]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

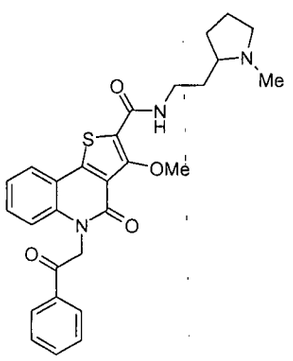


Del mismo modo que en el Ejemplo 25, el compuesto del título (124 mg, 81%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (130 mg, 0.33 mmol) y N,N-dimetiletilendiamina (44 mg, 0.49 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 2.23 (6H, s), 2.45 (2H, d, *J* = 6.2 Hz), 3.42 (2H, q, *J* = 5.9 Hz), 4.02 (3H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 7.57 (1H, dd, *J* = 7.2, 1.5 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.05 (1H, dd, *J* = 8.1, 1.5 Hz), 8.13 - 8.19 (3H, m).

Ejemplo 493.

Producción de 3-metoxi-N-[2-(1-metilpirrolidin-2-il)etil]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



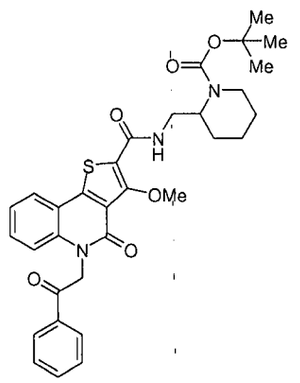
Del mismo modo que en el Ejemplo 25, el compuesto del título (86 mg, 52%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (130 mg, 0.33 mmol) y 2-(2-aminoetil)-1-metilpirrolidina (63 mg, 0.49 mmol).

1257

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.45 - 1.70 (4H, m), 1.78 - 2.15 (4H, m), 2.23 (3H, s), 2.90 - 2.97 (1H, m), 3.35 - 3.50 (2H, m), 4.01 (3H, s), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.56 (1H, dd, *J* = 7.2, 1.5 Hz), 7.60 - 7.67 (2H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.04 (1H, dd, *J* = 7.8, 1.5 Hz), 8.16 - 8.22 (3H, m).

Ejemplo 494.

Producción de *terc*-butilo 2-[({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)metil]piperidina-1-carboxilato.



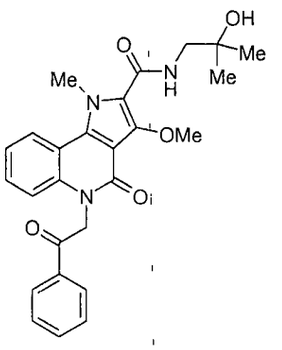
Del mismo modo que en el Ejemplo 25, el compuesto del título (190 mg, 85%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (150 mg, 0.38 mmol) y 2-aminometil-N-boc-piperidina (122 mg, 0.57 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.39 (9H, s), 1.40 - 1.60 (1H,m), 1.60 - 1,80 (5H, m), 2.94 (1H, t, *J* = 12.6 Hz), 3.51 - 3.57 (1H, m), 3.70 - 3.90 (1H, amplio), 4.03 (1H, d, *J* = 14.4 Hz), 4.15 (3H, s), 4.45 - 4.60 (1H, m), 5.86 (2H, s), 7.01 (1H, d, *J* = 8.4 Hz), 7.26 - 7.28 (1H, m), 7.37 (1H, td, *J* = 8.1, 1.5 Hz), 7.59 (2H, t, *J* = 7.3 Hz), 7.65 - 7.70 (2H, m), 7.90 (1H, dd, *J* = 7.8, 1.2 Hz), 8.10 - 8.13 (2H, m).

Ejemplo 495.

Producción de N-(2-hidroxi-2-metilpropil)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

1258

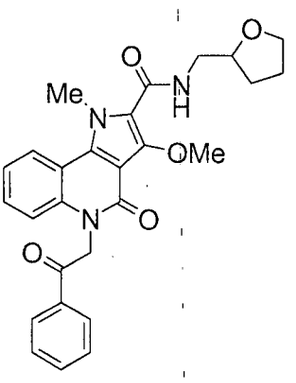


Del mismo modo que en el Ejemplo 25, el compuesto del título (215 mg, 91%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-amino-2-metilpropan-2-ol (59.3 mg, 0.666 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.16 (6H, s), 3.29 (2H, d, *J* = 5.7 Hz), 4.02 (3H, s), 4.38 (3H, s), 4.69 (1H, s), 5.98 (2H, s), 7.29 - 7.30 (2H, m), 7.36 - 7.51 (1H, m), 7.64 (2H, t, *J* = 7.3 Hz), 7.73 - 7.79 (1H, m), 8.03 (1H, t, *J* = 5.7 Hz), 8.16 - 8.19 (2H, m), 8.39 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 496.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 25, el compuesto del título (199 mg, 82%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-(tetrahidrofuran-2-il)metanamina (68.7 µl, 0.666 mmol).

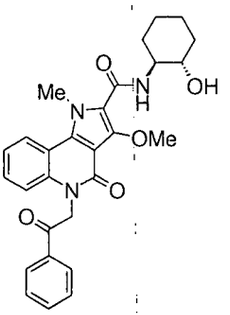
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.56 - 1.67 (1H, m), 1.76 - 1.99 (3H, m), 3.36 - 3.48 (2H, m), 3.63 - 3.71 (1H, m), 3.79 - 3.86

1259

(1H, m), 3.96 - 4.04 (4H, m), 4.36 (3H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.03 (1H, t, *J* = 5.7 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 497.

Producción de N-[trans-2-hidroxiciclohexil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

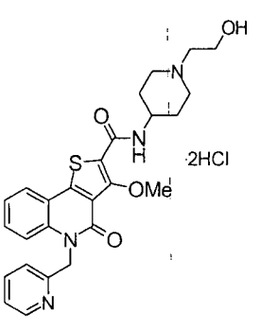


Del mismo modo que en el Ejemplo 25, el compuesto del título (168 mg, 67%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y trans-2-aminociclohexanol clorhidrato (101 mg, 0.666 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.36 (4H, m), 1.55 - 1.70 (2H, m), 1.80 - 1.95 (1H, m), 1.95 - 2.10 (1H, m), 3.30 - 3.45 (1H, m), 3.55 - 3.70 (1H, m), 3.98 (3H, s), 4.36 (3H, s), 4.78 (1H, d, *J* = 5.4 Hz), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 7.87 (1H, d, *J* = 7.5 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 498.

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida diclorhidrato.



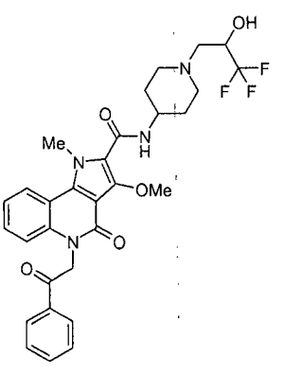
1260

Una mezcla del compuesto del Ejemplo 667 (60 mg, 0.15 mmol), 2-(clorometil)piridina clorhidrato (37 mg, 0.22 mmol), carbonato de potasio (52 mg, 0.37 mmol) y DMF (2 ml) se agitó a temperatura ambiente durante 3 hrs y a 4°C durante 1 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo, acetato de etilo/metanol=50/1 a 50/2) para dar un sólido blanco. A una solución del sólido blanco en acetato de etilo (2 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.1 ml), y el precipitado se recolectó por filtración, se lavó con dietil éter, y se secó bajo presión reducida para dar el compuesto del título (4.2 mg, 5%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.91 - 2.27 (4H, m), 3.05 - 3.30 (4H, m), 3.60 - 3.80 (4H, m), 4.07 - 4.10 (4H, m), 5.69 (2H, s), 7.28 - 7.34 (3H, m), 7.31 - 7.58 (2H, m), 7.77 (1H, t, *J* = 8.6 Hz), 7.88 (1H, d, *J* = 7.5 Hz), 8.02 (1H, d, *J* = 8.1 Hz), 8.50 (1H, d, *J* = 2.7 Hz), 9.40 - 9.55 (2H, amplio), 9.60 - 9.70 (1H, amplio).

Ejemplo 499.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-[1-(3.3,3-trifluoro-2-hidroxipropil)piperidin-4-il]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



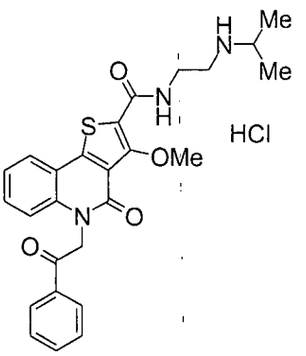
1261

Del mismo modo que en el Ejemplo 79, el compuesto del título (150 mg, 64%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 77 (200 mg, 0.400 mmol), 3-bromo-1,1,1-trifluoropropan-2-ol (62.2 µl, 0.600 mmol) y carbonato de potasio (249 mg, 1.80 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.70 (2H, m), 1.80 - 1.95 (2H, m), 2.15 - 2.35 (2H, m), 2.45 - 2.60 (2H, m), 2.75 - 2.90 (2H, m), 3.75 - 3.90 (1H, m), 3.98 (3H, s), 4.05 - 4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.09 – 6.16 (1H, m), 7.28 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1H, m), 7.90 (1H, d, *J* = 8.1 Hz), 8.16 - 8.18 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.4 Hz).

Ejemplo 500.

Producción de 3-metoxi-N-{2-[(1-metiletil)amino]etil}-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



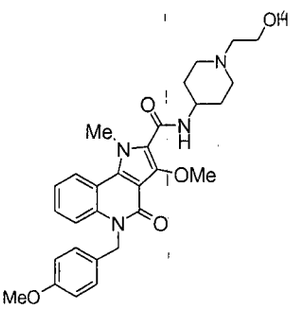
A una solución del compuesto del Ejemplo 97 (150 mg, 0.30 mmol) en acetato de etilo (10 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (0.1 ml), y el precipitado resultante se recolectó por filtración, se lavó con acetato de etilo, y se secó bajo presión reducida para dar el compuesto del título (107 mg, 69%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.25 (6H, d, *J* = 6.6 Hz), 3.13 (2H, s amplio), 3.30 - 3.45 (1H, m), 3.68 (2H, q, *J* = 5.9 Hz), 4.07 (3H, s), 6.00 (2H, s), 7.36 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J*

= 8.4 Hz), 7.57 - 7.67 (3H, m), 7.78 (1H, t, *J* = 7.3 Hz), 8.06 (1H, dd, *J* = 7.8, 1.2 Hz), 8.18 (2H, d, *J* = 8.4 Hz), 8.29 (1H, t, *J* = 5.9 Hz), 8.77 (2H, s amplio).

Ejemplo 501.

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

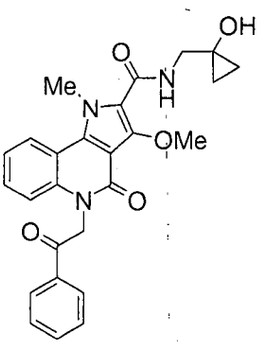


Del mismo modo que en el Ejemplo 79, el compuesto del título (1.91 g, 75%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 681 (2.50 g, 4.89 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58 (2H, q, *J* = 9.9 Hz), 1.85 (2H, d, *J* = 9.6 Hz), 2.18 (2H, t, *J* = 9.9 Hz), 2.40 (2H, t, *J* = 6.3 Hz), 2.78 (2H, d, *J* = 11.4 Hz), 3.50 (2H, q, *J* = 6.0 Hz), 3.69 (3H, s), 3.70 - 3.85 (1H, amplio), 4.04 (3H, s), 4.29 (3H, s), 4.35 - 4.40 (1H, m), 5.40 - 5.65 (2H, amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.4 Hz), 7.24 - 7.30 (1H, m), 7.32 - 7.39 (2H, m), 7.91 (1H, d, *J* = 7.8 Hz), 8.33 (1H, d, *J* = 8.1 Hz).

Ejemplo 502.

Producción de N-[(1-hidroxiciclopropil)metil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



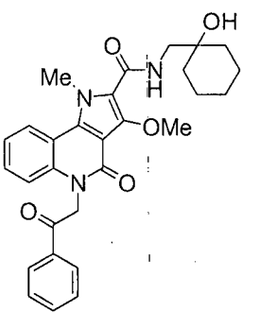
1263

Del mismo modo que en el Ejemplo 25, el compuesto del título (219 mg, 93%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-(aminometil)ciclopropanol (58.0 mg, 0.666 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.55 - 0.65 (4H, m), 3.46 (2H, d, *J* = 5.8 Hz), 4.01 (3H, s), 4.37 (3H, s), 5.50 (1H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.64 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.10 (1H, t, *J* = 5.8 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.1, 1.2 Hz).

Ejemplo 503.

Producción de N-[(1-hidroxiciclohexil)metil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

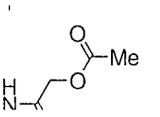


Del mismo modo que en el Ejemplo 25, el compuesto del título (235 mg, 92%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.512 mmol) y 1-(aminometil)ciclohexanol (110 mg, 0.666 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.70 (10H, m), 3.25 - 3.40 (2H, m), 4.01 (3H, s), 4.38 (3H, s), 4.50 (1H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1H, m), 8.02 (1H, t, *J* = 5.6 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 504.

Producción de 2-({2-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]etil}amino)-2-



1264

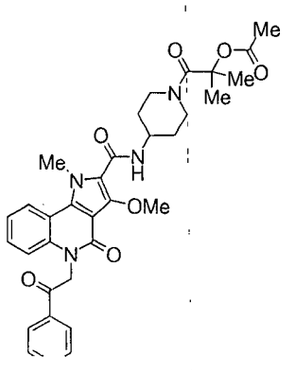
oxoacetato de etilo.

A una solución del compuesto del Ejemplo 103 (150 mg, 0.31 mmol) y trietilamina (69 mg, 0.68 mmol) en THF (10 ml) se agregó cloruro de acetoxiacetilo (46 mg, 0.34 mmol) enfrió con hielo. Luego de agitar a temperatura ambiente durante 1 hrs, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo a acetato de etilo/metanol=50/1) para dar un sólido blanco. La recristalización del sólido blanco a partir de acetato de etilo-hexano dio el compuesto del título (140 mg, 82%) como cristales blancos.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 2.28 (3H, s), 3.19 (3H, s), 3.62 (2H, s amplio), 3.77 (2H, s amplio), 4.02 (3H, s), 4.60 (2H, s), 5.87 (2H, s), 7.04 (1H, d, *J* = 8.4 Hz), 7.20 - 7.28 (1H, m), 7.35 - 7.50 (2H, m), 7.56 (2H, t, *J* = 7.5 Hz), 7.67 (1H, dd, *J* = 7.5, 1.5 Hz), 7.84 (1H, dd, *J* = 8.1, 1.2 Hz), 8.10 - 8.13 (2H, m).

Ejemplo 505.

Producción de 2-[4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-1,1-dimetil-2-oxoacetato de etilo.



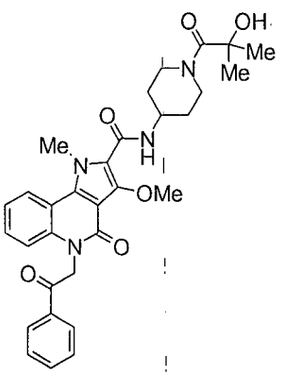
1765

Del mismo modo que en el Ejemplo 504, el compuesto del título se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 77 (200 mg, 0.423 mmol) y 2-cloro-1,1-dimetil-2-oxoacetato de etilo (63.0 µl, 0.440 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.36 - 1.50 (10 H, m), 1.80 - 1.95 (2 H, m), 2.07 (3 H, s), 2.75 - 3.40 (2 H, m), 3.96 (3 H, s), 4.00 - 4.25 (1 H, m), 4.29 (3 H, s), 5.97 (2 H, s), 7.29 - 7.39 (2 H, m), 7.35 - 7.50 (1 H, m), 7.63 (2 H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1 H, m), 7.98 (1 H, d, *J* = 7.8 Hz), 8.16 - 8.18 (2 H, m), 8.37 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 506.

Producción de N-[1-(2-hidroxi-2-metilpropanoil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 508, el compuesto del título (123 mg, 55%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 505, solución 8N de hidróxido de sodio (1.5 ml) y etanol (12 ml).

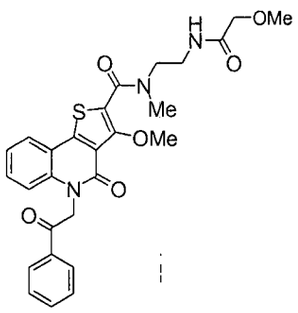
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.33 (6 H, s), 1.40 - 1.60 (2 H, m), 1.80 - 1.95 (2 H, m), 2.75 - 3.45 (2 H, m), 3.97 (3 H, s), 4.00 - 4.20 (1 H, m), 4.31 (3H, s), 4.20 - 4.80 (2H, m), 5.39 (1 H, s), 5.97 (2 H, s), 7.29 - 7.39 (2 H, m), 7.35 - 7.50 (1 H, m), 7.63

1766

(2 H, t, J = 7.5 Hz), 7.73 - 7.79 (1 H, m), 7.93 (1 H, d, J = 8.1 Hz), 8.15 - 8.18 (2 H, m), 8.37 (1 H, d, J = 8.3, 1.4 Hz).

Ejemplo 507.

Producción de 3-metoxi-N-{2-[(metoxiacetil)amino]etil}-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

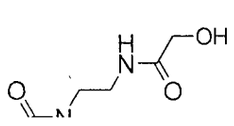


A una solución del compuesto del Ejemplo 103 (100 mg, 0.21 mmol) y trietilamina (46 mg, 0.45 mmol) en THF (10 ml) se agregó cloruro de metoxiacetilo (25 mg, 0.23 mmol) enfrió con hielo. Luego de agitar a temperatura ambiente durante 2 hrs, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo a acetato de etilo/metanol=50/1) para dar un sólido blanco. La recristalización del sólido blanco a partir de acetato de etilo-hexano dio el compuesto del título (61 mg, 56%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.06 (3H, s), 3.30 - 3.50 (5H, m), 3.50 - 3.65 (2H, amplio), 3.70 - 3.95 (5H, m), 5.98 (2H, s), 7.34 (1H, t, J = 7.3 Hz), 7.36 - 7.96 (7H, m), 8.18 (2H, d, J = 7.5 Hz).

Ejemplo 508.

Producción de N-{2-[(hidroxiacetil)amino]etil}-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-



1267

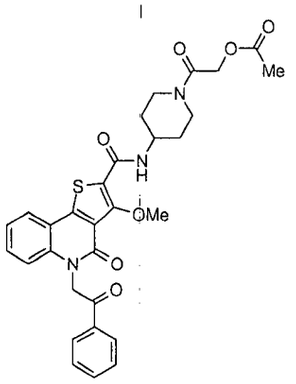
carboxamida.

Una solución mixta del compuesto del Ejemplo 504 (120 mg, 0.22 mmol) y solución acuosa 4N de hidróxido de sodio (2 ml) en THF (4 ml)-metanol (4 ml) se agitó a temperatura ambiente durante 2 hrs, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. La recristalización del sólido en bruto a partir de acetato de etilo-hexano dio el compuesto del título (65 mg, 58%) como cristales blancos.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 3.06 (3H, s), 3.20 - 3.40 (2H, m), 3.45 - 3.60 (2H, amplio), 3.70 - 3.86 (5H, m), 5.40 - 5.55 (1H, amplio), 5.98 (2H, s), 7.34 (1H, t, *J* = 7.5 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 7.87 - 7.96 (2H, m), 8.16 - 8.19 (2H, m).

Ejemplo 509.

Producción de 2-[4-({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo.



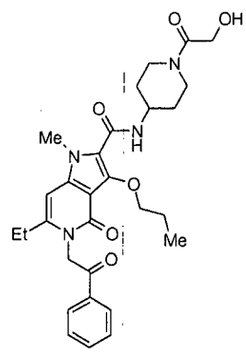
1268

Del mismo modo que en el Ejemplo 123, el compuesto del título (429 mg; 56%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 105 (620 mg, 1.20 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.44 - 1.64 (2H, m), 2.01 - 2.28 (5H, m), 2.88 - 3.05 (1H, m), 3.17 - 3.34 (1H, m), 3.59 - 3.75 (1H, m), 4.15 (3H, s), 4.19 - 4.35 (1H, m), 4.41 - 4.54 (1H, m), 4.65 - 4.84 (2H, m), 5.87 (2H, s), 7.03 (1H, d, *J* = 8.5 Hz), 7.28 - 7.35 (1H, m), 7.33 - 7.52 (1H, m), 7.52 - 7.63 (3H, m), 7.65 - 7.74 (1H, m), 7.91 (1H, dd, *J* = 7.9, 1.3 Hz), 8.06 - 8.18 (2H, m).

Ejemplo 510.

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-propoxi-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



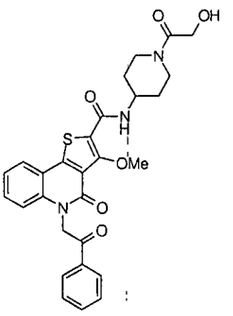
Del mismo modo que en el Ejemplo 140, el compuesto del título (199 mg, 74%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 173 (198 mg, 0.50 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.92 (3H, t, *J* = 7.3 Hz), 1.18 (3H, t, *J* = 7.3 Hz), 1.26 - 1.55 (2H, m), 1.59 - 1.75 (2H, m), 1.83 - 1.97 (2H, m), 2.57 (2H, q, *J* = 7.3 Hz), 2.77 - 2.91 (1H, m), 3.01 - 3.18 (1H, m), 3.60 - 3.75 (1H, m), 3.89 (3H, s), 3.97 - 4.14 (3H, m), 4.20 - 4.34 (3H, m), 4.51 (1H, t, *J* = 5.4 Hz), 5.59 (2H, s), 6.48 (1H, s), 7.56 - 7.68 (3H, m), 7.69 - 7.78 (1H, m), 8.07 - 8.15 (2H, m).

1269

Ejemplo 511.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

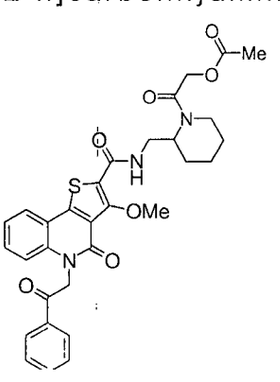


A una solución mixta del compuesto del Ejemplo 509 (200 mg, 0.35 mmol) en THF (3,2 ml)-etanol (11 ml) se agregó solución 8N de hidróxido de sodio (1.6 ml, 13 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se neutralizó con ácido clorhídrico 2N, y se extrajo con solvente mixto de acetato de etilo-THF. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se sometió a aminofiltración con gel de sílice. El filtrado se concentró bajo presión reducida, el residuo se recristalizó a partir de THF-acetato de etilo para dar el compuesto del título (93 mg, 50%) como un sólido blanco.

^{1}H-RMN (300 MHz, $CDCl_3$) δ: 1.43 - 1.64 (2H, m), 2.07 - 2.24 (2H, m), 2.98 - 3.24 (2H, m), 3.44 - 3.58 (1H, m), 3.62 (1H, t, *J* = 4.3 Hz), 4.15 (3H, s), 4.19 (2H, d, *J* = 4.3 Hz), 4.22 - 4.35 (1H, m), 4.44 - 4.57 (1H, m), 5.86 (2H, s), 7.03 (1H, d, *J* = 8.5 Hz), 7.28 - 7.34 (1H, m), 7.34 - 7.63 (4H, m), 7.64 - 7.73 (1H, m), 7.91 (1H, dd, *J* = 7.8, 1.4 Hz), 8.06 - 8.16 (2H, m).

Ejemplo 512.

Producción de 2-{2-[({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)metil]piperidin-1-il}-2-oxoacetato de etilo.



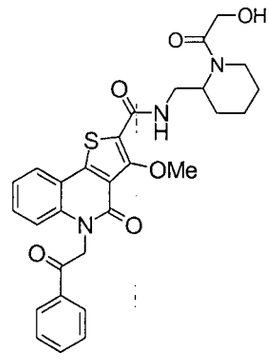
1270

Del mismo modo que en el Ejemplo 123, el compuesto del título se obtuvo como un aceite incoloro a partir del compuesto del Ejemplo 84 (500 mg, 0.95 mmol) y cloruro de acetoxiacetilo (142 mg, 1.04 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.80 (6 H, m), 2.00 (3 H, s), 2.81 (0.5 H, t, *J* = 13.1 Hz), 3.20 - 3.90 (3 H, m), 3.99 - 4.04 (3.5 H, m), 4.24 (0.5 H, d, *J* = 10.5 Hz), 4.65 (0.5H, d, *J* = 14.7 Hz), 4.80 - 4.82 (2H, m), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.7 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.2 Hz), 7.89 (0.5H, amplio t), 8.04 (1H, d, *J* = 8.1 Hz), 8.17 - 8.19 (2H, m), 8.26 (0.5H, s amplio).

Ejemplo 513.

Producción de N-{[1-(hidroxiacetil)piperidin-2-il]metil}-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 508, el compuesto del título (109 mg, 58%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 512 (200 mg, 0.34 mmol).

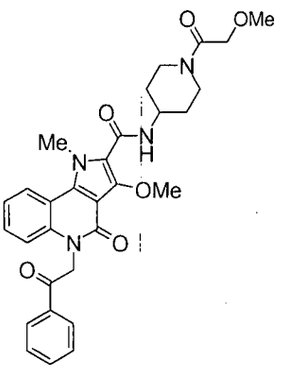
^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.10 - 1.80 (6H, m), 2.86 (0.5H, t, *J* = 12.9 Hz), 3.26 (0.5H, t, *J* = 15.0 Hz), 3.35 - 3.48 (1.5H, m), 3.70 - 3.90 (0.5H, m), 3.90 - 4.05 (4H, m), 4.05 - 4.15 (1.5H, m), 4.25 - 4.40 (1.5H, m), 4.75 - 4.90 (0.5H, m), 5.99 (2H,

1271

s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 7.85 - 7.95 (0.5H, amplio), 8.04 (1H, dd, *J* = 7.8, 1.2 Hz), 8.16 - 8.19 (2.5H, m).

Ejemplo 514.

Producción de 3-metoxi-N-[1-(metoxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

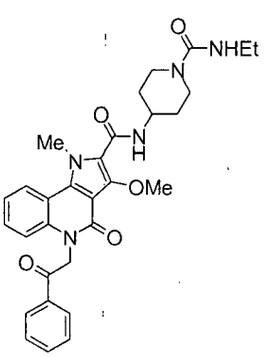


Del mismo modo que en el Ejemplo 507, el compuesto del título se obtuvo (159 mg, 73%) como un polvo blanco a partir del compuesto del Ejemplo 77 (200 mg, 0.423 mmol) y cloruro de metoxiacetilo (40.3 µl, 0.440 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.65 (2 H, m), 1.80 - 2.00 (2 H, m), 2.80 - 2.95 (1 H, m), 3.05 - 3.25 (1 H, m), 3.30 (3 H, s), 3.65 - 3.85 (1 H, m), 3.97 (3 H, s), 4.00 - 4.25 (4 H, m), 4.31 (3 H, s), 5.97 (2 H, s), 6.48 (1H, t, *J* = 5.4 Hz), 7.29 - 7.39 (2 H, m), 7.35 - 7.50 (1 H, m), 7.63 (2 H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1 H, m), 7.95 (1 H, d, *J* = 8.1 Hz), 8.15 - 8.18 (2 H, m), 8.37 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 515.

Producción de N-[1-(etilcarbamoil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



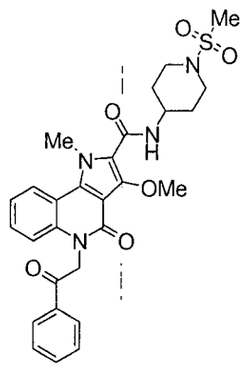
1272

A una mezcla del compuesto del Ejemplo 77 (200 mg, 0.423 mmol) y THF (10 ml) se agregó etil isocianato (101 µl, 1.27 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). La recristalización del sólido obtenido a partir de acetato de etilo-THF dio el compuesto del título (172 mg, 75%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.01 (3H, t, *J* = 7.1 Hz), 1.35 - 1.50 (2H, m), 1.75 - 1.90 (2H, m), 2.80 - 3.10 (4H, m), 3.80 - 3.95 (2H, m), 3.96 (3H, s), 3.95 - 4.10 (1H, m), 4.30 (3H, s), 5.97 (2H, s), 6.48 (1H, t, *J* = 5.4 Hz), 7.28 - 7.39 (2H, m), 7.34 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 7.93 (1H, d, *J* = 8.1 Hz), 8.15 - 8.18 (2H, m), 8.36 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 516.

Producción de 3-metoxi-1-metil-N-[1-(metilsulfonil)piperidin-4-il]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



A una mezcla del compuesto del Ejemplo 77 (200 mg, 0.423 mmol), trietilamina (423 µl, 3.18 mmol) y THF (10 ml) se agregó

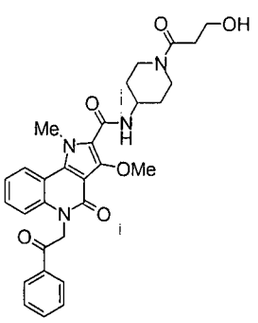
1273

cloruro de metansulfonilo (98.3 µl, 1.27 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). La recristalización del sólido obtenido a partir de acetato de etilo dio el compuesto del título (141 mg, 61%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.60 - 1.75 (2H, m), 1.90 - 2.05 (2H, m), 2.85 - 3.05 (5H, m), 3.45 - 3.60 (2H, m), 3.90 - 4.05 (1H, m), 3.98 (3H, s), 4.30 (3H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 8.00 (1H, d, *J* = 7.8 Hz), 8.16 - 8.18 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 517.

Producción de N-[1-(3-hidroxipropanoil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



A una mezcla del compuesto del Ejemplo 77 (200 mg, 0.423 mmol), trietilamina (423 µl, 3.18 mmol) y THF (10 ml) se agregó β-propiolactona (39.9 µl, 0.635 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice

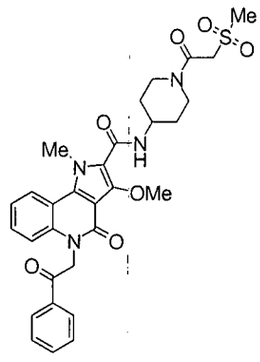
1274

(eluato; acetato de etilo). La recristalización del sólido obtenido a partir de acetato de etilo dio el compuesto del título (70.0 mg, 30%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.30 - 1.60 (2 H, m), 1.80 - 2.00 (2 H, m), 2.45 - 2.55 (2 H, m), 2.80 - 2.90 (1 H, m), 3.15 - 3.25 (1 H, m), 3.61 - 3.70 (2 H, m), 3.80 - 3.95 (1 H, m), 3.97 (3 H, s), 4.00 - 4.15 (1 H, m), 4.15 - 4.35 (1 H, m), 4.31 (3H, s), 4.51 (1 H, t, *J* = 5.4 Hz), 5.97 (2 H, s), 7.29 -7.39 (2 H, m), 7.35 - 7.50 (1 H, m), 7.63 (2 H, t, *J* =7.5 Hz), 7.73 - 7.79 (1 H, m), 7.94 (1 H, d, *J* = 7.8 Hz), 8.15 - 8.22 (2 H, m), 8.37 (1 H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 518.

Producción de 3-metoxi-1-metil-N-{1-[(metilsulfonil)acetil]piperidin-4-il}-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



A una solución del compuesto del Ejemplo 77 (200 mg, 0.423 mmol), ácido (metilsulfonil)acético (76.0 mg, 0.550 mmol) y HOBt (85.8 mg, 0.635 mmol) en DMF (4 ml) se agregó WSCD (122 mg, 0.635 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). La

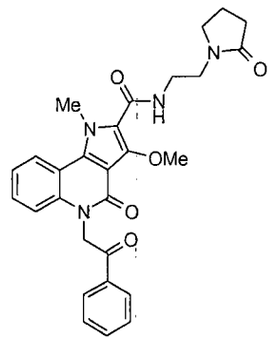
1275

recristalización del sólido obtenido a partir de acetato de etilo dio el compuesto del título (60.3 mg, 24%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.70 (2H, m), 1.85 - 2.00 (2H, m), 2.90 - 3.05 (1H, m), 3.10 (3H, s), 3.20 - 3.35 (1H, m), 3.90 - 4.20 (5H, m), 4.20 - 4.35 (1H, m), 4.30 (3H, s), 4.50 (2H, s), 5.97 (2H, s), 7.29 - 7.39 (2H, m), 7.35 - 7.50 (1H, m), 7.63 (2H, t, *J* = 7.7 Hz), 7.73 - 7.79 (1H, m), 7.98 (1H, d, *J* = 7.8 Hz), 8.16 - 8.18 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 519.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-[2-(2-oxopirrolidin-1-il)etil]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



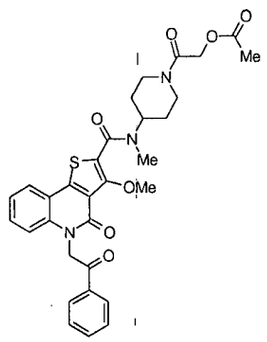
Del mismo modo que en el Ejemplo 25, el compuesto del título (153 mg, 60%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol), 1-(2-aminoetil)pirrolidin-2-ona (72 mg, 0.56 mmol), HOBt (89 mg, 0.66 mmol), WSCD (127 mg, 0.66 mmol) y DMF (6.0 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.97 - 2.14 (2H, m), 2.40 (2H, t, *J* = 8.1 Hz), 3.44 - 3.59 (4H, m), 3.60 - 3.70 (2H, m), 4.18 (3H, s), 4.47 (3H, s), 5.88 (2H, s), 7.00 - 7.09 (1H, m), 7.21 - 7.33 (1H, m), 7.35 - 7.35 (1H, m), 7.39 - 7.59 (2H, m), 7.62 - 7.71 (1H, m), 7.81 (1H, t, *J* = 5.4 Hz), 8.07 - 8.16 (2H, m), 8.25 (1H, dd, *J* = 8.3, 1.3 Hz).

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Ejemplo 520.

Producción de 2-{4-[{[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}(metil)amino]piperidin-1-il}-2-oxoacetato de etilo.

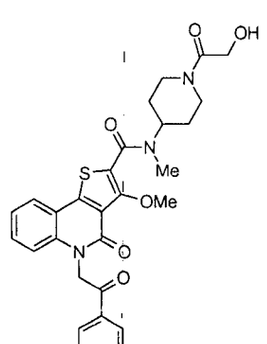


Del mismo modo que en el Ejemplo 73, se obtuvo N-metil-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida hidroclorido a partir del compuesto del Ejemplo de Referencia 7 (500 mg, 1.3 mmol), y *terc*-butil 4-(metilamino)piperidina-1-carboxilato (327 mg, 1.5 mmol), y se seguido del mismo modo que en el Ejemplo 500 y 130 el compuesto del título (182 mg, 24%) se obtuvo como sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.59 - 1.91 (4H, m), 2.08 (3H, s), 2.57 - 2.77 (1H, m), 2.91 (3H, s), 2.99 - 3.17 (1H, m), 3.32 (1H, m), 3.69 - 3.90 (4H, m), 4.29 - 4.50 (1H, m), 4.78 (2H, s), 5.98 (2H, s), 7.30 - 7.38 (1H, m), 7.33 - 7.70 (4H, m), 7.73 - 7.82 (1H, m), 7.97 (1H, dd, *J* = 7.9, 1.3 Hz), 8.11 - 8.22 (2H, m).

Ejemplo 521.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-N-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



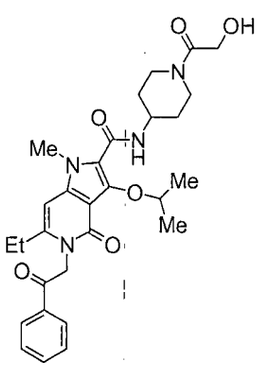
1277

Del mismo modo que en el Ejemplo 511, el compuesto del título (115 mg, 66%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 520 (187 mg, 0.32 mmol), solución 8N de hidróxido de sodio (1.6 ml), THF (3.2 ml) y etanol (11 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.64 - 1.98 (4H, m), 2.67 - 2.89 (1H, m), 3.00 (3H, s), 3.05 - 3.19 (1H, m), 3.52 - 3.66 (2H, m), 4.01 (3H, s), 4.10 - 4.26 (3H, m), 4.66 - 4.85 (1H, m), 5.87 (2H, s), 7.04 (1H, d, *J* = 8.5 Hz), 7.23 - 7.32 (1H, m), 7.32 - 7.51 (1H, m), 7.52 - 7.62 (2H, m), 7.63 - 7.75 (1H, m), 7.84 (1H, dd, *J* = 7.9, 1.3 Hz), 7.99 - 8.20 (2H, m).

Ejemplo 522.

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-3-(1-metiletoxi)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida.



Del mismo modo que en el Ejemplo 140, el compuesto del título (237 mg, 88%) se obtuvo como polvo sin color a partir del compuesto del Ejemplo 174 (188 mg, 0.50 mmol).

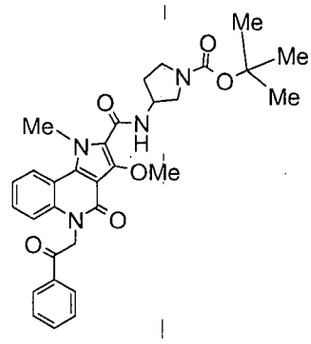
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.12 - 1.26 (9H, m), 1.26 - 1.57 (2H, m), 1.84 - 1.97 (2H, m), 2.57 (2H, q, *J* = 7.3 Hz), 2.76 - 2.94 (1H, m), 3.02 - 3.20 (1H, m), 3.59 - 3.76 (1H, m), 3.91 (3H, s), 3.96 - 4.19 (3H, m), 4.21 - 4.34 (1H, m), 4.50 (1H, t, *J* = 5.5 Hz), 4.94 - 5.09 (1H, m), 5.59 (2H, s), 6.48 (1H, s), 7.56 - 7.69

1278

(3H, m), 7.69 - 7.78 (1H, m), 8.06 - 8.16 (2H, m).

Ejemplo 523.

Producción de *terc*-butilo 3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)pirrolidina-1-carboxilato.

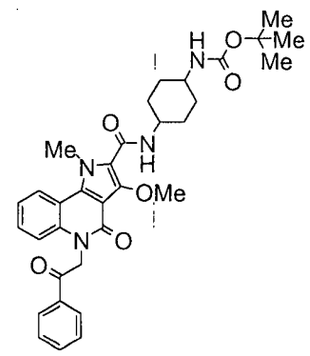


Del mismo modo que en el Ejemplo 25, el compuesto del título se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (400 mg, 1.02 mmol) y *terc*-butil 3-aminopirrolidina-1-carboxilato (248 mg, 1.33 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.41 (9 H, s), 1.87 - 2.02 (1 H, m), 2.05 - 2.19 (1 H, m, *J* = 14.7 Hz), 3.19 - 3.46 (3 H, m), 3.48 - 3.61 (1 H, m), 3.95 (3 H, s), 4.30 (3 H, s), 4.40 - 4,52 (1 H, m), 5.97 (2 H, s), 7.27 - 7.31 (2 H, m), 7.34 - 7.53 (1 H, m), 7.63 (2 H, t, *J* =7.6 Hz), 7.72 - 7.80 (1 H, m), 8.11 - 8.22 (3 H, m), 8.37 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 524.

Producción de *terc*-butil [4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexil]carbamato.



Del mismo modo que en el Ejemplo 25, el compuesto del

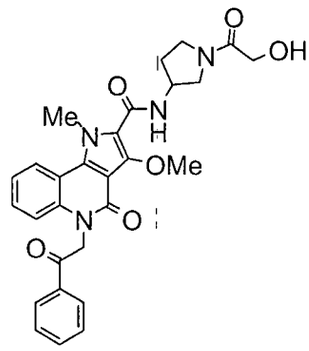
1279

título se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (400 mg, 1.02 mmol) y *terc*-butilo (4-aminociclohexil)carbamato (285 mg, 1.33 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 - 1.69 (13 H, m), 1.72 - 1.96 (4 H, m), 3.16 - 3.29 (1 H, m), 3.65 - 3.80 (1 H, m, *J* = 11.1 Hz), 3.95 (2.5 H, s), 4.07 (0.5 H, s), 4.30 (2.5 H, s), 4.39 (0.5 H, s), 5.97 (2 H, s), 6.70 - 6.81 (0.8 H, m), 6.85 - 6.94 (0,2 H, m), 7.25 - 7.32 (2 H, m), 7.33 - 7.53 (1 H, m), 7.58 - 7.68 (2 H, m), 7.72 - 7.86 (2 H, m), 8.14 - 8.22 (2 H, m), 8.36 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 525.

Producción de N-[1-(hidroxiacetil)pirrolidin-3-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Una mezcla del compuesto del Ejemplo 523, acetato de etilo (2 ml) y solución 4N de hidrógeno cloruro de acetato de etilo (2 ml) se agitó a temperatura ambiente durante 1 hrs. La mezcla se concentró bajo presión reducida, solución de hidrógeno carbonato de sodio se agregó al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida para dar 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-pirrolidin-3-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida (153 mg, 27%) como cristales blancos.

A una mezcla del así obtenido 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-pirrolidin-3-il-4,5-dihidro-1H-pirrolo[3,2-

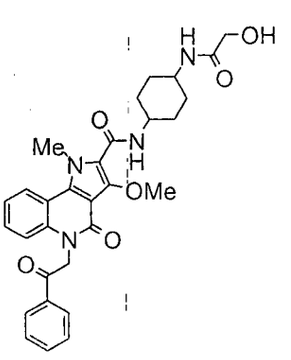
1280

c]quinolin-2-carboxamida (153 mg, 0.327 mmol), trietilamina (99.7 µl, 0.720 mmol) y THF (3 ml) se agregó cloruro de acetoxiacetilo (38.7 µl, 0.360 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). El aceite obtenido se disolvió en THF (4 ml) y etanol (12 ml), solución 8N de hidróxido de sodio (1 ml) se agregó y la mezcla se agitó a temperatura ambiente durante 1.5 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 1N (8.5 ml), y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=10/0 - 9/1). La recristalización del sólido obtenido a partir de acetato de etilo-THF dio el compuesto del título (121 mg, 72%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.86 - 2,31 (2 H, m), 3.33 - 3.56 (3 H, m), 3.58 - 3.72 (1 H, m), 3.94 (3 H, s), 4.02 (2 H, dd, *J* = 10.2, 5.7 Hz), 4.29 (3 H, d, *J* = 2.1 Hz), 4.40 - 4.64 (2 H, m), 5.97 (2 H, s), 7.27 - 7.31 (2 H, m), 7.33 - 7.52 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.72 - 7.81 (1 H, m), 8.12 - 8.23 (3 H, m), 8.37 (1 H, d, *J* = 7.9 Hz).

Ejemplo 526.

Producción de N-{4-[(hidroxiacetil)amino]ciclohexil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



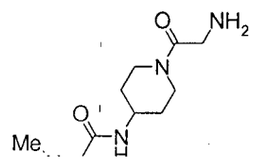
1281

A una mezcla del compuesto del Ejemplo 88 (190 mg, 0.363 mmol), trietilamina (151 µl, 1.09 mmol) y THF (7 ml) se agregó cloruro de acetoxiacetilo (46.9 µl, 0.436 mmol) a 0°C, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de magnesio, y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). El aceite obtenido se disolvió en THF (2.5 ml) y etanol (5 ml), solución 8N de hidróxido de sodio (0.5 ml) se agregó y la mezcla se agitó a temperatura ambiente durante 1.5 hrs. La mezcla de reacción se diluyó con agua, se acidificó con ácido clorhídrico 1N (4.5 ml), y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio y concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/THF=10/0 - 0/10). La recristalización del sólido obtenido a partir de acetato de etilo-THF dio el compuesto del título (91,1 mg, 46%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.44 (4 H, t, *J* = 10.1 Hz), 1.67 - 1.85 (2 H, m), 1.88 - 2.02 (2 H, m), 3.55 - 3.84 (4 H, m), 3.96 (3 H, s), 4.30 (3 H, s), 5.43 (1 H, t, *J* = 5.8 Hz), 5.97 (2 H, s), 7.23 - 7.30 (2 H, m), 7.33 - 7.55 (2 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.89 (2 H, m), 8.11 - 8.23 (2 H, m), 8.36 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 527.

Producción de N-(1-glycilpiperidin-4-il)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



1282

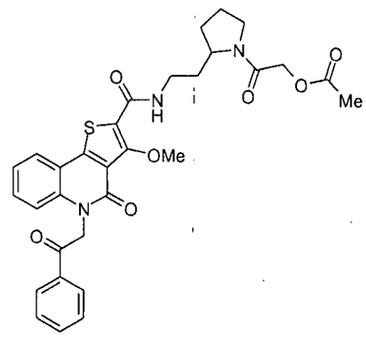
A una solución del compuesto del Ejemplo 77 (250 mg, 0.529 mmol), N-boc-glicina (111 mg, 0.635 mmol) y HOBt (107 mg, 0.794 mmol) en DMF (5 ml) se agregó WSCD (152 mg, 0.794 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se disolvió en acetato de etilo (2 ml), se agregó solución 4N de hidrógeno cloruro de acetato de etilo (2 ml), y la mezcla se agitó a temperatura ambiente durante 1 hrs. El sólido precipitado se recolectó por filtración, se lavó con acetato de etilo, y se recristalizó a partir de etanol-acetato de etilo para dar el compuesto del título (236 mg, 79%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.70 (2H, m), 1.85 - 2.00 (2H, m), 2.95 - 3.10 (1H, m), 3.15 - 3.30 (1H, m), 3.60 - 3.75 (1H, m), 3.80 - 3.95 (2H, m), 3.97 (3H, s), 4.05 - 4.30 (2H, m), 4.31 (3H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.35 - 7.51 (1H, m), 7.63 (2H, t, *J* = 7.5 Hz), 7.73 - 7.79 (1H, m), 7.99 (1H, d, *J* = 7.8 Hz), 8.08 - 8.21 (5H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 528.

Producción de 2-{2-[2-({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)etil]pirrolidin-1-il}-2-oxoacetato de etilo.

4283

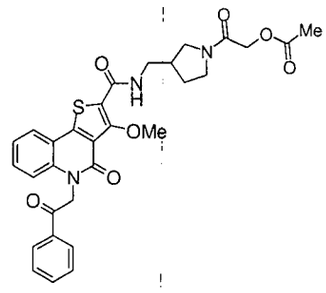


Del mismo modo que en el Ejemplo 504, el compuesto del título (200 mg, 89%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 82 (200 mg, 0.38 mmol) y cloruro de acetoxiacetilo (57 mg, 0.42 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 2.00 (6 H, m), 2.08 (3 H, s), 2.90 - 3.10 (1H, m), 3.38 - 3.49 (2 H, m), 3.50 - 3.65 (1H, m), 4.05 (3H, s), 4.10 - 4.20 (1H, m), 4.73 (2 H, s), 5.99 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.57 (1H, d, *J* = 7.2 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.77 (1H, t, *J* = 7.5 Hz), 8.04 (1H, d, *J* = 7.8 Hz), 8.18 (2H, d, *J* = 7.5 Hz), 8.45 (1H, t, *J* = 6.0 Hz).

Ejemplo 529.

Producción de 2-{3-[({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)metil]pirrolidin-1-il}-2-oxoacetato de etilo.



Del mismo modo que en el Ejemplo 504, el compuesto del título (160 mg, 71%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 669 (200 mg, 0.39 mmol) y cloruro de acetoxiacetilo (87 mg, 0.86 mmol).

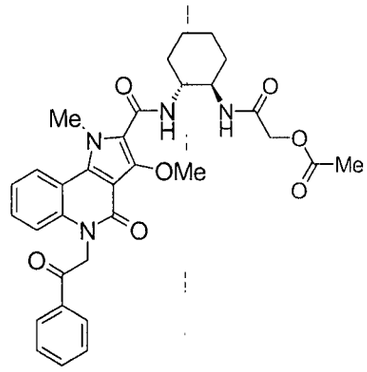
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.60 - 1.78 (2 H, m), 1.84 - 1.95 (1H, m), 2.07 (3 H, s), 2.50 - 2.70 (1H, m), 3.07 - 3.57 (6 H,

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m), 4.03 (1.5 H, m), 4.04 (1.5 H, s), 4.65 ((2H, m), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.58 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 8.16 - 8.23 (2H, m).

Ejemplo 530.

Producción de 2-{[trans-2-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexil]amino}-2-oxoacetato de etilo.

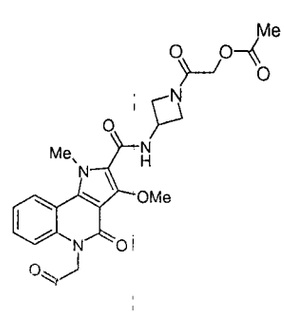


Del mismo modo que en el Ejemplo 504, el compuesto del título (190 mg, 85%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 85 (200 mg, 0.38 mmol) y cloruro de acetoxiacetilo (63 mg, 0.46 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.41 (4 H, m), 1.71 (2H, s amplio), 1.80 - 1.90 (1H, amplio d), 2.04 (3 H, s), 2.41 - 2.45 (1 H, m), 3.72 - 3.85 (2 H, m), 3.95 (3 H, s), 4.26 (3 H, s), 4.40 (2H, s), 5.97 (2H, s), 7.29 - 7.30 (2H, m), 7.38 (1H, t, *J* = 7.8 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.74 - 7.82 (2H, m), 7.95 (1H, d, *J* = 8.1 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, d, *J* = 6.9 Hz).

Ejemplo 531.

Producción de 2-[3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)azetidin-1-il]-2-oxoacetato de etilo.



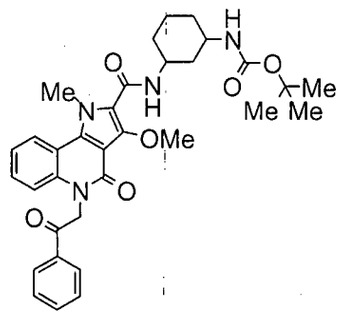
1285

Del mismo modo que en el Ejemplo 123, N-azetidin-3-il-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato (600 mg) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 670 (610 mg, 1.12 mmol). El Compuesto del título (121 mg, 17%) se obtuvo como un sólido blanco a partir del así obtenido polvo blanco por aplicación de un método similar al del Ejemplo 504.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 2.09 (3H, s), 3.30 - 3.50 (2 H, m), 3.86 (3 H, s), 4.16 (1 H, s), 4.36 (3 H, s), 4.40 - 4.42 (2H, m), 4.48 (2H, m), 5.97 (2H, s), 7.30 - 7.30 (2H, m), 7.38 (1H, d, *J* = 8.3 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.16 - 8.23 (3H, m), 8.40 (1H, d, *J* = 7.5 Hz).

Ejemplo 532.

Producción de *terc*-butil [3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexil]carbamato.



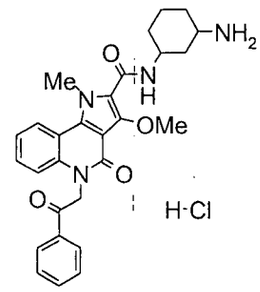
Del mismo modo que en el Ejemplo 25, el compuesto del título (395 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (400 mg, 1.02 mmol) y *terc*-butilo (3-aminociclohexil)carbamato (285 mg, 1.33 mmol).

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^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.98 - 1.46 (13 H, m), 1.65 - 1.90 (3 H, m), 2.00 - 2.12 (1 H, m), 3.23 - 3.42 (1 H, m), 3.73 - 3.88 (1 H, m), 3.96 (2 H, s), 4.04 (1 H, s), 4.30 (2 H, s), 4.35 (1 H, s), 5.97 (2 H, s), 6.76 - 6.94 (1 H, m), 7.24 - 7.32 (2 H, m), 7.33 - 7.53 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.80 (1 H, m), 7.86 (1 H, d, *J* = 7.9 Hz), 8.12 - 8.22 (2 H, m), 8.31 - 8.42 (1 H, m).

Ejemplo 533

Producción de N-(3-aminociclohexil)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



A una mezcla del compuesto del Ejemplo 532 (380 mg, 0.648) y acetato de etilo (4 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (4 ml), y la mezcla se agitó a temperatura ambiente durante 2 hrs. El sólido precipitado se recolectó por filtración, y se lavó con acetato de etilo para dar el compuesto del título (305 mg, 90%) como cristales blancos.

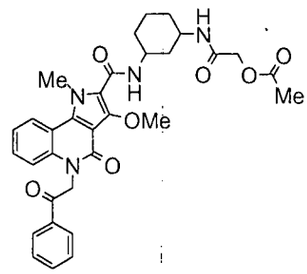
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.09 - 2.03 (7 H, m), 2.17 - 2.32 (1 H, m), 3.05 - 3.24 (1 H, m), 3.80 - 4.10 (4 H, m), 4.28 (2.5 H, s), 4.32 (0.5H, s), 5.97 (2 H, s), 7.26 - 7.53 (3 H, m), 7.63 (2 H, t, *J* = 7.3 Hz), 7.76 (1 H, t, *J* = 7.3 Hz), 7.95 - 8.22 (6 H, m), 8.37 (1 H, d, *J* = 8.3 Hz).

Ejemplo 534.

Producción de 2-{[3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-

1287

il]carbonil}amino)ciclohexil]amino}-2-oxoacetato de etilo.

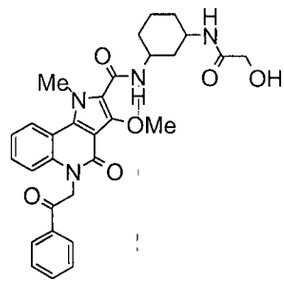


Del mismo modo que en el Ejemplo 504, el compuesto del título (223 mg, 70%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 533 (285 mg, 0.546 mmol) y cloruro de acetoxiacetilo (70.4 µl, 0.655 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.06 - 1.48 (4 H, m), 1.67 - 1.93 (3 H, m), 2.00 - 2.12 (4 H, m), 3.59 - 3.76 (1 H, m), 3.78 - 3.91 (1 H, m), 3.95 (2.7 H, s), 4.03 (0.3 H, s), 4.29 (2.7 H, s), 4.35 (0.3 H, s), 4.41 (1,8 H, s), 4.45 (0,2 H, s), 5.97 (2 H, s), 7.26 - 7.30 (2 H, m), 7.33 - 7.52 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.72 - 7.80 (1 H, m), 7.85 - 7.99 (2 H, m), 8.11 - 8.23 (2 H, m), 8.36 (1 H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 535.

Producción de N-{3-[(hidroxiacetil)amino]ciclohexil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 508, el compuesto del título (173 mg, 93%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 534 (200 mg, 0.34 mmol), solución 8N de hidróxido de sodio (0.5 ml), THF (2.5 ml) y etanol (5 ml).

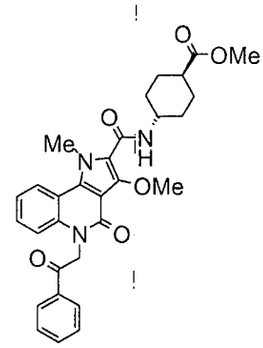
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.12 - 1.50 (4 H, m), 1.66 -

1288

1.82 (2 H, m), 1.84 - 1.94 (1 H, m), 1.98 - 2,10 (1 H, m), 3.65 - 3.91 (4 H, m), 3.95 (2.7 H, s), 4.06 (0.3 H, s), 4.30 (2.7 H, s), 4.35 (0.3 H, s), 5.39 (1 H, d, *J* = 5.1 Hz), 5.98 (2 H, s), 7.24 - 7.31 (2 H, m), 7.36 (1 H, d, *J* = 7.8 Hz), 7.54 - 7.69 (3 H, m), 7.76 (1 H, t, *J* =,3 Hz), 7.87 (1 H, d, *J* = 7.9 Hz), 8.17 (2 H, d, *J* = 7.7 Hz), 8.37 (1 H, d, *J* = 8.3 Hz).

Ejemplo 536.

Producción de metil trans-4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexanocarboxilato.

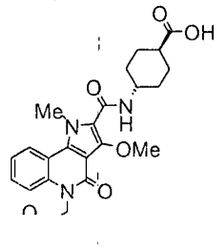


Del mismo modo que en el Ejemplo 25, el compuesto del título (535 mg, 79%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (500 mg, 1.28 mmol), trietilamina (230 µl, 1.66 mmol) y metil trans-4-aminociclohexanocarboxilato clorhidrato (321 mg, 1.66 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.27 - 1.60 (4 H, m), 1.87 - 2.07 (4 H, m), 2.25 - 2.41 (1 H, m), 3.60 (3 H, s), 3.69 - 3.86 (1 H, m), 3.96 (3 H, s), 4.30 (3 H, s), 5.96 (2 H, s), 7.25 - 7.31 (2 H, m), 7.33 - 7.53 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.88 (2 H, m), 8.11 - 8.23 (2 H, m), 8.36 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 537.

Producción de ácido trans-4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexanocarboxílico.



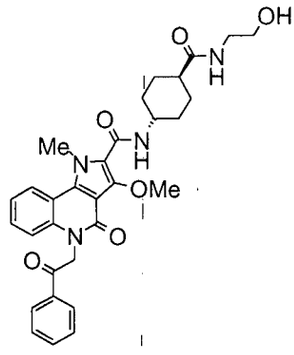
1289

Una mezcla del compuesto del Ejemplo 536 (300 mg, 0.566 mmol), solución 8N de hidróxido de sodio (1 ml) y etanol (7 ml) se agitó a temperatura ambiente durante 6 hrs. La mezcla de reacción se acidificó con ácido clorhídrico 6N (1.5 ml), y el sólido precipitado se recolectó por filtración. El sólido obtenido se lavó con agua, y se secó bajo presión reducida para dar el compuesto del título (225 mg, 81%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.25 - 1.57 (4 H, m), 1.85 - 2.05 (4 H, m), 2.10 - 2.26 (1 H, m), 3.67- 3.85 (1 H, m), 3.98 (3 H, s), 4.29 (3 H, s), 5.97 (2 H, s), 7.25 - 7.31 (2 H, m), 7.32 - 7.52 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.88 (2 H, m), 8.12 - 8.24 (2 H, m), 8.37 (1 H, dd, *J* = 8.3, 1.1 Hz), 12.23 (1 H, s amplio.).

Ejemplo 538.

Producción de N-{trans-4-[(2-hidroxietil)carbamoil]ciclohexil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



A una solución del compuesto del Ejemplo 537 (215 mg, 0.417 mmol), 2-aminoetanol (32.5 µl, 0.542 mmol) y HOBt (84.6 mg, 0.626 mmol) en DMF (5 ml) se agregó WSCD (120 mg, 0.626 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con

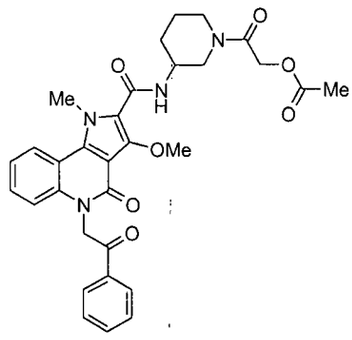
1290

solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=10/0 - 8/2). La recristalización del sólido obtenido a partir de acetato de etilo-THF dio el compuesto del título (131 mg, 56%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.22 - 1.58 (4 H, m), 1.71 - 1.86 (2 H, m), 1.90 - 2.03 (2 H, m), 2.05 - 2.20 (1 H, m), 3.03 - 3.18 (2 H, m), 3.34 - 3.44 (2 H, m), 3.65 - 3.84 (1 H, m), 3.98 (3 H, s), 4.30 (3 H, s), 4.63 (1 H, t, *J* = 5.6 Hz), 5.97 (2 H, s), 7.25 - 7.31 (2 H, m), 7.37 (1 H, t, *J* = 7.7 Hz), 7.58 - 7.68 (2 H, m), 7.70 - 7.88 (3 H, m), 8.17 (2 H, d, *J* = 7.6 Hz), 8.37 (1 H, d, *J* = 8.1 Hz).

Ejemplo 539.

Producción de 2-[3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo.



Del mismo modo que en el Ejemplo 25, el compuesto del título (284 mg, 39%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (500 mg, 1.3 mmol), *terc*-butilo 3-aminopiperidina-1-carboxilato (257 mg, 1.3 mmol), HOBt (203 mg, 1.5 mmol), WSCD (294 mg, 1.5 mmol), DMF (15 ml), solución 4N de hidrógeno cloruro de acetato de etilo (4.0 ml),

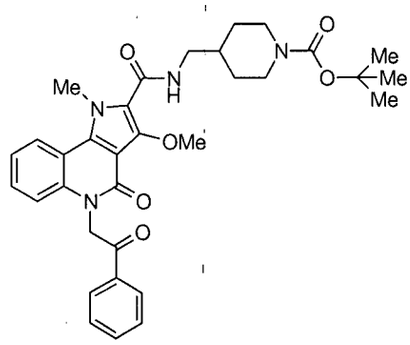
1291

THF (4.0 ml), metanol (4.0 ml), cloruro de acetoxiacetilo (0.098 ml, 0.91 mmol), trietilamina (0,28 ml, 2.0 mmol) y THF (16 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.64 - 1.88 (3H, m), 1.93 - 2.09 (1H, m), 2.16 (3H, s), 3.24 - 3.59 (2H, m), 3.67 - 3.82 (2H, m), 4.04 - 4.24 (4H, m), 4.47 (3H, s), 4.67 - 4.88 (2H, m), 5.79 - 5.97 (2H, m), 7.05 (1H, d, *J* = 7.9 Hz), 7.20 - 7.34 (1H, m), 7.37 - 7.36 (1H, m), 7.55 (2H, t, *J* = 7.6 Hz), 7.61 - 7.71 (1H, m), 7.82 (1H, d, *J* = 7.0 Hz), 8.07 - 8.16 (2H, m), 8.26 (1H, dd, *J* = 8.2, 1.4 Hz).

Ejemplo 540.

Producción de *terc*-butil 4-[({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)metil]piperidina-1-carboxilato.



Del mismo modo que en el Ejemplo 25, el compuesto del título (521 mg, 69%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (500 mg, 1.3 mmol), *terc*-butil 4-(aminometil)piperidina-1-carboxilato (302 mg, 1.4 mmol), HOBt (208 mg, 1.5 mmol), WSC (294 mg, 1.5 mmol) y DMF (15 ml).

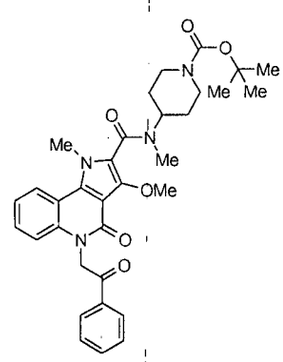
^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.14 - 1.33 (2H, m), 1.41 - 1.51 (9H, m), 1.70 - 1.85 (3H, m), 2.63 - 2.80 (2H, m), 3.37 (2H, t, *J* = 6.1 Hz), 4.03 - 4.25 (5H, m), 4.47 (3H, s), 5.89 (2H, s), 7.05 (1H, d, *J* = 8.5 Hz), 7.21 - 7.31 (1H, m), 7.36 - 7.36 (1H, m), 7.50 - 7.60 (2H, m), 7.62 - 7.70 (1H, m), 7.76 (1H, t, *J* = 5.9 Hz), 8.05 -

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8.16 (2H, m), 8.26 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 541.

Producción de *terc*-butil 4-[{[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}(metil)amino]piperidina-1-carboxilato.

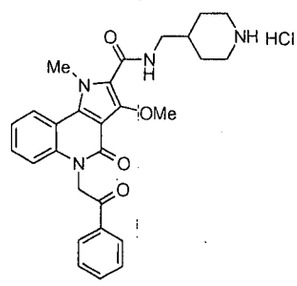


Del mismo modo que en el Ejemplo 25, el compuesto del título (565 mg, 75%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (500 mg, 1.3 mmol), *terc*-butil 4-(metilamino)piperidina-1-carboxilato (274 mg, 1.3 mmol), HOBt (208 mg, 1.5 mmol), WSCD (294 mg, 1.5 mmol) y DMF (15 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.42 - 1.52 (9 H, m), 1.65 - 1.86 (4H, m), 2.56 - 2.97 (2H, m), 3.03 (3H, s), 3.97 - 4.20 (7H, m), 4.22 - 4.37 (1H, m), 4.61 - 4.81 (1H, m), 5.89 (2H, s), 7.05 (1H, d, *J* = 8.5 Hz), 7.19 - 7.30 (1H, m), 7.33 - 7.33 (1H, m), 7.39 - 7.59 (2H, m), 7.60 - 7.70 (1H, m), 8.05 - 8.15 (2H, m), 8.18 (1H, d, *J* = 7.3 Hz).

Ejemplo 542.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(piperidin-4-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato.



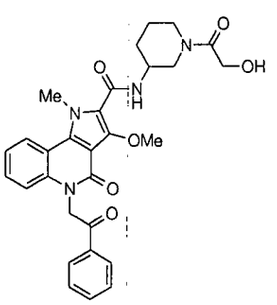
1293

Una solución mixta del compuesto del Ejemplo 540 (500 mg, 0.85 mmol) y solución 4N de hidrógeno cloruro de acetato de etilo (4.0 ml) en THF (4.0 ml)-metanol (4.0 ml) se agitó a temperatura ambiente durante 2 hrs. solución 4N de hidrógeno cloruro de acetato de etilo (4.0 ml) y metanol (8.0 ml) se agregaron, y la mezcla se agitó a temperatura ambiente durante 1.5 hrs. La mezcla de reacción se concentró bajo presión reducida, y se recristalizó a partir de metanol-dietil éter para dar el compuesto del título (356 mg, 80%) como un sólido amarillo pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.29 - 1.48 (2H, m), 1.75 - 1.95 (3H, m), 2.78 - 2.94 (2H, m), 3.18 - 3.38 (4H, m), 4.00 (3H, s), 4.31 (3H, s), 5.98 (2H, s), 7.27 - 7.32 (2H, m), 7.34 - 7.53 (1H, m), 7.59 - 7.69 (2H, m), 7.72 - 7.81 (1H, m), 8.07 - 8.22 (3H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz), 8.51 (2H, s amplio).

Ejemplo 543.

Producción de N-[1-(hidroxiacetil)piperidin-3-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 511, el compuesto del título (69 mg, 43%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 539 (174 mg, 0.30 mmol), solución 8N de hidróxido de sodio (1.6 ml), THF (3.2 ml) y etanol (11 ml).

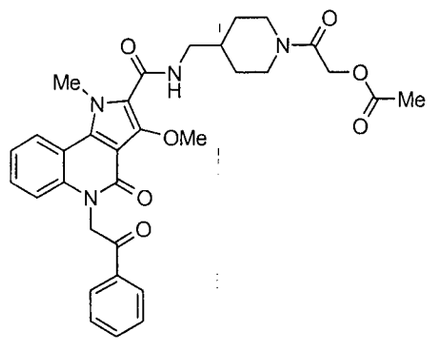
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.44 - 1.81 (3H, m), 1.84 -

1294

1.96 (1H, m), 3.29 - 3.61 (3H, m), 3.80 - 3.90 (1H, m), 3.91 - 4.02 (4H, m), 4.04 - 4.17 (2H, m), 4.35 (3H, s), 4.54 (1H, t, *J* = 5.4 Hz), 5.97 (2H, s), 7.27 - 7.32 (2H, m), 7.34 - 7.53 (1H, m), 7.59 - 7.69 (2H, m), 7.71 - 7.81 (1H, m), 7.89 - 8.01 (1H, m), 8.12 - 8.21 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 544.

Producción de 2-{4-[({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)metil]piperidin-1-il}-2-oxoacetato de etilo.



A una solución del compuesto del Ejemplo 542 (400 mg, 0.76 mmol) y trietilamina (0,29 ml, 2.1 mmol) en THF (17 ml) se agregó cloruro de acetoxiacetilo (0.10 ml, 0.95 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 4 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se filtró a través de gel de aminosílice. El filtrado se concentró, y el residuo se recristalizó a partir de etanol-hexano para dar el compuesto del título (321 mg, 71%) como un sólido blanco.

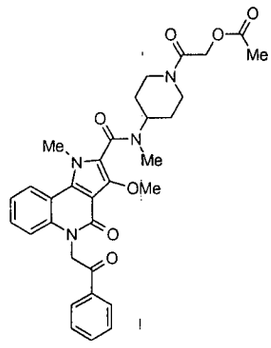
^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.16 - 1.37 (2H, m), 1.78 - 1.99 (3H, m), 2.18 (3H, s), 2.58 - 2.71 (1H, m), 2.99 - 3.15 (1H, m), 3.31- 3.43 (2H, m), 3.63 - 3.76 (1H, m), 4.17 (3H, s), 4.47 (3H, s), 4.57 - 4.66 (1H, m), 4.73 (2H, s), 5.89 (2H, s), 7.01 - 7.08 (1H, m), 7.20 - 7.33 (1H, m), 7.37 - 7.37 (1H, m), 7.50 - 7.60 (2H, m),

1295

7.62 - 7.71 (1H, m), 7.79 (1H, t, *J* = 5.9 Hz), 8.07 - 8.17 (2H, m), 8.26 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 545.

Producción de 2-{4-[{[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}(metil)amino]piperidin-1-il}-2-oxoacetato de etilo.

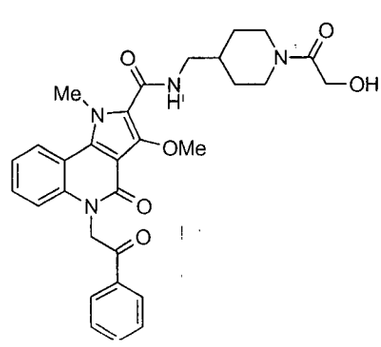


Del mismo modo que en el Ejemplo 123, el compuesto del título (226 mg, 40%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 541 (565 mg, 0.96 mmol), solución 4N de hidrógeno cloruro de acetato de etilo (4.0 ml), THF (4.0 ml), metanol (4.0 ml), cloruro de acetoxiacetilo (0.077 ml, 0.71 mmol), trietilamina (0,22 ml, 1.6 mmol) y THF (13 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.70 - 1.97 (4H, m), 2.15 - 2.24 (3H, m), 2.50 - 2.83 (1H, m), 3.03 (3H, s), 3.10 - 3.33 (1H, m), 3.63 - 3.86 (1H, m), 4.02 (3H, s), 4.04 - 4.11 (3H, m), 4.60 - 4.87 (4H, m), 5.89 (2H, s), 7.02 - 7.10 (1H, m), 7.17 - 7.32 (1H, m), 7.35 - 7.34 (1H, m), 7.37 - 7.60 (2H, m), 7.61 - 7.71 (1H, m), 8.07 - 8.15 (2H, m), 8.19 (1H, dd, *J* = 8.1, 1.3 Hz).

Ejemplo 546.

Producción de N-{[1-(hidroxiacetil)piperidin-4-il]metil}-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



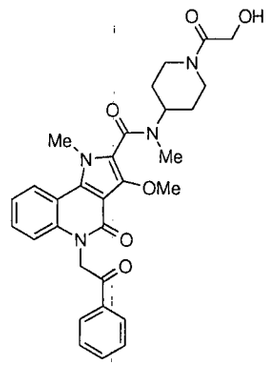
1296

Del mismo modo que en el Ejemplo 511, el compuesto del título (77 mg, 41%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 544 (200 mg, 0.34 mmol), solución 8N de hidróxido de sodio (1,8 ml), THF (3.6 ml) y etanol (13 ml).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.99 - 1.26 (2H, m), 1.65 - 1.93 (3H, m), 2.57 - 2.71 (1H, m), 2.87 - 3.01 (1H, m), 3.18 - 3.27 (2H, m), 3.65 - 3.75 (1H, m), 3.98 (3H, s), 4.07 (2H, t, *J* = 5.4 Hz), 4.27 - 4.40 (4H, m), 4.41 - 4.50 (1H, m), 5.97 (2H, s), 7.25 - 7.32 (2H, m), 7.34 - 7.53 (1H, m), 7.59 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 8.07 (1H, t, *J* = 6.0 Hz), 8.13 - 8.21 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 547.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-N,1-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 511, el compuesto del título (117 mg, 62%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 545 (205 mg, 0.35 mmol), solución 8N de hidróxido de sodio (1,8 ml), THF (3.6 ml) y etanol (13 ml).

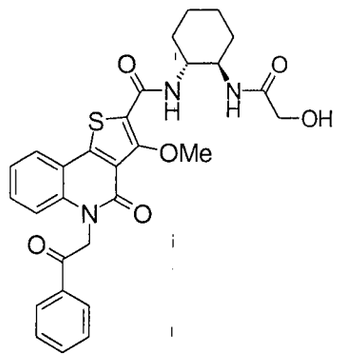
^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.65 - 2.01 (4H, m), 2.78 - 2.92 (1H, m), 2.99 - 3.09 (3H, m), 3.12 - 3.27 (1H, m), 3.48 - 3.69 (2H, m), 3.99 - 4.04 (3H, m), 4.04 - 4.11 (3H, m), 4.14 - 4.30 (2H, m), 4.61 - 4.88 (2H, m), 5.89 (2H, s), 7.06 (1H, d, *J* = 8.7 Hz), 7.22 - 7.32 (1H, m), 7.35 - 7.34 (1H, m), 7.54 (2H, t, *J* = 7.6 Hz), 7.62 -

1297

7.72 (1H, m), 8.11 (2H, d, *J* = 7.6 Hz), 8.19 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 548.

Producción de N-{trans-2-[(hidroxiacetil)amino]ciclohexil}-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

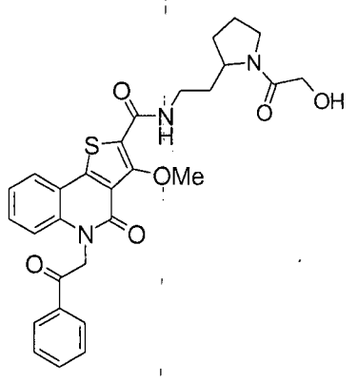


Del mismo modo que en el Ejemplo 508, el compuesto del título (88 mg, 58%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 530 (150 mg, 0.26 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.20 - 1.50 (6H, m), 1.70 (2H, s amplio), 1.87 (1H, d, *J* = 11,1 Hz), 2.05 (1H, d, *J* = 9.6 Hz), 3.72 - 3.94 (7H, m), 4.31 (3H, s), 5.48 (1H, t, *J* = 5.7 Hz), 5.97 (2H, s), 7.28 - 7.39 (2H, m), 7.37 (1H, t, *J* = 7.8 Hz), 7.61 - 7.67 (3H, m), 7.76 (1H, t, *J* = 7.5 Hz), 7.83 (1H,d, *J* = 7.8 Hz), 8.15 - 8.18 (2H, m), 8.137 (1H, d, *J* = 7,2 Hz).

Ejemplo 549.

Producción de N-{2-[1-(hidroxiacetil)pirrolidin-2-il]etil}-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



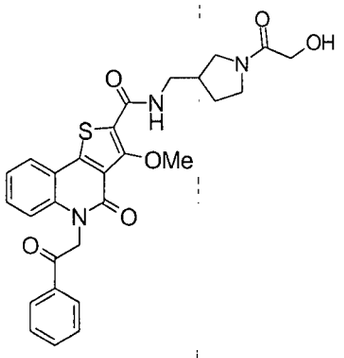
1298

Del mismo modo que en el Ejemplo 508, el compuesto del título (70 mg, 51%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 528 (150 mg, 0.25 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 2.00 (7H, m), 3.00 - 3.15 (1H, m), 3.30 - 3.45 (1H, m), 3.55 - 3.70 (1H, m), 4.02 - 4.25 (7H, m), 4.52 (1H, t, *J* = 5.3 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.56 - 7.67 (2H, m), 7.77 (1H, t, *J* = 7.2 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 8.18 (2H, d, *J* = 7.8 Hz), 8.46 (1H, t, *J* = 5.3 Hz).

Ejemplo 550.

Producción de N-{[1-(hidroxiacetil)pirrolidin-3-il]metil}-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.



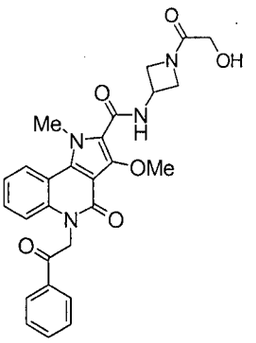
Del mismo modo que en el Ejemplo 508, el compuesto del título (31 mg, 29%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 529 (120 mg, 0.20 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58 - 1.76 (1H, m), 1.90 - 2.10 (1H, m), 2.50 - 2.65 (1H, m), 3.11 - 3.17 (1H, m), 3.30 - 3.65 (5H, m), 3.99 (2H, d, *J* = 4.2 Hz), 4.03 (3H, d, *J* = 0.9 Hz), 4.46 (1H, t, *J* = 4.8 Hz), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 (1H, d, *J* = 8.4 Hz), 7.56 - 7.67 (3H, m), 7.77 (1H, t, *J* = 7.5 Hz), 8.05 (1H, d, *J* = 7.5 Hz), 8.18 (3H, d, *J* = 7.5 Hz).

1299

Ejemplo 551.

Producción de N-[1-(hidroxiacetil)azetidin-3-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.

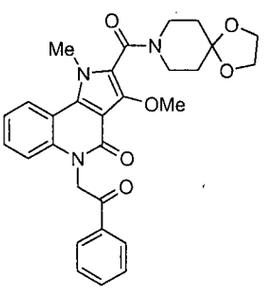


Del mismo modo que en el Ejemplo 508, el compuesto del título (58 mg, 64%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 531 (100 mg, 0.18 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.28-3.44 (2H, m), 3.84-3.86 (5H, tm), 4.22 (1H, t, *J* = 6.3 Hz), 4.36 (3H, s), 4.39-4.43 (2H, m), 5.55 (1H, t, *J* = 5.7 Hz), 5.96 (2H, s), 7.30 - 7.30 (2H, m), 7.38 (1H, t, *J* = 7.5 Hz), 7.63 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 7.90 (1H, t, *J* = 6.2 Hz), 8.16 - 8.19 (2H, m), 8.40 (1H, dd, *J* = 8.1, 0.9 Hz).

Ejemplo 552.

Producción de 2-(1,4-dioxa-8-azaspiro[4,5]dec-8-ilcarbonil)-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona.



Del mismo modo que en el Ejemplo 25, el compuesto del título (279 mg, 60%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (350 mg, 0.90 mmol),

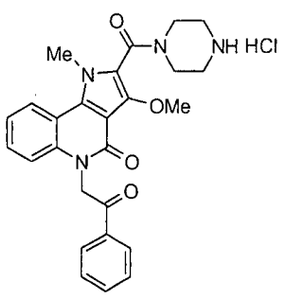
1300

1.4-dioxa-8-azaspiro[4,5]decano (154 mg, 1.1 mmol), HOBt (146 mg, 1.1 mmol), WSCD (206 mg, 1.1 mmol) y DMF (10 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.72 - 1.88 (4H, m), 3.64 - 3.77 (2H, m), 3.82 - 3.96 (2H, m), 3.98 - 4.02 (4H, m), 4.03 (3H, s), 4.09 (3H, s), 5.89 (2H, br. s), 7.01 - 7.10 (1H, m), 7.19 - 7.30 (1H, m), 7.34 - 7.32 (1H, m), 7.39 - 7.58 (2H, m), 7.61 - 7.69 (1H, m), 8.06 - 8.14 (2H, m), 8.19 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 553.

Producción de 3-metoxi-1-metil-5-(2-oxo-2-feniletil)-2-(piperazin-1-ilcarbonil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato.

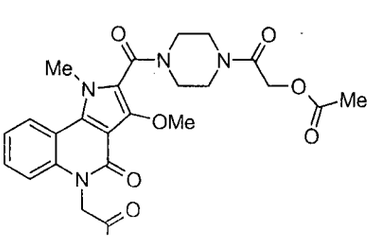


Del mismo modo que en el Ejemplo 542, el compuesto del título (478 mg, 95%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 680 (571 mg, 1.0 mmol), solución 4N de ácido clorhídrico acetato de etilo (11 ml), acetato de etilo (8.0 ml) y metanol (8.0 ml).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 3.07 - 3.27 (4H, m), 3.65 - 3.78 (2H, m), 3.81- 3.96 (5H, m), 4.05 (3H, s), 5.98 (2H, s), 7.24 - 7.52 (3H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 8.08 - 8.24 (2H, m), 8.35 (1H, dd, *J* = 8.2, 1.0 Hz), 9.20 (2H, br. s).

Ejemplo 554.

Producción de 2-(4-{[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}piperazin-1-il)-2-oxoacetato de etilo.



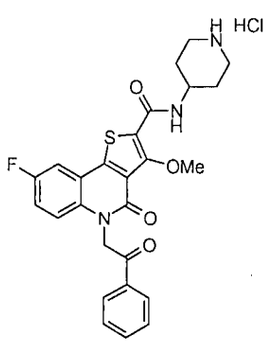
1301

Del mismo modo que en el Ejemplo 544, el compuesto del título (34 mg, 10%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 553 (300 mg, 0.61 mmol), cloruro de acetoxiacetilo (0.081 ml, 0.76 mmol), trietilamina (0.23 ml, 1.7 mmol) y THF (13 ml).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 2.09 (3H, s), 3.43 - 3.79 (8H, m), 3.91 (3H, s), 4.03 (3H, s), 4.76 - 4.88 (2H, m), 5.98 (2H, s), 7.25 - 7.51 (3H, m), 7.59 - 7.68 (2H, m), 7.71 - 7.80 (1H, m), 8.13 - 8.22 (2H, m), 8.30 - 8.38 (1H, m).

Ejemplo 555.

Producción de 8-fluoro-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato.



Del mismo modo que en el Ejemplo 542, el compuesto del título (335 mg, 83%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 673 (452 mg, 0.76 mmol), solución 4N de hidrógeno cloruro de acetato de etilo (6.0 ml), THF (4.0 ml) y metanol (4.0 ml).

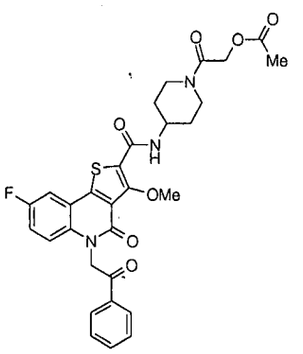
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.70 - 1.91 (2H, m), 1.95 - 2.12 (2H, m), 2.93 - 3.13 (2H, m), 3.19 - 3.52 (2H, m), 3.95 - 4.22 (4H, m), 6.00 (2H, s), 7.31 - 7.52 (1H, m), 7.53 - 7.71 (3H, m), 7.72 - 7.84 (1H, m), 7.86 - 8.03 (2H, m), 8.11 - 8.25 (2H, m), 8.63

1302

(2H, amplio. s).

Ejemplo 556.

Producción de 2-[4-({[8-fluoro-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo.

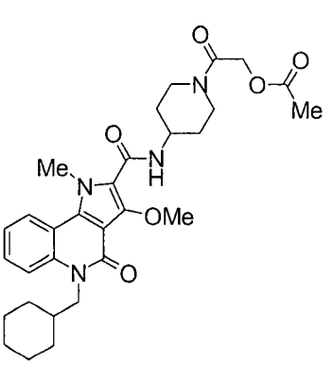


Del mismo modo que en el Ejemplo 544, el compuesto del título (161 mg, 80%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 555 (180 mg, 0.34 mmol), cloruro de acetoxiacetilo (0.046 ml, 0.42 mmol), trietilamina (0.13 ml, 0.93 mmol) y THF (7.5 ml).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.45 - 1.64 (2H, m), 2.01 - 2.26 (5H, m), 2.89 - 3.05 (1H, m), 3.15 - 3.34 (1H, m), 3.60 - 3.77 (1H, m), 4.15 (3H, s), 4.20 - 4.34 (1H, m), 4.41 - 4.54 (1H, m), 4.67 - 4.84 (2H, m), 5.85 (2H, s), 6.95 - 7.04 (1H, m), 7.16 - 7.24 (1H, m), 7.51 - 7.62 (4H, m), 7.64 - 7.74 (1H, m), 8.06 - 8.14 (2H, m).

Ejemplo 557.

Producción de 2-[4-({[5-(ciclohexilmetil)-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo.



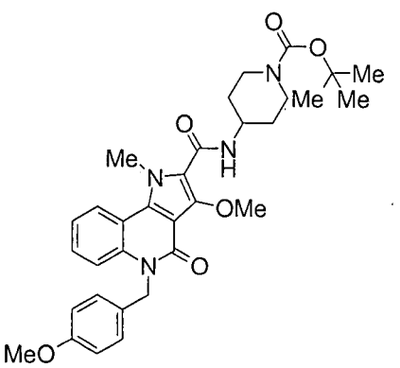
1303

Una mezcla del compuesto del Ejemplo 672 (110 mg, 0.24 mmol), bromometilciclohexano (108 mg, 0.60 mmol), carbonato de potasio (72 mg, 0.60 mmol) y DMF (3 ml) se agitó a 8°C durante 24 hrs. Luego de enfriar hasta la temperatura ambiente, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato: acetato de etilo) para dar el compuesto del título (34 mg, 16%) como un aceite incoloro.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.05 - 1.20 (5H, m), 1.35 - 2.00 (9H, m), 2.09 (3H, s), 2.90 (1H, t, *J* = 11,4 Hz), 3.19 (1H, t, *J* = 12.2 Hz), 3.70 (1H, d, *J* = 13.5 Hz), 3.97 (3H, s), 4.10 - 4.40 (8H, m), 4.80 (2H, d, *J* = 2.1 Hz), 7.30 (1H, t, *J* = 7.5 Hz), 7.54 - 7.62 (2H, m), 7.96 (1H, d, *J* = 7.8 Hz), 8.32 (1H, d, *J* = 7.8 Hz).

Ejemplo 558.

Producción de *terc*-butil 4-({[3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato.



Del mismo modo que en el Ejemplo 25, el compuesto del título (6.09 g, 74%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 107 (5.65 g, 14.4 mmol) y 1-boc-4-aminopiperidina (5.77 g, 28.80 mmol).

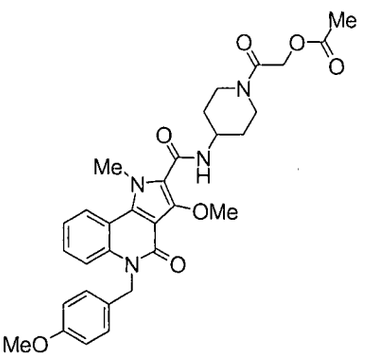
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.32 - 1.53 (11H, m), 1.85 (2H, d, *J* = 10,2 Hz), 2.85 - 3.10 (2H, m), 3.69 (3H, s), 3.88 (2H,

1304

d, *J* = 13.2 Hz), 3.95 - 4.05 (4H, m), 4.27 (3H, s), 5.52 (2H, s amplio), 6.85 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.27 (1H, t, *J* = 7.1 Hz), 7.31 - 7.38 (2H, m), 7.96 (1H, d, *J* = 7.8 Hz), 8.32 (1H, d, *J* = 8.1 Hz).

Ejemplo 559.

Producción de 2-[4-({[3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo.

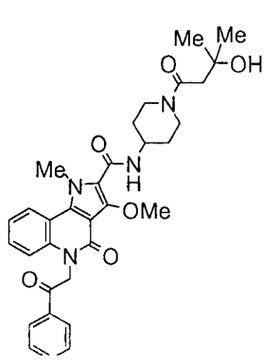


Del mismo modo que en el Ejemplo 123, el compuesto del título (360 mg, 73%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 681 (440 mg, 0.87 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.65 (2H, m), 1.72 - 1.95 (2H, m), 2.09 (3H, s), 2.91 (1H, t, *J* = 11.7 Hz), 3.20 (1H, t, *J* = 12.0 Hz), 3.58 - 3.75 (4H, m), 4.00 - 4.20 (5H, m), 4.27 (3H, s), 4.80 (2H, d, *J* = 2.4 Hz), 5.40 - 5.60 (2H, amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.27 (1H, td, *J* = 7.1, 2.1 Hz), 7.31 - 7.39 (2H, m), 8.00 (1H, d, *J* = 8.1 Hz), 8.33 (1H, d, *J* = 8.1 Hz).

Ejemplo 560.

Producción de N-[1-(3-hidroxi-3-metilbutanoil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



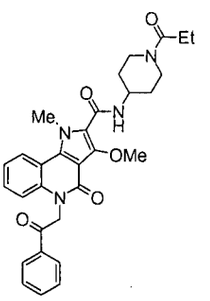
1305

Del mismo modo que en el Ejemplo 518, el compuesto del título (109 mg, 60%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 77 (150 mg, 0.317 mmol) y ácido 3-hidroxi-3-metilbutanoico (45.0 mg, 0.381 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (6 H, s), 1.33 - 1.63 (2 H, m), 1.79 - 1.97 (2 H, m), 2.43 - 2.52 (2 H, m), 2.81 - 2.96 (1 H, m), 3.14 - 3.29 (1 H, m), 3.90 - 4.00 (4 H, m), 4.02 - 4.16 (1 H, m), 4.22 - 4.36 (4 H, m), 4.89 (1 H, s), 5.97 (2 H, s), 7.26 - 7.31 (2 H, m), 7.38 (1 H, t, *J* = 7.6 Hz), 7.63 (2 H, t, *J* = 7.5 Hz), 7.72 - 7.81 (1 H, m), 7.95 (1 H, d, *J* = 7.9 Hz), 8.17 (2 H, d, *J* = 7.7 Hz), 8.37 (1 H, d, *J* = 8.3 Hz).

Ejemplo 561.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-propanoilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 123, el compuesto del título (90,2, 81%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo 77 (100 mg, 0.212 mmol) y cloruro de propionilo (20,2 µl, 0.233 mmol).

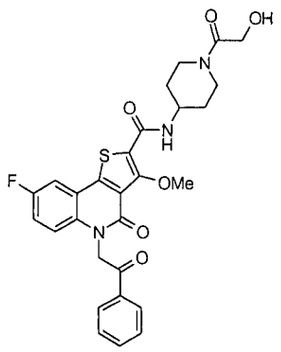
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.00 (3 H, t, *J* = 7.5 Hz), 1.31 - 1.61 (2 H, m), 1.77 - 1.96 (2 H, m), 2.34 (2 H, q, *J* = 7.3 Hz), 2.77 - 2.92 (1 H, m), 3.10 - 3.25 (1 H, m), 3.76 - 3.88 (1 H, m), 3.97 (3 H, s), 4.01 - 4.14 (1 H, m), 4.19 - 4.29 (1 H, m), 4.31

1306

(3 H, s), 5.97 (2 H, s), 7.26 - 7.31 (2 H, m), 7.33 - 7.52 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.81 (1 H, m), 7.94 (1 H, d, *J* = 7.7 Hz), 8.12 - 8.22 (2 H, m), 8.37 (1 H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 562.

Producción de 8-fluoro-N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida.

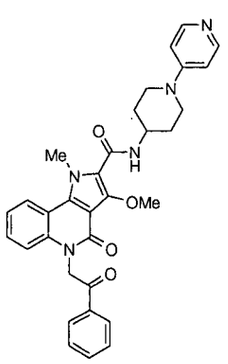


Del mismo modo que en el Ejemplo 511, el compuesto del título (59 mg, 39%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 556 (164 mg, 0.28 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.42-1.63 (2H, m), 2.08 - 2.25 (2H, m), 2.97 - 3.26 (2H, m), 3.47 - 3.59 (1H, m), 3.62 (1H, t, *J* = 4.2 Hz), 4.14 (3H, s), 4.20 (2H, d, *J* = 4.0 Hz), 4.23-4.34 (1H, m), 4.45 - 4.58 (1H, m), 5.85 (2H, s), 6.94 - 7.04 (1H, m), 7.15 - 7.25 (1H, m), 7.50 - 7.63 (4H, m), 7.64 - 7.77 (1H, m), 8.04-8.15 (2H, m).

Ejemplo 563.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-piridin-4-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



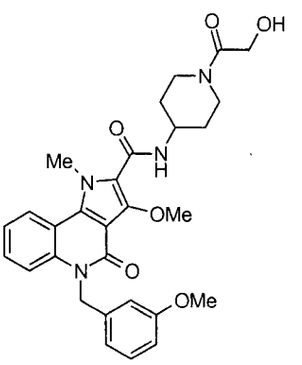
1307

A una solución del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol), 1-piridin-4-ilpiperidin-4-amina, clorhidrato (128 mg, 0.51 mmol) y HOBt (83 mg, 0.61 mmol) en DMF (5.0 ml) se agregaron WSCD (118 mg, 0.61 mmol) y trietilamina (0.23 ml, 1.6 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 67 hrs. La mezcla de reacción se diluyó con salmuera, y se extrajo 4 veces con acetato de etilo. El extracto se combinó y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=40/60 - 100/0) y se recristalizó a partir de THF para dar el compuesto del título (121 mg, 43%) como un sólido violeta pálido.

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.52-1.68 (2H, m), 1.87-1.98 (2H, m), 3.08 (2H, m), 3.89 (2H, m), 3.95 (3H, s), 4.04-4.17 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.85 (2H, d, *J* = 6.4 Hz), 7.26 - 7.31 (2H, m), 7.33 - 7.53 (1H, m), 7.63 (2H, m), 7.71 - 7.80 (1H, m), 7.98 (1H, d, *J* = 7.7 Hz), 8.10 - 8.21 (4H, m), 8.37 (1H, d, *J* = 7.3 Hz).

Ejemplo 564.

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-5-(3-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Una mezcla del compuesto del Ejemplo 672 (110 mg, 0.24 mmol), cloruro de 3-metoxibencilo (150 mg, 0.96mmol), carbonato de potasio (55 mg, 0.40 mmol) y DMF (5 ml) se agitó a 8°C durante 5 hrs. Luego de enfriar hasta la temperatura ambiente, solución acuosa 2N de hidróxido de sodio (1 ml) se

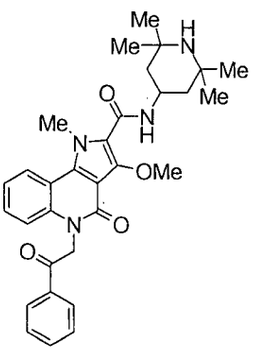
1308

agregó, y la mezcla se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato: acetato de etilo - acetato de etilo/metanol=10/1) y se volvió a precipitar a partir de acetato de etilo-hexano para dar el compuesto del título (14 mg, 10%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.65 (2H, m), 1.90 (2H, d, *J* = 10.2 Hz), 2.93 (1H, t, *J* = 10.2 Hz), 3.19 (1H, t, *J* = 14.3 Hz), 3.60 - 3.30 (4H, m), 4.00 - 4.04 (4H, m), 4.04 - 4.10 (2H, m), 4.30 - 4.36 (4H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.58 (2H, s amplio), 6.69 (1H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 6.3 Hz), 7.20 (1H, t, *J* = 8.4 Hz), 7.28 (1H, t, *J* = 6.3 Hz), 7.34 - 7.38 (2H, m), 7.89 (1H, d, *J* = 8.1 Hz), 8. 34 (1H, d, *J* = 8.4 Hz).

Ejemplo 565.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(2,2.6.6-tetrametilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 25, el compuesto del título (410 mg, 76%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (400 mg, 1.02 mmol) y 4-amino-2,2.6.6-tetrametilpiperidina (320 mg, 2.04 mmol).

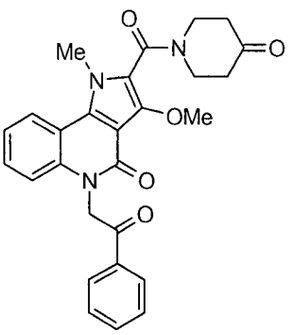
^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.86 - 1.24 (14 H, m), 1.78 (2 H, dd, *J* = 12.6, 2.4 Hz), 3.96 (3 H, s), 4.28 - 4.31 (4 H, m),

1309

5.97 (2 H, s), 7.29 -7.37 (3 H, m), 7.63 (2 H, t, *J* = 7.5 Hz), 7.76 (2 H, t, *J* = 6.9 Hz), 8.17 (2 H, d, *J* = 7.5 Hz), 8.37 (1 H, d, *J* = 8.4 Hz).

Ejemplo 566.

Producción de 3-metoxi-1-metil-5-(2-oxo-2-feniletil)-2-[(4-oxopiperidin-1-il)carbonil]-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona.



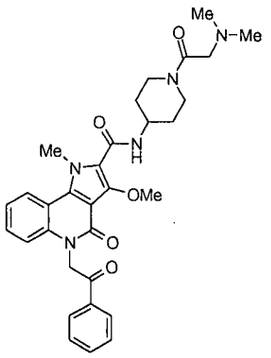
A una solución del compuesto del Ejemplo 552 (285 mg, 0.55 mmol) y ácido clorhídrico 5N (3.0 ml) en THF (6.0 ml) se agitó a temperatura ambiente durante 2 hrs. Se agregó ácido clorhídrico 5N (1.5 ml), y la mezcla se agitó a temperatura ambiente durante 2 hrs. Se agregó ácido clorhídrico 5N (1.5 ml), y la mezcla se agitó a temperatura ambiente durante 3.5 hrs y se concentró bajo presión reducida. El residuo se alcalinizó con solución de hidrógeno carbonato de sodio y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, y se concentró bajo presión reducida. El residuo se lavó con agua, y se recristalizó a partir de metanol-dietil éter para dar el compuesto del título (123 mg, 47%) como un sólido blanco.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.78-1.93 (3H, m), 1.95 - 1.99 (1H, m), 3.58-3.73 (2H, m), 3.79-3.94 (2H, m), 4.03 (3H, s), 4.07-4.11 (3H, m), 5.90 (2H, s), 7.02 - 7.11 (1H, m), 7.19 - 7.30 (1H, m), 7.34 - 7.33 (1H, m), 7.39 - 7.58 (2H, m), 7.61 - 7.70 (1H, m), 8.07-8.14 (2H, m), 8.16 - 8.26 (1H, m).

1310

Ejemplo 567.

Producción de N-[1-(N,N-dimetilglycil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

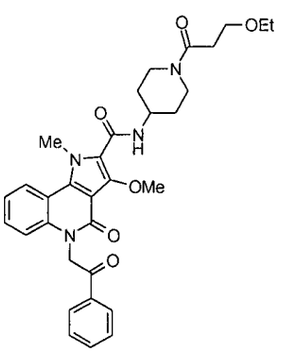


Del mismo modo que en el Ejemplo 25, el compuesto del título (125 mg, 57%) se obtuvo como un sólido violeta pálido a partir del compuesto del Ejemplo 77 (200 mg, 0.39 mmol), y N,N-dimetilglicina (49 mg, 0.47 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.40 - 1.64 (2H, m), 1.99 - 2.17 (2H, m), 2.31 (6H, s), 2.90 - 3.05 (1H, m), 3.08-3.21 (2H, m), 3.22-3.36 (1H, m), 3.99-4.11 (1H, m), 4.14 (3H, s), 4.18 - 4.29 (1H, m), 4.36-4.45 (1H, m), 4.47 (3H, s), 5.88 (2H, d, *J* = 4.2 Hz), 7.05 (1H, d, *J* = 7.7 Hz), 7.20 - 7.32 (1H, m), 7.37 - 7.36 (1H, m), 7.50 - 7.59 (2H, m), 7.62 -7.73 (2H, m), 8.06 - 8.16 (2H, m), 8.26 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 568

Producción de N-[1-(3-etoxipropanoil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 25, el compuesto del

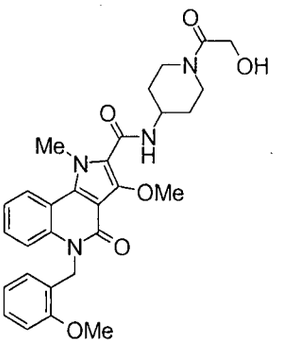
1311

título (159 mg, 70%) se obtuvo como un sólido violeta pálido a partir del compuesto del Ejemplo 77 (200 mg, 0.39 mmol), y ácido 3-etoxipropanoico (56 mg, 0.47 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.09 (3H, t, *J* = 7.0 Hz), 1.36-1.60 (2H, m), 1.80- 1.96 (2H, m), 2.54 - 2.63 (2H, m), 2.78 - 2.92 (1H, m), 3.13 - 3.26 (1H, m), 3.42 (2H, q, *J* = 6.9 Hz), 3.59 (2H, t, *J* = 6.7 Hz), 3.81-3.91 (1H, m), 3.96 (3H, s), 4.02 - 4.14 (1H, m), 4.18 - 4.27 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.26 - 7.31 (2H, m), 7.34 - 7.53 (1H, m), 7.58 - 7.68 (2H, m), 7.72 - 7.80 (1H, m), 7.94 (1H, d, *J* = 7.9 Hz), 8.12-8.21 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 569

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-5-(2-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



A una solución del compuesto del Ejemplo 570 (40 mg, 0.07 mmol) en THF (1 ml)-metanol (1 ml) se agregó solución acuosa 2N de hidróxido de sodio (1 ml), y la mezcla se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se diluyó con agua, y se extrajo con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. La recristalización a partir de acetato de etilo-hexano dio el compuesto del título (30 mg, 80 %) como cristales blancos.

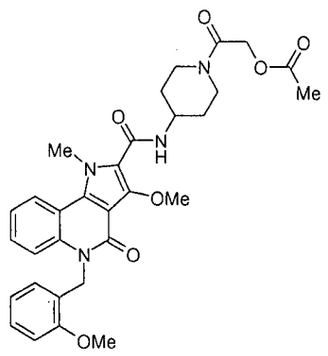
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.60 (2H, m), 1.90 (2H, d, *J* = 10.2 Hz), 2.93 (1H, t, *J* = 12.5 Hz), 3.15 (1H, t, *J* =

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12.5 Hz), 3.67 (1H, d, *J* = 13.2 Hz), 3.95 (3H, s), 4.00 (3H, s), 4.05 - 4.20 (3H, m), 4.20 - 4.30 (4H, m), 4.51 (1H, t, *J* = 5.4 Hz), 5.47 (2H, s), 6.50 (1H, d, *J* = 7.5 Hz), 6.75 (1H, t, *J* = 7.5 Hz), 7.09 (1H, d, *J* = 8.4 Hz), 7.21 - 7.31 (3H, m), 7.34 (1H, t, *J* = 7.8 Hz), 7.97 (1H, d, *J* = 7.8 Hz), 8.36 (1H, d, *J* = 8.1 Hz).

Ejemplo 570

Producción de 2-[4-({[3-metoxi-5-(2-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo

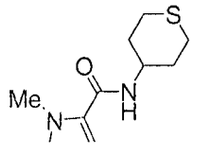


Del mismo modo que en el Ejemplo 557, un sólido amorfo (90 mg) se obtuvo a partir del compuesto del Ejemplo 672 (120 mg, 0.24 mmol), cloruro de 2-metoxibencilo (50% diclorometano solución; 0.1 ml, 0.79 mmol) y carbonato de potasio (110 mg, 0.79 mmol). La recristalización a partir de acetato de etilo-diisopropil éter dio el compuesto del título (44 mg, 29 %) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.70 (2H, m), 2.07-2.28 (5H, m), 3.04(1H, t, *J* = 11.1 Hz), 3.29 (1H, t, *J* = 11.1 Hz), 3.70 (1H, d, *J* = 14.4 Hz), 3.99 (3H, s), 4.21-4.28 (4H, m), 4.40 - 4,56 (4H, m), 4.78 (2H, s), 5.62 (2H, s amplio), 6.77 (2H, d, *J* = 4.2 Hz), 6.95 (1H, d, *J* = 10.8 Hz), 7.19 - 7.32 (4H, m), 7.77 (1H, d, *J* = 7.8 Hz), 8. 25 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 571.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidro-2H-tiopiran-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-



1313

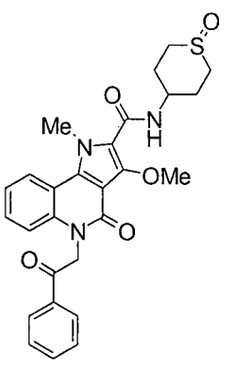
2-carboxamida

Del mismo modo que en el Ejemplo 25, el compuesto del título (2.51 g, 90%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (2.22 g, 5.69 mmol) y tetrahidrotiopiran-4-ilamina (1.0 g, 8.53 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.63 - 1.77 (2 H, m), 1.99 - 2.17 (2H, m), 2.66 - 2.78 (4H, m), 3.87 - 3.97 (4H, m), 4.30 (3H, s), 5.97 (2H, s), 7.28 - 7.39 (2 H, m), 7.37 (1H, td, *J* = 7.8, 1.2 Hz), 7.63 (2 H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 8.1 Hz), 7.97 (1 H, d, *J* = 8.1 Hz), 8.16 - 8.18 (2H, m), 8.36 (1 H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 572

Producción de 3-metoxi-1-metil-N-(1-oxidotetrahidro-2H-tiopiran-4-il)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



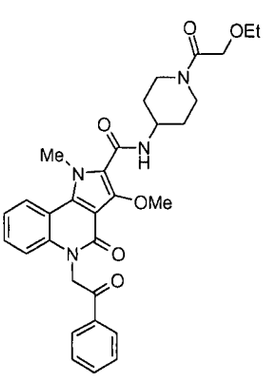
A una solución del compuesto del Ejemplo 571 (200 mg, 0.41 mmol) y mCPBA (70% que contiene agua, 106 mg, 0.43 mmol) en acetato de etilo (25 ml) se agitó a 0°C durante 1 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto

se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró bajo presión reducida. La recristalización del residuo a partir de acetato de etilo-hexano dio el compuesto del título (54 mg, 26 %) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.88 (2 H, d, *J* = 12.9 Hz), 2.20 (2H, q, *J* = 12.7 Hz), 2.70 - 3.00 (4H, m), 3.97-4.06 (4H, m), 4.29 (3H, s), 5.97 (2H, s), 7.29 -7.30 (2 H, m), 7.38 (1H, t, *J* = 7.5 Hz), 7.63 (2 H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.05 (1 H, d, *J* = 8.1 Hz), 8.16 - 8.19 (2H, m), 8.37 (1 H, d, *J* = 7.5 Hz).

Ejemplo 573

Producción de N-[1-(etoxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 25, el compuesto del título (134 mg, 61%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 77 (200 mg, 0.39 mmol), y ácido etoxiacético (0.045 ml, 0.47 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.14 (3H, t, *J* = 7.0 Hz), 1.35 - 1.64 (2H, m), 1.81- 1.97 (2H, m), 2.81-2.95 (1H, m), 3.09 - 3.24 (1H, m), 3.42-3.55 (2H, m), 3.73- 3.85 (1H, m), 3.96 (3H, s), 4.02 - 4.25 (4H, m), 4.31 (3H, s), 5.97 (2H, s), 7.26 - 7.31 (2H, m), 7.33 -7.53 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 7.95 (1H, d, *J* = 7.7 Hz), 8.12 -8.22 (2H, m), 8.37 (1H, dd, *J* = 8.2, 1.2 Hz).

Ejemplo 574

1315

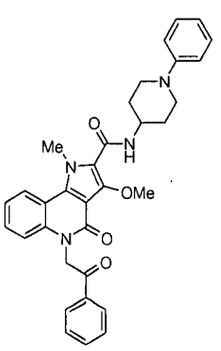
Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-piridin-4-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato

A una solución del compuesto del Ejemplo 563 (250 mg, 0.46 mmol) y solución 4N de hidrógeno cloruro de acetato de etilo (0.114 ml, 0.46 mmol) en metanol (3.0 ml)-acetato de etilo (3.0 ml) se agitó a temperatura ambiente durante 10 min. La mezcla de reacción se concentró bajo presión reducida, y el residuo se recristalizó a partir de metanol-dietil éter para dar el compuesto del título (45 mg, 17%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.54 - 1.74 (2H, m), 1.95 - 2.10 (2H, m), 3.36-3.48 (2H, m), 3.96 (3H, s), 4.11-4.36 (6H, m), 5.97 (2H, s), 7.17 - 7.27 (2H, m), 7.28 - 7.32 (2H, m), 7.33 - 7.53 (1H, m), 7.58 - 7.69 (2H, m), 7.71 - 7.82 (1H, m), 8.00 (1H, d, *J* = 7.7 Hz), 8.12-8.19 (2H, m), 8.21-8.28 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz), 13.40 (1H, amplio s).

Ejemplo 575

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-fenilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



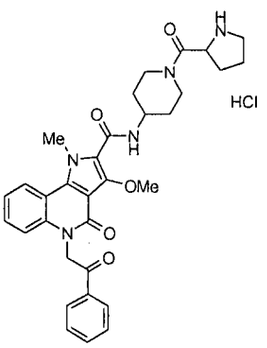
136

A una solución del compuesto del Ejemplo 77 (200 mg, 0.42 mmol), yodobenceno (0.50 ml), tris(dibencilideneacetona)dipaladio (0) (38 mg, 0.042 mmol), x-phos (40 mg, 0.085 mmol) y *terc*-butóxido de sodio (102 mg, 1.1 mmol) en ter-butanol (4.0 ml) se agitó bajo irradiación en microondas a 130°C durante 35 min. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. Los extractos se combinaron, se secaron sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=30/70 - 100/0) y se recristalizó a partir de acetato de etilo para dar el compuesto del título (70 mg, 30%) como un sólido blanco.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.67-1.85 (2H, m), 2.09 – 2.25 (2H, m), 2.92-3.08 (2H, m), 3.53 - 3.69 (2H, m), 4.06 - 4.25 (4H, m), 4.48 (3H, s), 5.88 (2H, s), 6.82 - 6.92 (1H, m), 6.94 - 7.09 (3H, m), 7.20 - 7.32 (3H, m), 7.35 - 7.36 (1H, m), 7.39 - 7.59 (2H, m), 7.61 - 7.81 (2H, m), 8.03 - 8.16 (2H, m), 8.26 (1H, dd, *J* = 8.3, 1.3 Hz).

Ejemplo 576

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-prolilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato



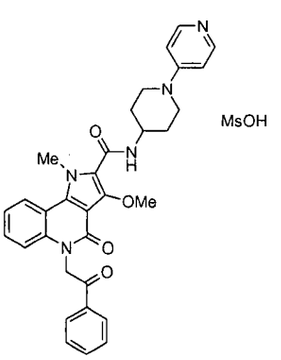
A una solución del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), 1-(ter-butoxicarbonil)prolina (152 mg, 0.71 mmol) y HOBt (96 mg, 0.71 mmol) en DMF (7.5 ml) se agregaron WSCD (136 mg, 0.71 mmol) y trietilamina (0.18 ml, 1.3 mmol) enfrió con hielo,

y la mezcla se agitó a temperatura ambiente durante 17 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. Los extractos se combinaron, se secaron sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=20/80 - 100/0). El compuesto obtenido se disolvió en metanol (4.5 ml), se agregó solución 4N de hidrógeno cloruro de acetato de etilo (4.5 ml), y la mezcla se agitó a temperatura ambiente durante 7 hrs. La mezcla de reacción se concentró bajo presión reducida y se recristalizó a partir de metanol-dietil éter para dar el compuesto del título (234 mg, 65%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.37 - 1.69 (2H, m), 1.69 - 1.84 (1H, m), 1.84 - 2.05 (4H, m), 2.29 - 2.46 (1H, m), 2.91 - 3.27 (4H, m), 3.75 - 3.91 (1H, m), 3.97 (3H, d, *J* = 1.5 Hz), 4.06 - 4.29 (2H, m), 4.32 (3H, d, *J* = 3.2 Hz), 4.48 - 4.67 (1H, m), 5.97 (2H, s), 7.27 - 7.33 (2H, m), 7.34 - 7.54 (1H, m), 7.56 - 7.70 (2H, m), 7.70 - 7.83 (1H, m), 7.97 (1H, dd, *J* = 11.8, 7.8 Hz), 8.08 - 8.26 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz), 8.93 (2H, amplio. s).

Ejemplo 577.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-piridin-4-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, metansulfonato.



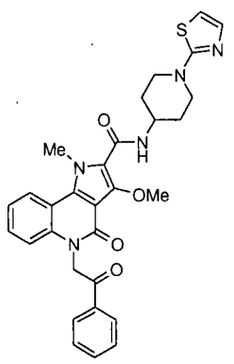
1318

Del mismo modo que en el Ejemplo 574, el compuesto del título (142 mg, 36%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 563 (333 mg, 0.61 mmol), ácido metansulfónico (0.041 ml, 0.64 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.55 - 1.73 (2H, m), 1.96 - 2.09 (2H, m), 2.30 (3H, s), 3.36 - 3.49 (2H, m), 3.96 (3H, s), 4.14 - 4.37 (6H, m), 5.97 (2H, s), 7.17 - 7.27 (2H, m), 7.28 - 7.32 (2H, m), 7.33 - 7.52 (1H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 8.00 (1H, d, *J* = 7.9 Hz), 8.11 - 8.19 (2H, m), 8.21 - 8.28 (2H, m), 8.38 (1H, dd, *J* = 8.2, 1.2 Hz), 13.22 (1H, amplio. s).

Ejemplo 578

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-[1-(1,3-tiazol-2-il)piperidin-4-il]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



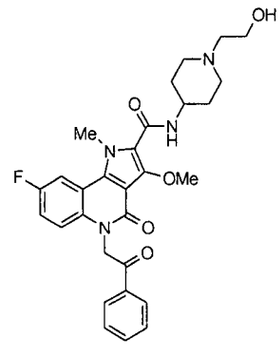
Del mismo modo que en el Ejemplo 25, el compuesto del título (152 mg, 53%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol), y 1-(1,3-tiazol-2-il)piperidin-4-amina hidroclorido (124 mg, 0.56 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58-1.79 (2H, m), 1.90 - 2.04 (2H, m), 3.15- 3.28 (2H, m), 3.81-3.92 (2H, m), 3.96 (3H, s), 4.03-4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.83 (1H, d, *J* = 3.6 Hz), 7.16 (1H, d, *J* = 3.6 Hz), 7.27 - 7.31 (2H, m), 7.34 - 7.52 (1H, m), 7.58 - 7.68 (2H, m), 7.70 - 7.82 (1H, m), 8.00 (1H, d, *J* = 7.9 Hz), 8.10 - 8.23 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.3 Hz).

1319

Ejemplo 579

Producción de 8-fluoro-N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



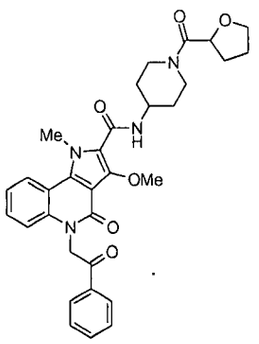
A una solución del compuesto del Ejemplo 675 (300 mg, 0.57 mmol), carbonato de potasio (629 mg, 4.6 mmol) y trietilamina (0.11 ml, 0.76 mmol) en DMF (13 ml) se agitó a 10°C durante 5 min, y 2-bromoetanol (0.16 ml, 2.3 mmol) se agregó. Luego de agitar a 10°C durante 1.5 hrs, la mezcla de reacción se concentró bajo presión reducida. La mezcla de reacción se diluyó con agua, y se extrajo 3 veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; metanol/acetato de etilo=0/100 - 5/95) y se recristalizó a partir de THF-dietil éter para dar el compuesto del título (205 mg, 51%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.47 - 1.67 (2H, m), 1.75 - 1.89 (2H, m), 2.08 - 2.25 (2H, m), 2.40 (2H, t, *J* = 6.3 Hz), 2.70 - 2.86 (2H, m), 3.49 (2H, q, *J* = 6.1 Hz), 3.74 - 3.89 (1H, m), 3.97 (3H, s), 4.31 (3H, s), 4.38 (1H, t, *J* = 5.4 Hz), 5.97 (2H, s), 7.28 - 7.30 (1H, m), 7.30 - 7.39 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.82 (1H, m), 7.92 (1H, d, *J* = 7.7 Hz), 8.05 - 8.23 (3H, m).

Ejemplo 580

1320

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-[1-(tetrahidrofuran-2-ilcarbonil)piperidin-4-il]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

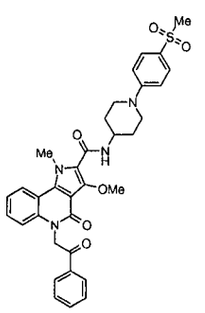


Del mismo modo que en el Ejemplo 25, el compuesto del título (41 mg, 17%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 77 (200 mg, 0.42 mmol), y ácido tetrahidrofuran-2-carboxílico (0.049 ml, 0.51 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.34 - 1.63 (2H, m), 1.74 - 1.95 (4H, m), 1.96 - 2.12 (2H, m), 2.78 - 2.97 (1H, m), 3.09 - 3.28 (1H, m), 3.68 - 3.86 (2H, m), 3.88 - 4.02 (4H, m), 4.03 - 4.27 (2H, m), 4.28 - 4.35 (3H, m), 4.68 (1H, dd, *J* = 7.3, 5.9 Hz), 5.97 (2H, s), 7.26 - 7.31 (2H, m), 7.33 - 7.53 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 7.89 - 8.03 (1H, m), 8.12-8.22 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 581

Producción de 3-metoxi-1-metil-N-{1-[4-(metilsulfonil)fenil]piperidin-4-il}-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 575, el compuesto del título (28 mg, 8.0%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 77 (260 mg, 0.55 mmol), y 1-bromo-4-

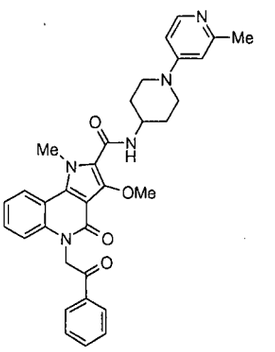
1321

(metilsulfonil)benceno (259 mg, 1.1 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.54 - 1.72 (2H, m), 1.88 - 2.04 (2H, m), 3.05 - 3.20 (5H, m), 3.85 - 3.99 (5H, m), 4.04 - 4.22 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.06 - 7.17 (2H, m), 7.26 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.57 - 7.71 (4H, m), 7.72 - 7.82 (1H, m), 7.99 (1H, d, *J* = 7.9 Hz), 8.14 - 8.23 (2H, m), 8.37 (1H, dd, *J* = 8.1, 1.1 Hz).

Ejemplo 582.

Producción de 3-metoxi-1-metil-N-[1-(2-metilpiridin-4-il)piperidin-4-il]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida.



Del mismo modo que en el Ejemplo 575, el compuesto del título (51 mg, 14%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 77 (300 mg, 0.64 mmol), y 4-bromo-2-metilpiridina (0.15 ml, 1.3 mmol).

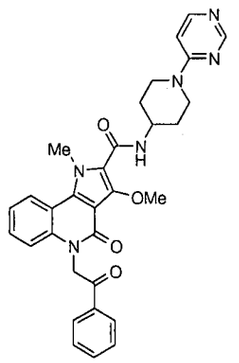
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.48 - 1.68 (2H, m), 1.84 - 1.98 (2H, m), 2.32 (3H, s), 2.95 - 3.14 (2H, m), 3.80 - 3.91 (2H, m), 3.95 (3H, s), 4.02 - 4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.62-6.70 (1H, m), 6.71 - 6.75 (1H, m), 7.24 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.58 - 7.67 (2H, m), 7.70 - 7.81 (1H, m), 7.92 - 8.06 (2H, m), 8.12 - 8.22 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 583.

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-pirimidin-4-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-

1322

carboxamida

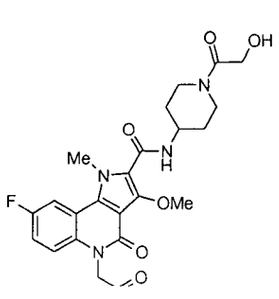


A una solución del compuesto del Ejemplo 77 (200 mg, 0.42 mmol), 4-cloropirimidina (58 mg, 0.51 mmol) y trietilamina (0.12 ml, 0.85 mmol) en 2-propanol (4.0 ml) se calentó a reflujo durante 23 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con una mezcla de solvente de acetato de etilo-metanol. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/metanol=0/100 - 5/95) y se recristalizó a partir de THF para dar el compuesto del título (97 mg, 42%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.44-1.65 (2H, m), 1.88 - 2.02 (2H, m), 3.10 - 3.24 (2H, m), 3.95 (3H, s), 4.08 - 4.23 (1H, m), 4.25 - 4.39 (5H, m), 5.97 (2H, s), 6.88 (1H, dd, *J* = 6.4, 1.1 Hz), 7.26 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.58 - 7.68 (2H, m), 7.72 - 7.81 (1H, m), 7.97 (1H, d, *J* = 7.9 Hz), 8.11-8.23 (3H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz), 8.49 (1H, s).

Ejemplo 584

Producción de 8-fluoro-N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



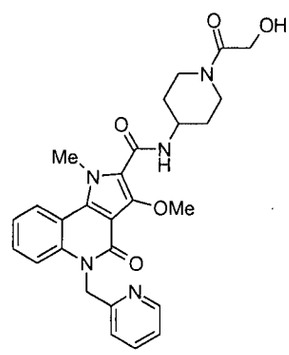
1323

Del mismo modo que en el Ejemplo 511, el compuesto del título (103 mg, 38%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 676 (293 mg, 0.50 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.36-1.63 (2H, m), 1.81-1.96 (2H, m), 2.84 - 2.99 (1H, m), 3.06-3,20 (1H, m), 3.61-3.74 (1H, m), 3.95 (3H, s), 4.03-4.15 (3H, m), 4.17-4.27 (1H, m), 4.30 (3H, s), 4.52 (1H, t, *J* = 5.5 Hz), 5.97 (2H, s), 7.30 - 7.30 (1H, m), 7.31 - 7.39 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.80 (1H, m), 8.01 (1H, d, *J* = 7.7 Hz), 8.07 -8.21 (3H, m).

Ejemplo 585

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



A una suspensión del compuesto del Ejemplo 672 (300 mg, 0.66 mmol) en DMF (5 ml) se agregó hidruro de sodio (60% en aceite; 79 mg, 1.98 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. Se agregó 2-Clorometilpiridina clorhidrato (238 mg, 1.46 mmol) a la mezcla, y la mezcla se agitó a 6°C durante 16 hrs. Luego de enfriar, la mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera,

1324

se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo) para dar 2-[4-({[3-metoxi-1-metil-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (60 mg).

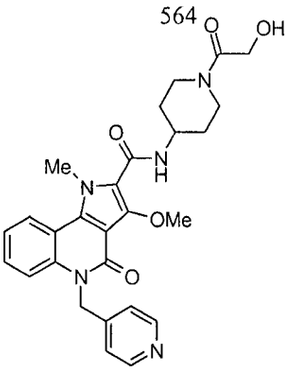
A una solución de 2-[4-({[3-metoxi-1-metil-4-oxo-5-(piridin-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (60 mg) en THF (2 ml)-metanol (2 ml) se agregó solución 2N de hidróxido de sodio (2 ml), y la mezcla se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. La recristalización a partir de acetato de etilo-diisopropil éter dio el compuesto del título (25 mg, 45%) como cristales beige.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.60 (2H, m), 1.90 (2H, d, *J* = 11.4 Hz), 2.93 (1H, t, *J* = 11.2 Hz), 3.15 (1H, t, *J* = 11.9 Hz), 3.67 (1H, d, *J* = 1 3.8 Hz), 4.01-4.29 (10H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.66 (2H, s), 7.11 (1H, d, *J* = 7.8 Hz), 7.24 - 7.31 (2H, m), 7.30 - 7.34 (2H, m), 7.71 (1H, td, *J* = 7.5, 1.8 Hz), 7.97 (1H, d, *J* = 7.8 Hz), 8.34 (1H, d, *J* = 8.1 Hz), 8.49 - 8.51 (1H, m).

Ejemplo 586

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(piridin-4-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

564

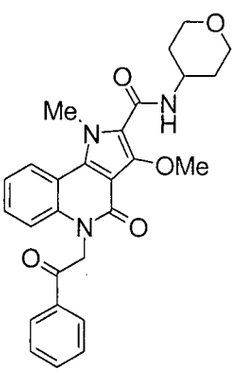


Del mismo modo que en el Ejemplo 585, el compuesto del título (14 mg, 5%) se obtuvo como cristales beige a partir del compuesto del Ejemplo 672 (300 mg, 0.66 mmol) y 4-clorometilpiridina clorhidrato (130 mg, 0.80 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.60 (2H, m), 1.90 (2H, d, *J* = 11,4 Hz), 2.93 (1H, t, *J* = 12.4 Hz), 3.14 (1H, t, *J* = 14.2 Hz), 3.60 - 3.75 (1H, m), 4.10 - 4.29 (10H, m), 4.45 - 4.60 (1H, amplio), 5.63 (2H, s), 7.16 (2H, d, *J* = 5.1 Hz), 7.28 - 7.36 (2H, m), 7.36 (1H, t, *J* = 8.1 Hz), 7.99 (1H, d, *J* = 7.8 Hz), 8.36 (1H, d, *J* = 8.4 Hz), 8.48 (2H, d, *J* = 4.8 Hz).

Ejemplo 587

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidro-2H-piran-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 25, el compuesto del título (204 mg, 84%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol) y 4-aminotetrahidropirano (62 mg, 0.61 mmol).

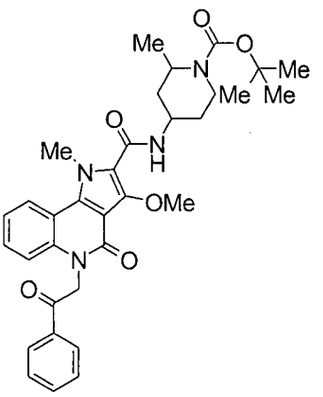
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.59 (2H, q, *J* = 10.0 Hz), 1.84 (2H, d, *J* = 13.5 Hz), 3.44 (2H, t, *J* = 11.0 Hz), 3.86 (2H, d, *J* = 11.4 Hz), 3.97 (3H, s), 4.00 - 4.10 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.29 -7.39 (2H, m), 7.38 (1H, t, *J* = 7.5 Hz), 7.63 (2H, t, *J*

1326

= 7.5 Hz), 7.76 (1H, t, *J* = 7.1 Hz), 7.96 (1H, d, *J* = 7.8 Hz), 8.17 (2H, d, *J* = 7.5 Hz), 8.37 (1H, d, *J* = 8.1Hz).

Ejemplo 588

Producción de *terc*-butil 4-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)-2-metilpiperidina-1-carboxilato

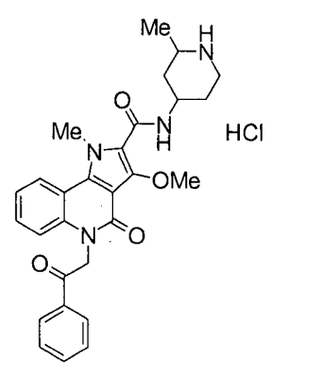


Del mismo modo que en el Ejemplo 25, el compuesto del título (220 mg, 75%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol) y 1-boc-4-amino-2-metilpiperidina (131 mg, 0.61 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.24 (3H, d, *J* = 6.9 Hz), 1.41 (9H, s), 1.65 - 1.95 (4H, m), 3.13 (1H, t, *J* = 10.7 Hz), 3.73 (1H, d, *J* = 13.2 Hz), 4.02 (3H, s), 4.10 - 4.20 (2H, m), 4.35 (3H, s), 5.98 (2H, s), 7.30 - 7.31 (2H, m), 7.38 (1H, t, *J* = 7.2 Hz), 7.63 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.02 (1H, d, *J* = 6.6 Hz), 8.16 - 8.19 (2H, m), 8.38 (1H, d, *J* = 7.2 Hz).

Ejemplo 589

Producción de 3-metoxi-1-metil-N-(2-metilpiperidin-4-il)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato



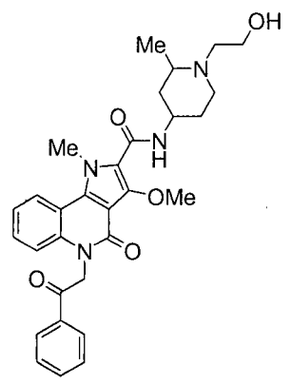
1327

Del mismo modo que en el Ejemplo 61, el compuesto del título (163 mg, 100%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 588 (200 mg, 0.34 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.26 (3H, d, *J* = 6.3 Hz), 1.45 - 1.90 (3H, m), 2.08 (2H, t, *J* = 14.1 Hz), 3.04 (1H, t, *J* = 11.9 Hz), 3.96 (3H, s), 4.04-4.14 (1H, m), 4.28 (3H, s), 5.98 (2H, s), 7.29 -7.30 (2H, m), 7.38 (1H, d, *J* = 7.8 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.09 (1H, d, *J* = 7.8 Hz), 8.16 - 8.19 (2H, m), 8.37 (1H, d, *J* = 8.4 Hz), 8.50 - 8.90 (2H, amplio).

Ejemplo 590

Producción de N-[1-(2-hidroxietil)-2-metilpiperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 79, el compuesto del título (25 mg, 36%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 589 (70 mg, 0.13 mmol).

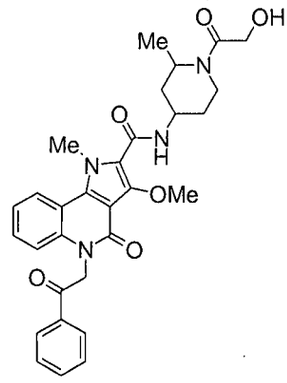
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.06 (3H, d, *J* = 6.3 Hz), 1.23 (1H, q, *J* = 11.6 Hz), 1.40 - 1.60 (1H, m), 1.85 (2H, d, *J* = 10.8 Hz), 2.21-2.32 (3H, m), 2.74 - 2.83 (1H, m), 2.96 (1H, t, *J* = 12.3 Hz), 3.45 - 3.51 (2H, m), 3.70 - 3.90 (1H, m), 3.98 (3H, s), 4.30 - 4.38 (4H, m), 5.97 (2H, s), 7.29 -7.35 (2H, m), 7.38 (1H, d, *J* = 7.5 Hz), 7.63 (2H, t, *J* = 7.5 Hz), 7.74 - 7.84 (2H, m), 8.17

1328

(2H, d, J = 7.8 Hz), 8.37 (1H, d, J = 8.4 Hz).

Ejemplo 591

Producción de N-[1-(hidroxiacetil)-2-metilpiperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

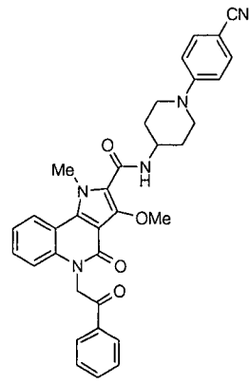


Del mismo modo que en el Ejemplo 130, el compuesto del título (35 mg, 40%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 589 (80 mg, 0.15 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.28 (3H, d, J = 6.9 Hz), 1.70 - 1.95 (4H, m), 3.10 - 3.25 (1H, m), 4.03-4.15 (7H, m), 4.30 - 4.34 (4H, m), 4.50 (1H, t, J = 5.4 Hz), 5.98 (2H, s), 7.30 - 7.31 (2H, m), 7.39 (1H, t, J = 8.1 Hz), 7.63 (2H, t, J = 7.5 Hz), 7.76 (1H, t, J = 7.2 Hz), 8.07 (1H, d, J = 6.6 Hz), 8.17 (2H, d, J = 7.2 Hz), 8.38 (1H, d, J = 7.5 Hz).

Ejemplo 592

Producción de N-[1-(4-cianofenil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



A una solución del compuesto del Ejemplo 77 (300 mg, 0.64

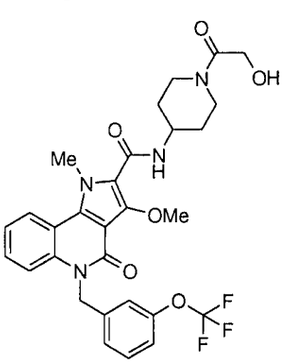
1329

mmol), 4-fluorobenzonitrilo (115 mg, 0.95 mmol) y carbonato de potasio (176 mg, 1.3 mmol) en N-metilpirrolidona (3.0 ml) se agitó a 120°C durante 16.5 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=30/70 - 100/0) y se recristalizó a partir de THF-dietil éter para dar el compuesto del título (73 mg, 20%) como un sólido amarillo pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.52-1.70 (2H, m), 1.87-2.03 (2H, m), 3.02-3.20 (2H, m), 3.81-4.00 (5H, m), 4.03-4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.98 - 7.12 (2H, m), 7.26 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.53 - 7.69 (4H, m), 7.71 - 7.82 (1H, m), 7.98 (1H, d, *J* = 7.9 Hz), 8.12 - 8.22 (2H, m), 8.37 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 593

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-[3-(trifluorometoxi)bencil]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 570, 2-{4-[({3-metoxi-1-metil-4-oxo-5-[3-(trifluorometoxi)bencil]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il}carbonil)amino]piperidin-1-il}-2-oxoacetato de etilo (70 mg) se obtuvo como un sólido amofo sin color a partir del compuesto del Ejemplo 672 (500 mg, 1.10 mmol) y 3-trifluorometoxibenzoil bromuro (1.0 g, 3.92 mmol).

A una solución de 2-{4-[({3-metoxi-1-metil-4-oxo-5-[3-

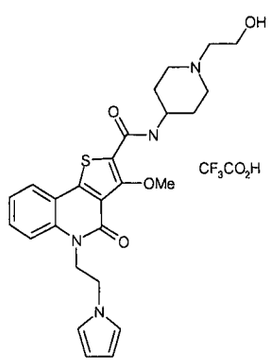
1330

(trifluorometoxi)bencil]-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il}carbonil)amino]piperidin-1-il}-2-oxoacetato de etilo (70 mg) y carbonato de potasio (77 mg, 0.55 mmol) en THF (2 ml)-metanol (1 ml)-agua (1 ml) se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (23 mg, 4%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 - 1.65 (2H, m), 1.85 - 1.95 (2H, m), 2.93 (1H, t, *J* = 11.7 Hz), 3.15 (1H, t, *J* = 11.7 Hz), 3.68 (1H, d, *J* = 12.3 Hz), 4.01-4.29 (10H, m), 4.53 (1H, t, *J* = 5.4 Hz), 5.50-5.70 (2H, amplio), 7.16 - 7.33 (4H, m), 7.31 - 7.37 (3H, m), 8.00 (1H, d, *J* = 8.1 Hz), 8.36 (1H, d, *J* = 8.1 Hz).

Ejemplo 594

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-4-oxo-5-[2-(1H-pirrol-1-il)etil]-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, trifluoroacetato



A una solución 0.2M de DMF del compuesto del Ejemplo 667 (500 µl, 100 µmol) se agregó carbonato de sodio (1 mmol, 138 mg), y una solución 0.3M de DMF (500 µl, 150 µmol) de 1-(2-bromoetil)-1H-pirrol se agregó gota a gota a lo anterior. La

1331

mezcla de reacción se agitó a 40°C hasta la mañana siguiente. Se agregaron acetato de etilo (3 ml) y agua (2 ml) a lo anterior, y la mezcla se extrajo y la fase orgánica se separó. Se evaporó el acetato de etilo bajo presión reducida y el residuo se disolvió en acetonitrilo (500 µl), se purificó (tipo ácido trifluoroacético) por HPLC preparativa para dar el compuesto del título.

rendimiento: 6.9 mg

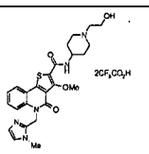
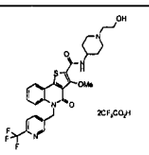
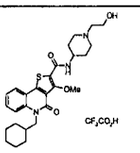
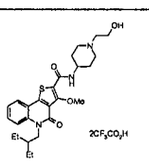
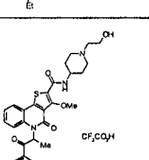
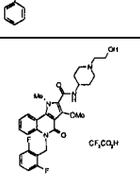
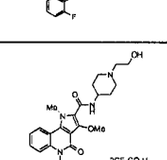
análisis de LC-EM: pureza 84%

EM(ESI+): 495(M+H)

Ejemplo 595 - Ejemplo 602

Del mismo modo que en el Ejemplo 594, los compuestos que se muestran en la Tabla 1 se obtuvieron a partir del compuesto del Ejemplo 667 o Ejemplo 683 y el haluro correspondiente.

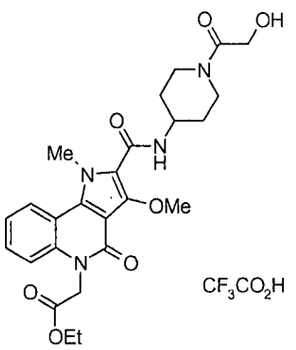
Tabla 1

Ejemplo No.	estructura	rendimiento (mg)	pureza (%)	EM (ESI+)
595		8.6	100	496
596		2.3	89	561
597		4.7	100	498
598		2.1	100	486
599		7.3	100	534
600		1.3	81	525
601		3.1	97	558
602		4.3	100	547

1332

Ejemplo 603

Producción de etil (2-{[1-(hidroxiacetil)piperidin-4-il]carbamoil}-3-metoxi-1-metil-4-oxo-1,4-dihidro-5H-pirrolo[3,2-c]quinolin-5-il)acetato



A una solución 0.2 M de DMF del compuesto del Ejemplo 672 (500 µl, 100 µmol) se agregó carbonato de sodio (1 mmol, 138 mg), y una solución 2M de DMF (500 µl, 1 mmol) de etil bromoacetato se agregó gota a gota a lo anterior. La mezcla de reacción se agitó a 80°C hasta la mañana siguiente. Luego de la compleción de la reacción, DMF se evaporó usando un concentrador al vacío centrífugo con aplicación de calor a 60°C. Se agregó acetonitrilo-DEMO (1:1, 500 µl) al residuo, y se eliminó por filtración el material insoluble. El filtrado se purificó (tipo carbonato de amonio) por HPLC preparativa para dar el compuesto del título.

rendimiento: 2.9 mg

Análisis por LC-EM: pureza 97%

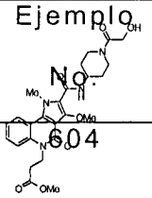
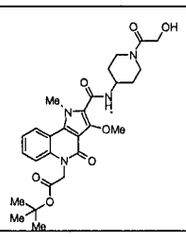
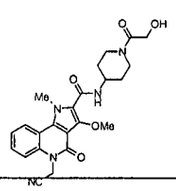
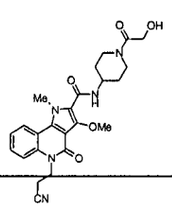
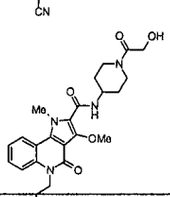
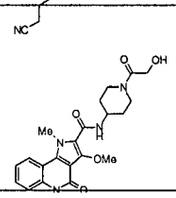
EM(ESI+): 499(M+H)

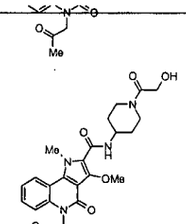
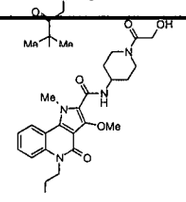
Ejemplo 604 - Ejemplo 618

1333

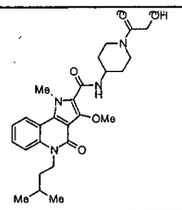
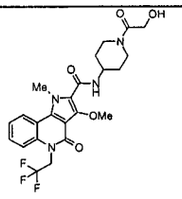
Del mismo modo que en el Ejemplo 594, los compuestos que se muestran en la Tabla 2 se obtuvieron a partir del compuesto del Ejemplo 672 y el haluro correspondiente.

Tabla 2

Ejemplo No.	estructura	rendimiento (mg)	pureza (%)	EM (ESI+)
604		7.3	100	499
605		8.4	100	527
606		6.2	71	452
607		16.9	100	466
608		13.2	100	480
609		10.7	100	469

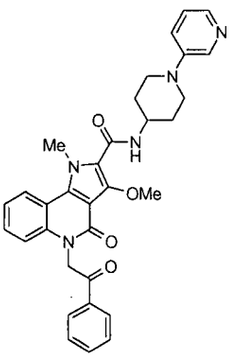
Ejemplo No.	estructura	rendimiento (mg)	pureza (%)	EM (ESI+)
610		11.7	100	511
611		17.3	100	547

1334

Ejemplo No.	estructura	rendimiento (mg)	pureza (%)	EM (ESI+)
617		6.6	100	483
618		8.2	100	495

Ejemplo 619

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-piridin-3-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

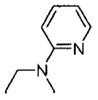


Del mismo modo que en el Ejemplo 575, el compuesto del título (19 mg, 5.4%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 77 (300 mg, 0.64 mmol), y 3-bromopiridina (0.50 ml, 5.2 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58-1.81 (2H, m), 1.89 - 2.04 (2H, m), 2.90 - 3.04 (2H, m), 3.64 - 3.77 (2H, m), 3.97 (3H, s), 4.00 - 4.13 (1H, m), 4.32 (3H, s), 5.97 (2H, s), 7.15 - 7.25 (1H, m), 7.27 - 7.31 (3H, m), 7.32 - 7.52 (1H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.82 (1H, m), 7.93-8.04 (2H, m), 8.11-8.21 (2H, m), 8.30 - 8.43 (2H, m).

Ejemplo 620

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-(1-



1335

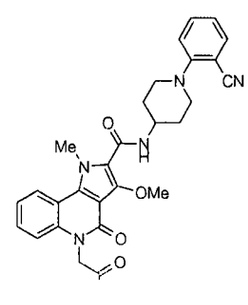
piridin-2-ilpiperidin-4-il)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

A una solución del compuesto del Ejemplo 77 (284 mg, 0.60 mmol), 2-yodopiridina (0.13 ml, 1.2 mmol) y carbonato de potasio (208 mg, 1.5 mmol) en DMF (3.0 ml) se agitó a 9°C durante 5.5 hrs. Se agregaron 2-Bromopiridina (0.23 ml, 2.5 mmol) y trietilamina (0.49 ml, 3.5 mmol) a la mezcla de reacción, y la mezcla se agitó bajo irradiación con microondas a 165°C durante 1 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=30/70 - 100/0) y se recristalizó a partir de THF-dietil éter para dar el compuesto del título (38 mg, 12%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.45 - 1.65 (2H, m), 1.86 - 2.00 (2H, m), 2.99 - 3.14 (2H, m), 3.95 (3H, s), 4.03-4.14 (1H, m), 4.16-4.26 (2H, m), 4.31 (3H, s), 5.97 (2H, s), 6.61 (1H, dd, *J* = 6.8, 5.1 Hz), 6.87 (1H, d, *J* = 8.7 Hz), 7.26 - 7.32 (2H, m), 7.33 - 7.57 (2H, m), 7.59 - 7.68 (2H, m), 7.70 - 7.81 (1H, m), 7.97 (1H, d, *J* = 7.9 Hz), 8.08-8.21 (3H, m), 8.37 (1H, d, *J* = 7.7 Hz).

Ejemplo 621

Producción de N-[1-(2-cianofenil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



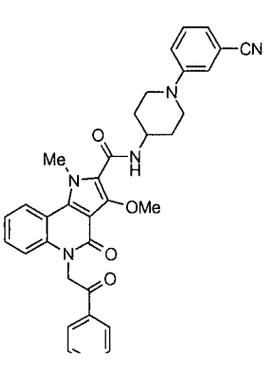
1336

A una solución del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), 2-fluorobenzonitrilo (0.50 ml, 4.6 mmol) y trietilamina (0.50 ml, 3.6 mmol) en DMF (3,5 ml) se agitó bajo irradiación en microondas a 13°C durante 30 min. Se agregaron 2-Bromobenzonitrilo (143 mg, 1.2 mmol) y carbonato de potasio (208 mg, 1.5 mmol) a la mezcla de reacción, y la mezcla se agitó bajo irradiación en microondas a 165°C durante 30 min. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=50/50 - 100/0) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (74 mg, 22%) como un sólido amarillo pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.72 - 1.89 (2H, m), 1.97-2.10 (2H, m), 2.94 - 3.08 (2H, m), 3.43 - 3.54 (2H, m), 3.95 - 4.14 (4H, m), 4.32 (3H, s), 5.98 (2H, s), 7.05 - 7.13 (1H, m), 7.22 (1H, d, *J* = 8.1 Hz), 7.28 - 7.32 (2H, m), 7.34 - 7.52 (1H, m), 7.56 - 7.81 (5H, m), 8.06 (1H, d, *J* = 7.9 Hz), 8.14-8.23 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 622

Producción de N-[1-(3-cianofenil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



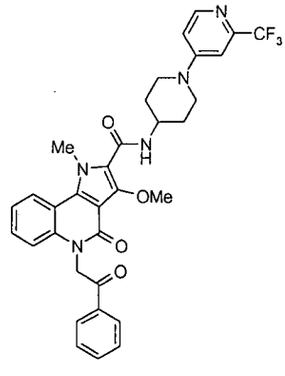
1337

A una solución del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), 3-bromobenzonitrilo (143 mg, 1.2 mmol), tris(dibencilideneacetona)dipaladio (0) (54 mg, 0.059 mmol), x-phos (56 mg, 0.12 mmol), *terc*-butóxido de sodio (142 mg, 1.5 mmol) y trietilamina (0.082 ml, 0.59 mmol) en 2-butanona (4.0 ml) se agitó bajo irradiación en microondas a 130°C durante 40 min. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=40/60 - 100/0) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (25 mg, 7.3%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58-1.74 (2H, m), 1.88 - 2.01 (2H, m), 2.94 - 3.07 (2H, m), 3.71- 3.83 (2H, m), 3.96 (3H, s), 4.00 - 4.12 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.10 - 7.16 (1H, m), 7.27 - 7.32 (5H, m), 7.34 - 7.52 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.80 (1H, m), 7.99 (1H, d, *J* = 7.9 Hz), 8.11-8.22 (2H, m), 8.38 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 623

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-{1-[2-(trifluorometil)piridin-4-il]piperidin-4-il}-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



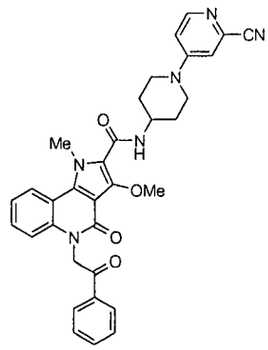
1338

A una solución del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), carbonato de potasio (204 mg, 1.5 mmol) y trietilamina (0.082 ml, 0.59 mmol) en DMF (3.0 ml) se calentó hasta 80°C, se agregó 4-bromo-2-(trifluorometil)piridina (133 mg, 0.59 mmol), y la mezcla se agitó a 10°C durante 23 hrs. La mezcla de reacción se diluyó con agua, y se extrajo 3 veces con acetato de etilo. El extracto se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=50/50 - 100/0) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (126 mg, 35%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.52-1.70 (2H, m), 1.89 - 2.02 (2H, m), 3.11-3,25 (2H, m), 3.90 - 4.07 (5H, m), 4.10 - 4.24 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.08 (1H, dd, *J* = 6.1, 2.5 Hz), 7.21 - 7.27 (1H, m), 7.27 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.57 - 7.67 (2H, m), 7.72 - 7.80 (1H, m), 7.98 (1H, d, *J* = 7.9 Hz), 8.13-8.21 (2H, m), 8.27 (1H, d, *J* = 5.9 Hz), 8.37 (1H, dd, *J* = 8.2, 1.2 Hz).

Ejemplo 624

Producción de N-[1-(2-cianopiridin-4-il)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



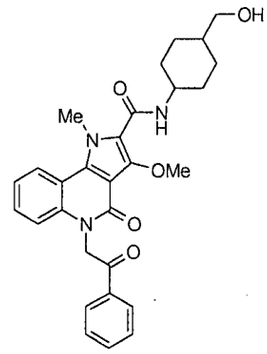
1339

Del mismo modo que en el Ejemplo 623, el compuesto del título (70 mg, 21%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 4-yodopiridin-2-carbonitrilo (136 mg, 0.59 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.69 (2H, m), 1.86-1.98 (2H, m), 3.10 - 3.25 (2H, m), 3.90 - 4.05 (5H, m), 4.08 - 4.24 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.10 (1H, dd, *J* = 6.1, 2.7 Hz), 7.25 - 7.32 (2H, m), 7.33 - 7.55 (2H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.80 (1H, m), 7.97 (1H, d, *J* = 7.7 Hz), 8.11-8.27 (3H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 625

Producción de N-[4-(hidroximetil)ciclohexil]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



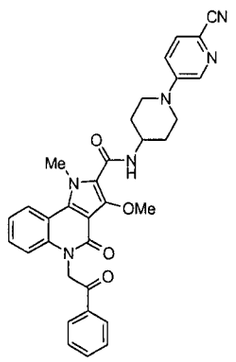
Del mismo modo que en el Ejemplo 25, el compuesto del título (165 mg, 64%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol), y (4-aminociclohexil)metanol (130 mg, 1.0 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.92 - 1.10 (2H, m), 1.21-1.43 (3H, m), 1.72 - 1.86 (2H, m), 1.89 - 2.02 (2H, m), 3.24 (2H, t, *J* = 5.8 Hz), 3.66- 3.83 (1H, m), 3.96 (3H, s), 4.31 (3H, s), 4.42 (1H, t, *J* = 5.3 Hz), 5.97 (2H, s), 7.25 - 7.31 (2H, m), 7.32 - 7.53 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.85 (2H, m), 8.10 - 8.22 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 626

1340

Producción de N-[1-(6-cianopiridin-3-il)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

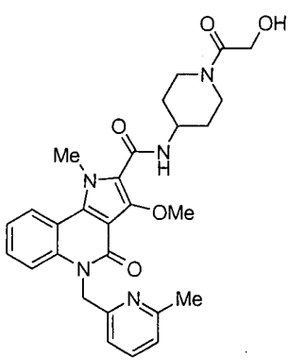


Del mismo modo que en el Ejemplo 623, el compuesto del título (52 mg, 15%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 5-bromopiridin-2-carbonitrilo (119 mg, 0.65 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.56-1.74 (2H, m), 1.88 - 2.02 (2H, m), 3.10 - 3.25 (2H, m), 3.91-4.04 (5H, m), 4.06-4.22 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.25 - 7.52 (4H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.81 (2H, m), 7.98 (1H, d, *J* = 7.9 Hz), 8.12-8.21 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz), 8.46 (1H, d, *J* = 2.8 Hz).

Ejemplo 627

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-5-[(6-metilpiridin-2-il)metil]-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 570, 2-{4-[({3-metoxi-1-metil-5-[(6-metilpiridin-2-il)metil]-4-oxo-4,5-dihidro-1H-pirrolo[3,2-

1341

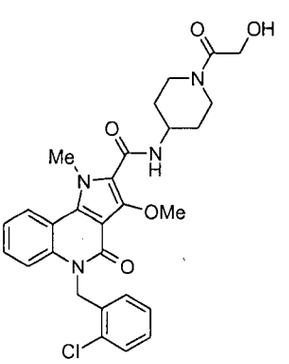
c]quinolin-2-il}carbonil)amino]piperidin-1-il}-2-oxoacetato de etilo (80 mg) se obtuvo como sólido amorfo incoloro a partir del compuesto del Ejemplo 672 (300 mg, 0.66 mmol), 2-(clorometil)-6-metilpiridina clorhidrato (940 mg, 5.28 mmol) y carbonato de cesio (2,18 g, 6.60 mmol).

A una solución de 2-{4-[({3-metoxi-1-metil-5-[(6-metilpiridin-2-il)metil]-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il}carbonil)amino]piperidin-1-il}-2-oxoacetato de etilo (80 mg) y carbonato de potasio (100 mg, 0.71 mmol) en THF (2 ml)-metanol (1 ml)-agua (1 ml) se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (37 mg, 11%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.60 (2H, m), 1.90 (2H, d, *J* = 9.6 Hz), 2.47 (3H, s), 2.93 (1H, t, *J* = 11.7 Hz), 3.14 (1H, t, *J* = 11.6 Hz), 3.67 (1H, d, *J* = 12.9 Hz), 3.99-4.29 (10H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.59 (2H, s), 6.71 (1H, d, *J* = 7.8 Hz), 7.12 (1H, d, *J* = 7.8 Hz), 7.29 (1H, t, *J* = 7.5 Hz), 7.37 - 7.38 (2H, m), 7.55 (1H, t, *J* = 7.8 Hz), 7.98 (1H, d, *J* = 7.8 Hz), 8.35 (1H, d, *J* = 7.2 Hz).

Ejemplo 628

Producción de 5-(2-clorobencil)-N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



1342

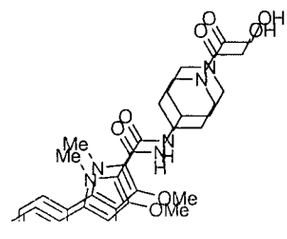
Del mismo modo que en el Ejemplo 570, 2-[4-({[5-(2-clorobencil)-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (80 mg) se obtuvo como un sólido amorfo sin color a partir del compuesto del Ejemplo 672 (300 mg, 0.66 mmol), cloruro de 2-clorobencilo (1.06 g, 6.60 mmol) y carbonato de cesio (2.18 g, 6.60 mmol).

A una solución de 2-[4-({[5-(2-clorobencil)-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (80 mg) y carbonato de potasio (100 mg, 0.71 mmol) en THF (2 ml)-metanol (1 ml)-agua (1 ml) se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (8 mg, 2%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.60 (2H, m), 1.90 (2H, d, *J* = 12.3 Hz), 2.93 (1H, t, *J* = 11.0 Hz), 3.15 (1H, t, *J* = 11.6 Hz), 3.68 (1H, d, *J* = 13.5 Hz), 3.99-4.34 (10H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.58 (2H, s), 6.59 (1H, d, *J* = 7.5 Hz), 7.14 - 7.20 (2H, m), 7.27 - 7.34 (2H, m), 7.37 (1H, t, *J* = 7.8 Hz), 7.57 (1H, d, *J* = 8.1 Hz), 7.99 (1H, d, *J* = 7.8 Hz), 8.39 (1H, d, *J* = 8.4 Hz).

Ejemplo 629

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-5-{[2-metil-6-(trifluorometil)piridin-3-il]metil}-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



1343

Del mismo modo que en el Ejemplo 570, 2-(4-{[(3-metoxi-1-metil-5-{[2-metil-6-(trifluorometil)piridin-3-il]metil}-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il)carbonil]amino}piperidin-1-il)-2-oxoacetato de etilo (50 mg) se obtuvo como un sólido amorfo sin color a partir del compuesto del Ejemplo 672 (300 mg, 0.66 mmol), 3-clorometil-2-metil-6-trifluorometilpiridina (980 mg, 4.68 mmol) y carbonato de cesio (1.09 g, 3.30 mmol).

A una solución de 2-(4-{[(3-metoxi-1-metil-5-{[2-metil-6-(trifluorometil)piridin-3-il]metil}-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il)carbonil]amino}piperidin-1-il)-2-oxoacetato de etilo (50 mg) y carbonato de potasio (55 mg, 0.40 mmol) en THF (2 ml)-metanol (1 ml)-agua (1 ml) se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (19 mg, 5%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.60 (2H, m), 1.89 (2H, d, *J* = 13.5 Hz), 2.77 (3H, s), 2.92 (1H, t, *J* = 9.9 Hz), 3.14 (1H, t, *J* = 11,4 Hz), 3.68 (1H, d, *J* = 12.9 Hz), 3.98 (3H, s), 4.00 - 4.33 (7H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.62 (2H, s), 6.99 (1H, d, *J* = 7.8 Hz), 7.29 -7.36 (2H, m), 7.37 (1H, t, *J* = 7.5 Hz), 7.54 (1H, d, *J* = 8.1 Hz), 7.99 (1H, d, *J* = 7.5 Hz), 8.40 (1H, d, *J* = 6.9 Hz).

Ejemplo 630

Producción de 5-(4-clorobencil)-N-[1-(hidroxiacetil)piperidin-4-il]-



1344

3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

Del mismo modo que en el Ejemplo 570, 2-[4-({[5-(4-clorobencil)-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (60 mg) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 672 (200 mg, 0.44 mmol), cloruro de 4-clorobencilo (708 mg, 4.40 mmol) y carbonato de cesio (572 g, 1.76 mmol).

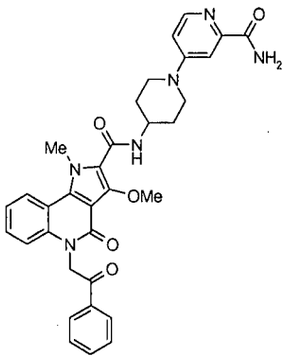
A una solución de 2-[4-({[5-(4-clorobencil)-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (60 mg) y carbonato de potasio (72 mg, 0.52 mmol) en THF (2 ml)-metanol (1 ml)-agua (1 ml) se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (7 mg, 2%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 - 1.60 (2H, m), 1.90 (2H, d, *J* = 10.8 Hz), 2.93 (1H, t, *J* = 12.0 Hz), 3.15 (1H, t, *J* = 12.0 Hz), 3.68 (1H, d, *J* = 13.5 Hz), 4.01-4.34 (10H, m), 4.52 (1H, t, *J* = 5.4 Hz), 5.59 (2H, s amplio), 7.20 - 7.39 (7H, m), 7.99 (1H, d, *J* = 5.4 Hz), 8.35 (1H, d, *J* = 8.1 Hz).

Ejemplo 631

1345

Producción de N-[1-(2-carbamoilpiridin-4-il)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

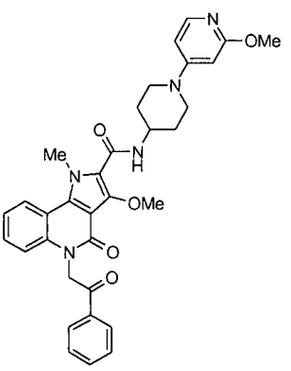


Del mismo modo que en el Ejemplo 623, el compuesto del título (58 mg, 17%) se obtuvo como un sólido rojo pálido a partir del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 4-bromopiridin-2-carboxamida (119 mg, 0.59 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.52-1.72 (2H, m), 1.88 - 2.05 (2H, m), 3.07 - 3.24 (2H, m), 3.86-4.03 (5H, m), 4.07-4.22 (1H, m), 4.31 (3H, s), 5.96 (2H, s), 6.93 - 7.08 (1H, m), 7.25 - 7.31 (2H, m), 7.33 - 7.54 (3H, m), 7.56 - 7.68 (2H, m), 7.70 - 7.82 (1H, m), 7.91-8.04 (2H, m), 8.10 - 8.25 (3H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 632

Producción de 3-metoxi-N-[1-(2-metoxipiridin-4-il)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 575, el compuesto del título (51 mg, 15%) se obtuvo como un sólido blanco a partir del

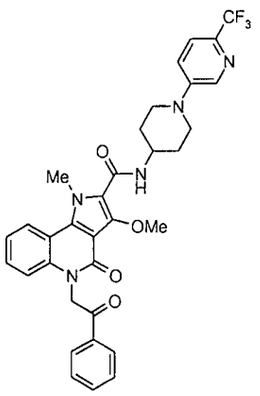
1346

compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 4-bromo-2-metoxipiridina (122 mg, 0.65 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.49-1.70 (2H, m), 1.85 - 2.00 (2H, m), 2.98-3.12 (2H, m), 3.73- 3.88 (5H, m), 3.95 (3H, s), 4.03-4.18 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 6.15 (1H, d, *J* = 2.3 Hz), 6.59 (1H, dd, *J* = 6.2, 2.3 Hz), 7.26 - 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.84 (2H, m), 7.96 (1H, d, *J* = 7.9 Hz), 8.09 - 8.23 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 633

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-{1-[6-(trifluorometil)piridin-3-il]piperidin-4-il}-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 623, el compuesto del título (51 mg, 14%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 5-bromo-2-(trifluorometil)piridina (147 mg, 0.65 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.59-1.77 (2H, m), 1.91-2.02 (2H, m), 3.07 - 3.20 (2H, m), 3.86-4.00 (5H, m), 4.05 - 4.20 (1H, m), 4.31 (3H, s), 5.97 (2H, s), 7.27 - 7.31 (2H, m), 7.33 - 7.52 (2H, m), 7.58 - 7.67 (3H, m), 7.72 - 7.80 (1H, m), 7.98 (1H, d, *J* = 7.9 Hz), 8.13-8.20 (2H, m), 8.37 (1H, dd, *J* = 8.2, 1.0 Hz), 8.46 (1H, d, *J* = 2.8 Hz).

Ejemplo 634

Producción de 3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-{1-[2-

1347

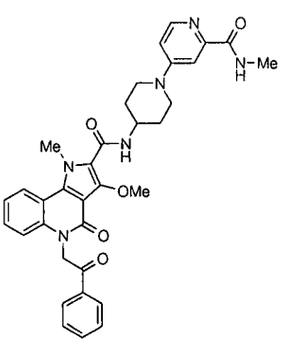
(trifluorometil)pirimidin-4-il]piperidin-4-il}-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

Del mismo modo que en el Ejemplo 623, el compuesto del título (210 mg, 58%) se obtuvo como un sólido rojo pálido a partir del compuesto del Ejemplo 77 (300 mg, 0.59 mmol), y 4-cloro-2-(trifluorometil)pirimidina (129 mg, 0.71 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.48-1.69 (2H, m), 1.91-2.07 (2H, m), 3.17 - 3.30 (2H, m), 3.96 (3H, s), 4.10 - 4.52 (6H, m), 5.97 (2H, s), 7.12 (1H, d, *J* = 6.4 Hz), 7.26- 7.31 (2H, m), 7.33 - 7.52 (1H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 7.97 (1H, d, *J* = 7.9 Hz), 8.11-8.22 (2H, m), 8.27-8.45 (2H, m).

Ejemplo 635

Producción de 3-metoxi-1-metil-N-{1-[2-(metilcarbamoil)piridin-4-il]piperidin-4-il}-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



A una solución de ácido 4-cloropiridin-2-carboxílico (200 mg, 1.3 mmol), metilamina, clorhidrato (103 mg, 1.5 mmol), HOBt (205 mg, 1.5 mmol) y trietilamina (0.42 ml, 3.0 mmol) en DMF (3.0 ml)

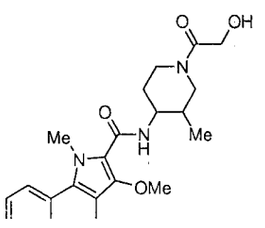
1348

se agregó WSCD (292 mg, 1.5 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 5 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró a través de gel de aminosílice, y el filtrado se concentró bajo presión reducida. El residuo se disolvió en DMF (3.0 ml), se agregaron el compuesto del Ejemplo 77 (300 mg, 0.59 mmol), carbonato de potasio (204 mg, 1.5 mmol) y trietilamina (0.082 ml, 0.59 mmol), y la mezcla se agitó a 10°C durante 16 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo dos veces con una mezcla de solvente de acetato de etilo-THF. El extracto se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=40/60 - 100/0) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (40 mg, 11%) como un sólido amarillo pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.52-1.72 (2H, m), 1.90 - 2.05 (2H, m), 2.79 (3H, d, *J* = 4.9 Hz), 3.09 - 3.22 (2H, m), 3.88 - 4.02 (5H, m), 4.07-4.22 (1H, m), 4.31 (3H, s), 5.96 (2H, s), 7.01 (1H, dd, *J* = 6.0, 2.8 Hz), 7.25 - 7.31 (2H, m), 7.33 - 7.52 (2H, m), 7.57 - 7.68 (2H, m), 7.70 - 7.81 (1H, m), 7.98 (1H, d, *J* = 7.9 Hz), 8.11-8.24 (3H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz), 8.53-8.70 (1H, m).

Ejemplo 636

Producción de N-[1-(hidroxiacetil)-3-metilpiperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



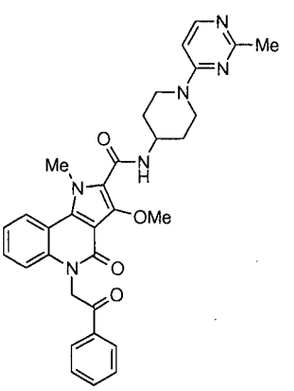
1350

Del mismo modo que en el Ejemplo 130, el compuesto del título (21 mg, 22%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 678 (83 mg, 0.17 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.82-1.02 (3H, m), 1.55 - 2.40 (3H, m), 3.14 - 3.77 (4H, m), 3.93-4.05 (3H, m), 4.07-4.17 (2H, m), 4.20 - 4.41 (4H, m), 4.45 – 4.57 (1H, m), 5.98 (2H, s), 7.25 - 7.32 (2H, m), 7.33 - 7.53 (1H, m), 7.58 - 7.68 (2H, m), 7.71 - 7.80 (1H, m), 7.85 - 8.05 (1H, m), 8.10 - 8.24 (2H, m), 8.38 (1H, dd, *J* = 8.4, 1.2 Hz).

Ejemplo 637

Producción de 3-metoxi-1-metil-N-[1-(2-metilpirimidin-4-il)piperidin-4-il]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 623, el compuesto del título (130 mg, 59%) se obtuvo como un sólido marrón pálido a partir del compuesto del Ejemplo 77 (200 mg, 0.39 mmol), y 4-cloro-2-metilpirimidina (61 mg, 0.47 mmol).

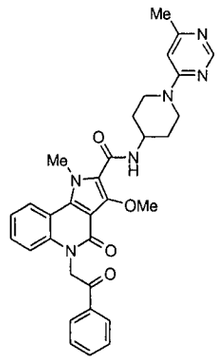
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.44-1.62 (2H, m), 1.85 - 2.01 (2H, m), 2.36 (3H, s), 3.06-3.23 (2H, m), 3.96 (3H, s), 4.06-4.23 (1H, m), 4.24-4.41 (5H, m), 5.97 (2H, s), 6.68

1351

(1H, d, *J* = 6.4 Hz), 7.25 - 7.32 (2H, m), 7.33 - 7.53 (1H, m), 7.57 - 7.69 (2H, m), 7.71 -7.82 (1H, m), 7.96 (1H, d, *J* = 7.9 Hz), 8.08 (1H, d, *J* = 6.2 Hz), 8.13-8.22 (2H, m), 8.37 (1H, d, *J* = 7.6 Hz).

Ejemplo 638

Producción de 3-metoxi-1-metil-N-[1-(6-metilpirimidin-4-il)piperidin-4-il]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

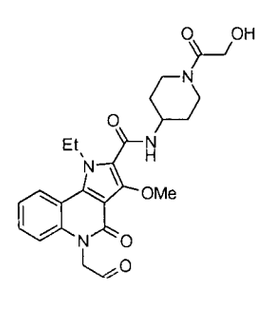


Del mismo modo que en el Ejemplo 623, el compuesto del título (137 mg, 62%) se obtuvo como un sólido marrón pálido a partir del compuesto del Ejemplo 77 (200 mg, 0.39 mmol), y 4-cloro-6-metilpirimidina (61 mg, 0.47 mmol).

^{1}H-RMN (300 MHz, DEMO-d_6) δ: 1.44-1.64 (2H, m), 1.85 - 2.01 (2H, m), 2.26 (3H, s), 3.05 - 3.23 (2H, m), 3.95 (3H, s), 4.07-4.23 (1H, m), 4.24 - 4.39 (5H, m), 5.97 (2H, s), 6.77 (1H, s), 7.25 - 7.32 (2H, m), 7.33 - 7.53 (1H, m), 7.57 - 7.69 (2H, m), 7.70 - 7.82 (1H, m), 7.96 (1H, d, *J* = 7.9 Hz), 8.11-8.23 (2H, m), 8.32-8.45 (2H, m).

Ejemplo 639

Producción de 1-etil-N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



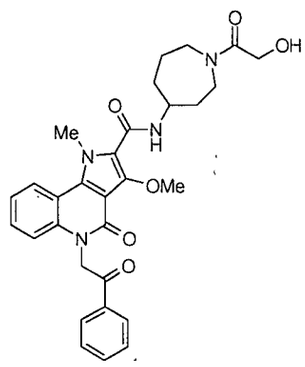
1352

Del mismo modo que en el Ejemplo 140, el compuesto del título (42 mg, 22%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 120 (140 mg, 0.35 mmol), y 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (81 mg, 0.42 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.39-1.61 (5H, m), 1.82-1.98 (2H, m), 2.84 - 3.01 (1H, m), 3.06-3.21 (1H, m), 3.59-3.74 (1H, m), 3.96 (3H, s), 4.03-4.14 (3H, m), 4.16-4.28 (1H, m), 4.51 (1H, t, *J* = 5.4 Hz), 4.82 (2H, q, *J* = 7.1 Hz), 5.98 (2H, s), 7.30 - 7.32 (2H, m), 7.33 - 7.52 (1H, m), 7.59 - 7.68 (2H, m), 7.71 - 7.81 (1H, m), 8.03 (1H, d, *J* = 7.7 Hz), 8.12-8.25 (3H, m).

Ejemplo 640

Producción de N-[1-(hidroxiacetil)azepan-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Una solución mixta del compuesto del Ejemplo de Referencia 123 (220 mg, 0.70 mmol) y solución 8N de hidróxido de sodio (0.36 ml) en etanol (3.0 ml)-agua (3.0 ml) se agitó durante 30 min enfrió con hielo. La mezcla de reacción se neutralizó con ácido clorhídrico 1N, se agitó durante 10 min enfrió con hielo y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se

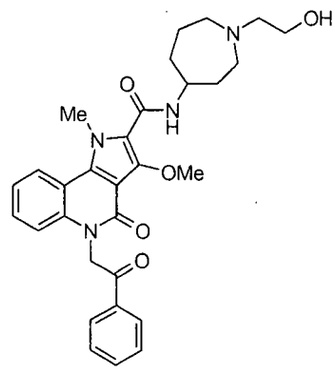
1353

disolvió en acetato de etilo (2.0 ml), y se agregó solución 4N de hidrógeno cloruro de acetato de etilo (2.0 ml). La mezcla se agitó a temperatura ambiente durante 2 hrs, y se concentró bajo presión reducida. A una solución de el residuo, el compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol), HOBt (90 mg, 0.67 mol) y trietilamina (0.22 ml, 1.6 mmol) en DMF (5.0 ml) se agregó WSC (128 mg, 0.67 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 62 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=80/20 - 100/0) y se recristalizó a partir de THF-dietil éter para dar el compuesto del título (122 mg, 44%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.55 - 1.92 (5H, m), 1.93 - 2.11 (1H, m), 3.25 - 3.45 (2H, m), 3.47 - 3.55 (1H, m), 3.63- 3.80 (1H, m), 3.92 - 4.06 (4H, m), 4.07-4.18 (2H, m), 4.25 - 4.36 (3H, m), 4.43 (1H, t, *J* = 4.7 Hz), 5.97 (2H, s), 7.24 - 7.32 (2H, m), 7.33 - 7.52 (1H, m), 7.58 - 7.67 (2H, m), 7.71 - 7.81 (1H, m), 7.94 (1H, d, *J* = 8.1 Hz), 8.12-8.22 (2H, m), 8.37 (1 H, d, *J* = 7.9 Hz).

Ejemplo 641

Producción de N-[1-(2-hidroxietil)azepan-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



1354

A una solución del compuesto del Ejemplo de Referencia 122 (157 mg, 0.73 mmol) y carbonato de potasio (607 mg, 4.4 mmol) en DMF (6.0 ml) se agitó a 10°C durante 5 min, 2-bromoetanol (0.16 ml, 2.2 mmol) se agregó a la mezcla de reacción, y la mezcla se agitó a 10°C durante 1 hrs. La mezcla de reacción se diluyó con agua, se agregó salmuera, y la mezcla se extrajo 4 veces con acetato de etilo. Los extractos se combinaron, se secaron sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; metanol/acetato de etilo=0/100 - 5/95). El residuo se disolvió en acetato de etilo (2.0 ml), y solución 4N de hidrógeno cloruro de acetato de etilo (2.0 ml) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, y se concentró bajo presión reducida. A una solución de el residuo, el compuesto del Ejemplo de Referencia 28 (200 mg, 0.51 mmol) y trietilamina (0.27 ml, 1.9 mmol) en DMF (5.0 ml) se agregó DMT-MM (167 mg, 0.61 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 62 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio y agua, y se extrajo dos veces con acetato de etilo. Los extractos se combinaron, se lavaron con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=50/50 - 100/0) y se recristalizó a partir de etanol-hexano para dar el compuesto del título (75 mg, 28%) como un sólido amarillo pálido.

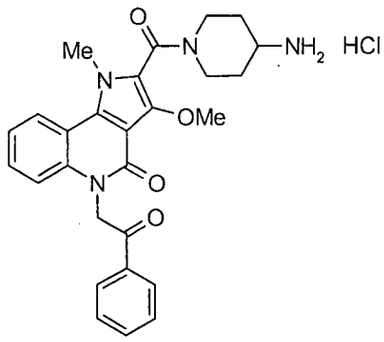
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.49 - 2.01 (6H, m), 2.53 - 2.84 (6H, m), 3.44 - 3.56 (2H, m), 3.90 - 4.03 (3H, m), 4.14-4.41 (5H, m), 5.97 (2H, s), 7.25 - 7.32 (2H, m), 7.33 - 7.53 (1 H, m),

1355

7.57 - 7.69 (2H, m), 7.71 - 7.82 (1H, m), 8.04 (1H, d, *J* = 8.3 Hz), 8.11-8.23 (2H, m), 8.37 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 642

Producción de 2-[(4-aminopiperidin-1-il)carbonil]-3-metoxi-1-metil-5-(2-oxo-2-feniletil)-1.5-dihidro-4H-pirrolo[3,2-c]quinolin-4-ona, clorhidrato

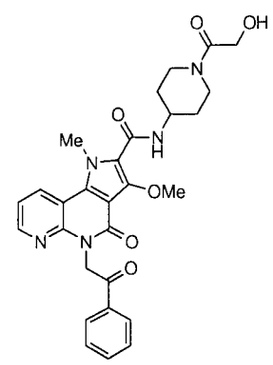


Del mismo modo que en el Ejemplo 542, el compuesto del título (119 mg, 79%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 679 (170 mg, 0.30 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.36-1.73 (2H, m), 1.84 - 2.15 (2H, m), 2.83 - 3.04 (1H, m), 3.08-3.30 (2H, m), 3.77 - 3.95 (4H, m), 4.00 (3H, s), 4.45 - 4.68 (1H, m), 5.98 (2H, s), 7.24 - 7.52 (3H, m), 7.58 - 7.70 (2H, m), 7.71 - 7.81 (1H, m), 8.00 (3H, br. s), 8.13 -8.23 (2H, m), 8.33 (1H, dd, *J* = 8.2, 1.0 Hz).

Ejemplo 643

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1,8]naftiridin-2-carboxamida



Del mismo modo que en el Ejemplo 141, el compuesto del

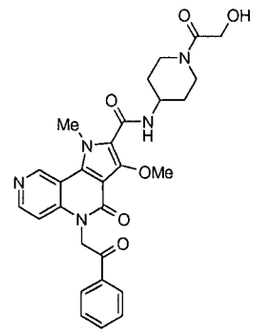
1356

título (141 mg, 69%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 131 (150 mg, 0.38 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.32-1.65 (2H, m), 1.81-1.97 (2H, m), 2.81-3.01 (1H, m), 3.04 - 3.22 (1H, m), 3.63 - 3.74 (1H, m), 3.98 (3H, s), 4.04-4.16 (3H, m), 4.17- 4.28 (1H, m), 4.32 (3H, s), 4.51 (1H, t, *J* = 5.4 Hz), 5.99 (2H, s), 7.35 (1H, dd, *J* = 8.1, 4.7 Hz), 7.54 - 7.68 (2H, m), 7.69 - 7.80 (1H, m), 8.00 (1H, d, *J* = 7.9 Hz), 8.08-8.22 (2H, m), 8.44 (1H, dd, *J* = 4.7, 1.5 Hz), 8.73 (1H, dd, *J* = 8.3, 1.5 Hz).

Ejemplo 644

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1.6]naftiridin-2-carboxamida



Del mismo modo que en el Ejemplo 141, el compuesto del título (97 mg, 48%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 139 (150 mg, 0.38 mmol).

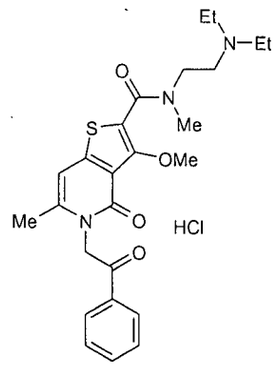
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.34 -1.63 (2H, m), 1.79-1.97 (2H, m), 2.83 - 3.01 (1H, m), 3.05 - 3.22 (1H, m), 3.59-3.74 (1H, m), 3.95 (3H, s), 4.01-4.17 (3H, m), 4.17- 4.28 (1H, m), 4.35 (3H, s), 4.50 (1H, t, *J* = 5.4 Hz), 5.95 (2H, s), 7.32 (1H, d, *J* = 6.2 Hz), 7.57 - 7.69 (2H, m), 7.71 - 7.82 (1H, m), 7.99 (1H, d, *J* = 7.7 Hz), 8.10 - 8.22 (2H, m), 8.48 (1H, d, *J* = 6.0 Hz), 9.51 (1H, s).

Ejemplo 645.

Producción de N-[2-(dietilamino)etil]-3-etoxi-N,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida,

1357

clorhidrato

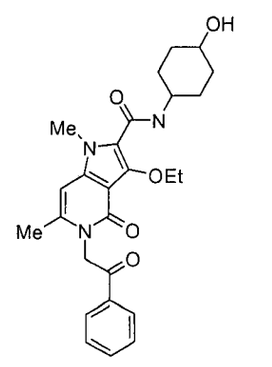


A una solución del compuesto del Ejemplo 146 (150 mg, 0.310 mmol) en acetato de etilo (20 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (93.0 µl, 0.372 mmol). La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (30 ml) y etanol (5 ml). Hexano (10 ml) se agregó, y la mezcla se agitó a temperatura ambiente durante 15 hrs. El sólido precipitado se recolectó por filtración, y se lavó con acetato de etilo para dar el compuesto del título (90.0 mg, 56%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.10 – 1.35 (9H, m), 2.30 (3H, s), 3.08 (3H, s), 3.00 - 3.40 (6H, m), 3.79 (2H, t, *J* = 7.2 Hz), 4.08 (2H, q, *J* = 7.0 Hz), 5.67 (2H, s), 6.84 (1H, d, *J* = 0.6 Hz), 7.62 (2H, t, *J* = 7.5 Hz), 7.72 - 7.78 (1H, m), 8.10 - 8.13 (2H, m), 10.03 (1H, s).

Ejemplo 646

Producción de 3-etoxi-N-(4-hidroxiciclohexil)-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



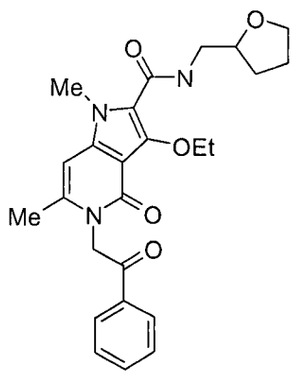
1358

Del mismo modo que en el Ejemplo 25, el compuesto del título (106 mg, 60%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 44 (140 mg, 0.380 mmol) y 4-aminociclohexanol (53 mg, 0.456 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19-1.35 (7 H, m), 1.86 (4 H, d, *J* = 12.8 Hz), 2.27 (3 H, s), 3.45 (1 H, s amplio), 3.71 (1 H, s amplio), 3.86 (3 H, s), 4.33 (2 H, q, *J* = 6.9 Hz), 4.56 (1 H, d, *J* = 4.3 Hz), 5.61 (2 H, s), 6.57 (1 H, s), 7.38 - 7.67 (3 H, m), 7.72 (1 H, d, *J* = 7.2 Hz), 8.10 (2 H, d, *J* = 7.3 Hz).

Ejemplo 647

Producción de 3-etoxi-1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidrofuran-2-ilmetil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida

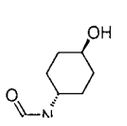


Del mismo modo que en el Ejemplo 25, el compuesto del título (114 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 35 (140 mg, 0.380 mmol) y 2-tetrahidrofurfurilamina (47 µl, 0.456 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.29 (3 H, t, *J* = 6.8 Hz), 1.48-1.62 (1 H, m), 1.78-1.99 (3 H, m), 2.28 (3 H, s), 3.41-3.52 (1 H, m), 3.60 - 3.71 (1 H, m), 3.75- 3.84 (1 H, m), 3.89 (3 H, s), 3.91-4.02 (2 H, m), 4.35 (2 H, t, *J* = 7.0 Hz), 5.61 (2 H, s), 6.59 (1 H, s), 7.61 (2 H, t, *J* = 7.3 Hz), 7.73 (1 H, m), 7.88 (1 H, s amplio), 8.11 (2 H, d, *J* = 7.6 Hz).

Ejemplo 648

Producción de 3-etoxi-6-etil-N-(trans-4-hidroxiciclohexil)-1-metil-



1359

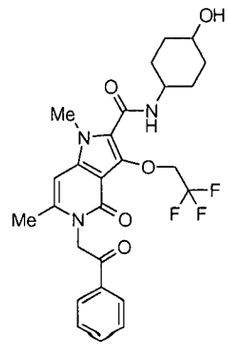
4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida

Del mismo modo que en el Ejemplo 25, el compuesto del título (76 mg, 79%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 42 (77 mg, 0.20 mmol) y trans-4-aminociclohexanol (28 mg, 0.24 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.22 - 1.36 (7 H, m), 1.75 - 1.96 (4 H, m), 2.57 (2 H, q, *J* = 7.3 Hz), 3.44 (1 H, s amplio.), 3.71 (1 H, s amplio.), 3.89 (3 H, s), 4.32 (2 H, q, *J* = 7.1 Hz), 4.57 (1 H, d, *J* =4.2 Hz), 5.58 (2 H, s), 6.48 (1 H, s), 7.51 - 7.66 (3 H, m), 7.67 - 7.78 (1 H, m), 8.11 (2 H, d, *J* = 7.2 Hz).

Ejemplo 649

Producción de N-[1-(hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c][1.6]naftiridin-2-carboxamida



Del mismo modo que en el Ejemplo 140, el compuesto del título (132 mg, 54%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo de Referencia 50 (200 mg, 0.47 mmol) y 4-aminociclohexanol (82 mg, 0.71 mmol).

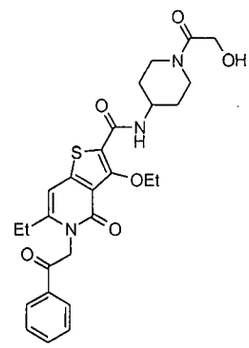
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.25 (4H, t, *J* = 9.6 Hz),

1360

1.80 - 1.90 (4H, m), 2.29 (3H, s), 3.30 - 3.45 (1H, amplio), 3.60 - 3.80 (1H, amplio), 3.83 (3H, s), 4.57 (1H, t, *J* = 4.5 Hz), 5.06 (2H, q, *J* = 9.3 Hz), 5.65 (2H, s), 6.64 (1H, s), 7.31 (1H, d, *J* = 7.8 Hz), 7.61 (1H, t, *J* = 7.5 Hz), 7.74 (1H, t, *J* = 7.5 Hz), 8.09 - 8.12 (2H, m).

Ejemplo 650

Producción de 3-etoxi-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo de Referencia 7, ácido 3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxílico (700 mg, 83%) se obtuvo como un polvo violeta a partir del compuesto del Ejemplo de Referencia 170 (900 mg, 2.25 mmol). *terc*-butil 4-({[3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-il]carbonil}amino)piperidina-1-carboxilato (125 mg, 15%) se obtuvo como un polvo blanco a partir del así obtenido ácido 3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-carboxílico (550 mg, 1.4 mmol) y 4-amino-1-boc-piperidina (361 mg, 1.8 mmol). 3-Etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida (94 mg, 85%) se obtuvo como un polvo blanco a partir del así obtenido *terc*-butil 4-({[3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-il]carbonil}amino)piperidina-1-carboxilato (125 mg, 0.22 mmol) por

1361

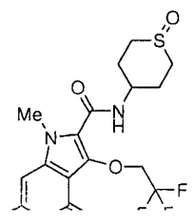
aplicación de un método similar al del Ejemplo 126. 2-[4-({[3-Etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (80 mg, 78%) se obtuvo como un sólido blanco a partir del así obtenido 3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]piridin-2-carboxamida (90 mg, 0.18 mmol) por aplicación de un método similar al del Ejemplo 127.

Una solución mixta de 2-[4-({[3-etoxi-6-etil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]piridin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo (90 mg, 0.18 mmol) y carbonato de potasio (39 mg, 0.28 mmol) en THF (8 ml)-metanol (2 ml)-agua (2 ml) se agitó a temperatura ambiente durante 1 hrs. La mezcla de reacción se concentró, y el residuo se repartió entre acetato de etilo y solución saturada de hidrógeno carbonato de sodio. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (64 mg, 69%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3H, t, *J* = 7.3 Hz), 1.30 (3H, t, *J* = 7.1 Hz), 1.35 - 1.60 (2H, m), 1.90 (2H, d, *J* = 9.9 Hz), 2.60 (2H, q, *J* = 7.3 Hz), 2.84 (1H, t, *J* = 12.0 Hz), 3.10 (1H, t, *J* = 14.0 Hz), 3.66 (1H, d, *J* = 13.5 Hz), 4.00 - 4.09 (3H, m), 4.28 (3H, q, *J* = 7.1 Hz), 4.50 (1H, t, *J* = 5.4 Hz), 5.66 (2H, s), 6.84 (1H, s), 7.60 - 7.68 (2H, m), 7.75 (1H, t, *J* = 7.5 Hz), 8.10 - 8.13 (2H, m).

Ejemplo 651

Producción de 1.6-dimetil-N-(1-oxidotetrahidro-2H-tiopiran-4-il)-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



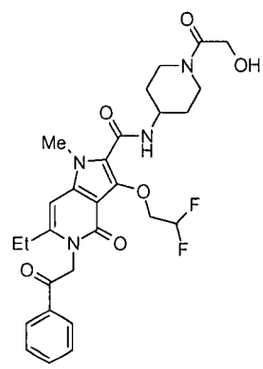
1362

Del mismo modo que en el Ejemplo 571, 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidro-2H-tiopiran-4-il)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida (150 mg) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 50 (200 mg, 0.47 mmol). El Compuesto del título (131 mg, 51%) se obtuvo como cristales blancos a partir del así obtenido 1.6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-N-(tetrahidro-2H-tiopiran-4-il)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida (150 mg) por aplicación de un método similar al del Ejemplo 571.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.60 - 1.75 (1H, m), 1.83 (1H, d, *J* = 10.2 Hz), 2.06 – 2.29 (5H, m), 2.70 - 2.85 (2H, m), 2.93 (1H, d, *J* = 12.9 Hz), 3.81 (3H, d, *J* = 6.3 Hz), 3.90 - 4.10 (1H, m), 5.00-5.13 (2H, m), 5.65 (2H, s), 6.64 (1H, s), 7.61 (3H, t, *J* = 7.8 Hz), 7.74 (1H, t, *J* = 7.2 Hz), 8.10 - 8.12 (2H, m).

Ejemplo 652

Producción de 3-(2,2-difluoroetoxi)-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 140, el compuesto del

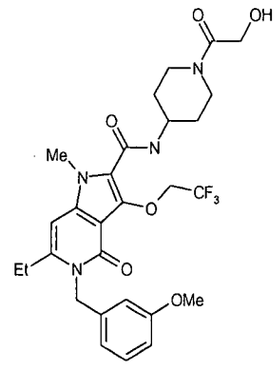
1363

título (340 mg, 84%) se obtuvo as un sólido amorfo blanco a partir del compuesto del Ejemplo de Referencia 171 (300 mg, 0.72 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3H, t, J = 7.3 Hz), 1.20 - 1.50 (2H, m), 1.90 (2H, d, J = 9.9 Hz), 2.59 (2H, q, J = 7.3 Hz), 2.83 (1H, t, J = 12,2 Hz), 3.09 (1H, t, J = 11.7 Hz), 3.68 (1H, d, J = 12.9 Hz), 3.90 (3H, s), 3.95 - 4.20 (3H, m), 4.26 (1H, d, J = 11.7 Hz), 4.51 (1H, t, J = 5.4 Hz), 4.67 (2H, td, J = 16.1, 3.0 Hz), 5.23 (1H, s), 5.61 (2H, s), 6.33 (1H,tt, J = 54.2, 3.0 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.61 (2H, t, J = 7.5 Hz), 7.73 (1H, t, J = 7.5 Hz), 8.10 - 8.12 (2H, m).

Ejemplo 653

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-5-(3-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Una mezcla del compuesto del Ejemplo de Referencia 143 (200 mg, 0.456 mmol), 2-(4-aminopiperidin-1-il)-2-oxoetanol, clorhidrato (115 mg, 0.593 mmol), HOBt (92.4 mg, 0.684 mmol), WSCD (131 mg, 0.684 mmol), trietilamina (0.126 ml, 0.912 mmol) y DMF (4.0 ml) se agitó a temperatura ambiente durante 16 hrs. La mezcla de reacción se diluyó con agua, y se extrajo dos veces con acetato de etilo. El extracto se combinó, se lavó con agua y salmuera, se secó sobre sulfato de sodio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo). La recristalización del

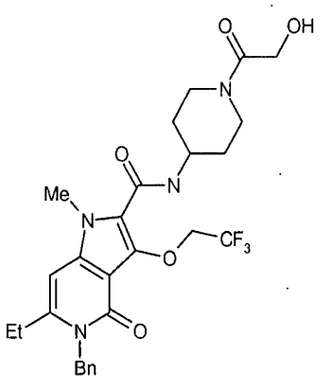
1364

sólido obtenido a partir de acetato de etilo dio el compuesto del título (162 mg, 61%) como cristales blancos.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 1.24 - 1.50 (2 H, m), 1.81 - 1.95 (2 H, m), 2.60 (2 H, q, *J* = 7.3 Hz), 2.76 - 2.91 (1 H, m), 3.01 - 3.18 (1 H, m), 3.64 - 3.74 (4 H, m), 3.84 (3 H, s), 3.95 - 4.14 (3 H, m), 4.20 - 4.33 (1 H, m), 4.52 (1 H, t, *J* = 5.4 Hz), 5.11 (2 H, q, *J* = 9.3 Hz), 5.32 (2 H, s amplio), 6.49 - 6.64 (3 H, m), 6.81 (1 H, dd, *J* = 8.0, 2.2 Hz), 7.22 (1 H, t, *J* = 8.0 Hz), 7.53 (1 H, d, *J* = 7.6 Hz).

Ejemplo 654

Producción de 5-bencil-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 653, el compuesto del título (182 mg, 75%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 145 (180 mg, 0.441 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.2 Hz), 1.25 - 1.48 (2 H, m), 1.83 - 1.95 (2 H, m), 2.60 (2 H, q, *J* = 7.2 Hz), 2.77 - 2.90 (1 H, m), 3.02 - 3.17 (1 H, m), 3.63 - 3.75 (1 H, m), 3.84 (3 H, s), 3.96 - 4.14 (3 H, m), 4.20 - 4.33 (1 H, m), 4.52 (1 H, t, *J* = 5.5 Hz), 5.10 (2 H, q, *J* = 9.4 Hz), 5.36 (2 H, s amplio), 6.52 (1 H, s), 7.00 - 7.09 (2 H, m), 7.19 - 7.36 (3 H, m), 7.53 (1 H, d, *J* = 7.7 Hz).

Ejemplo 655

Producción de 5-(2.5-dimetoxibencil)-6-etil-N-[1-

1365

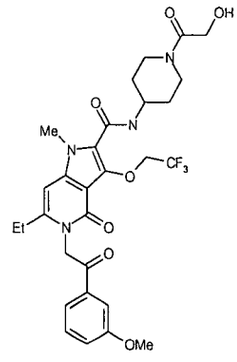
(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida

Del mismo modo que en el Ejemplo 653, el compuesto del título (86.0 mg, 80%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 147 (82.7 mg, 0.177 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, *J* = 7.3 Hz), 1.24 - 1.48 (2 H, m), 1.84 - 1.93 (2 H, m), 2.52 - 2.61 (2 H, m), 2.77 - 2.90 (1 H, m), 3.03 - 3.16 (1 H, m), 3.55 (3 H, s), 3.64 - 3.74 (1 H, m), 3.83 (3 H, s), 3.86 (3 H, s), 3.97 - 4.14 (3 H, m), 4.20 - 4.32 (1 H, m), 4.52 (1 H, t, *J* = 5.3 Hz), 5.08 (2 H, q, *J* = 9.2 Hz), 5.21 (2 H, s amplio), 5.89 (1 H, d, *J* = 3.0 Hz), 6.56 (1 H, s), 6.79 (1 H, dd, *J* = 8.9, 3.0 Hz), 6.97 (1 H, d, *J* = 8.9 Hz), 7.53 (1 H, d, *J* = 7.9 Hz).

Ejemplo 656

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-5-[2-(3-metoxifenil)-2-oxoetil]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 653, el compuesto del

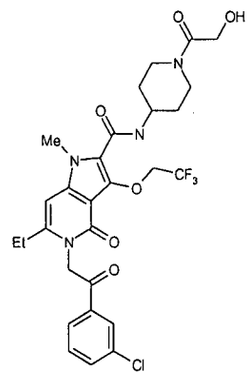
1366

título (65.1 mg, 29%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 151 (170 mg, 0.364 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 1.25 - 1.48 (2 H, m), 1.82 - 1.95 (2 H, m), 2.54 - 2.64 (2 H, m), 2.76 - 2.90 (1 H, m), 3.01 - 3.15 (1 H, m), 3.62 - 3.74 (1 H, m), 3.82 - 3.90 (6 H, m), 3.95 - 4.13 (3 H, m), 4.20 - 4.35 (1 H, m), 4.52 (1 H, t, *J* = 5.5 Hz), 5.05 (2 H, q, *J* = 9.3 Hz), 5.62 (2 H, s), 6.54 (1 H, s), 7.26 - 7.35 (1 H, m), 7.36 - 7.62 (3 H, m), 7.69 - 7.76 (1 H, m).

Ejemplo 657

Producción de 5-[2-(3-clorofenil)-2-oxoetil]-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 653, el compuesto del título (160 mg, 64%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 155 (192 mg, 0.408 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.19 (3 H, t, *J* = 7.3 Hz), 1.25 - 1.49 (2 H, m), 1.82 - 1.95 (2 H, m), 2.60 (2 H, q, *J* = 7.3 Hz), 2.76 - 2.90 (1 H, m), 3.01 - 3.17 (1 H, m), 3.62 - 3.74 (1 H, m), 3.86 (3 H, s), 3.96 - 4.15 (3 H, m), 4.20 - 4.32 (1 H, m), 4.52 (1 H, t, *J* = 5.4 Hz), 5.05 (2 H, q, *J* = 9.2 Hz), 5.62 (2 H, s), 6.55 (1 H, s), 7.50 (1 H, d, *J* = 7.6 Hz), 7.61 - 7.69 (1 H, m), 7.77 - 7.84(1 H, m), 8.03 - 8.09 (1 H, m), 8.14 (1 H, t, *J* = 1.8 Hz).

Ejemplo 658

1367

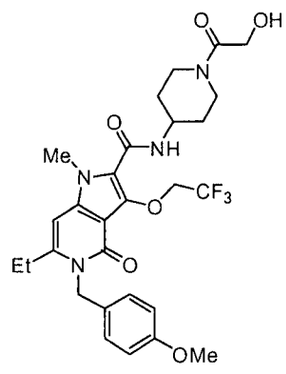
Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-5-(2-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida

Del mismo modo que en el Ejemplo 653, el compuesto del título (120 mg, 86%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 157 (104 mg, 0.237 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 1.26 - 1.49 (2 H, m), 1.81 - 1.95 (2 H, m), 2.52 - 2.61 (2 H, m), 2.77 - 2.91 (1 H, m), 3.00 - 3.19 (1 H, m), 3.56 - 3.77 (1 H, m), 3.86 (3 H, s), 3.88 (3 H, s), 3.97 - 4.14 (3 H, m), 4.19 - 4.33 (1 H, m), 4.52 (1 H, t, *J* = 5.4 Hz), 5.08 (2 H, q, *J* = 9.2 Hz), 5.23 (2 H, s amplio), 6.32 - 6.40 (1 H, m), 6.56 (1 H, s), 6.76 - 6.85 (1 H, m), 7.01 - 7.09 (1 H, m), 7.17 - 7.28 (1 H, m), 7.52 (1 H, d, *J* = 7.6 Hz).

Ejemplo 659

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-5-(4-metoxibencil)-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



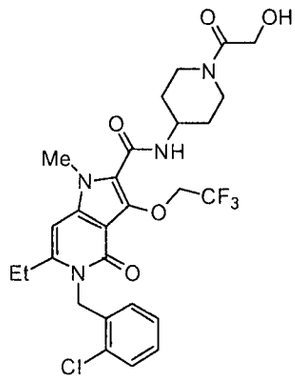
Del mismo modo que en el Ejemplo 653, el compuesto del título (147 mg, 71%) se obtuvo como un polvo blanco a partir del

compuesto del Ejemplo de Referencia 159 (157 mg, 0.358 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.3 Hz), 1.24 - 1.48 (2 H, m), 1.83 - 1.96 (2 H, m), 2.62 (2 H, q, *J* = 7.3 Hz), 2.76 - 2.91 (1 H, m), 3.02 - 3.17 (1 H, m), 3.63 - 3.76 (4 H, m), 3.83 (3 H, s), 3.95 - 4.14 (3 H, m), 4.20 - 4.33 (1 H, m), 4.52 (1 H, t, *J* = 5.4 Hz), 5.11 (2 H, q, *J* = 9.4 Hz), 5.28 (2 H, s amplio), 6.50 (1 H, s), 6.83 - 6.90 (2 H, m), 6.96 - 7.05 (2 H, m), 7.52 (1 H, d, *J* = 7.7 Hz).

Ejemplo 660

Producción de 5-(2-clorobencil)-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 653, el compuesto del título (119 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 161 (138 mg, 0.312 mmol).

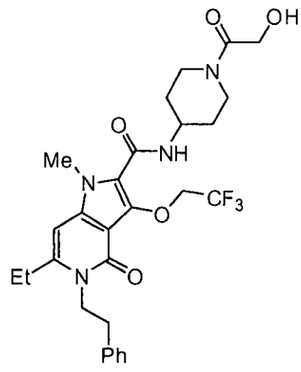
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.18 (3 H, t, *J* = 7.3 Hz), 1.26 - 1.47 (2 H, m), 1.82 - 1.94 (2 H, m), 2.53 - 2.61 (2 H, m), 2.76 - 2.90 (1 H, m), 3.02 - 3.17 (1 H, m), 3.61 - 3.76 (1 H, m), 3.86 (3 H, s), 3.95 - 4.14 (3 H, m), 4.19 - 4.33 (1 H, m), 4.46 - 4.56 (1 H, m), 5.06 (2 H, q, *J* = 9.4 Hz), 5.33 (2 H, s), 6.45 - 6.55 (1 H, m), 6.60 (1 H, s), 7.21 - 7.32 (2 H, m), 7.35 - 7.60 (2 H, m).

Ejemplo 661

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-

1369

pirrolo[3,2-c]piridin-2-carboxamida

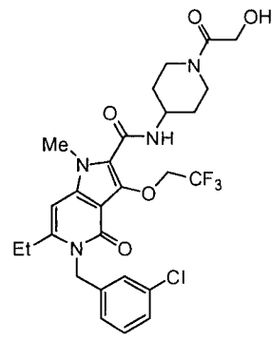


Del mismo modo que en el Ejemplo 653, el compuesto del título (123 mg, 65%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 165 (143 mg, 0.339 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.21 (3 H, t, J = 7.2 Hz), 1.25 - 1.49 (2 H, m), 1.82 - 1.94 (2 H, m), 2.66 (2 H, q, J = 7.2 Hz), 2.77 - 2.95 (3 H, m), 3.02 - 3.17 (1 H, m), 3.62 - 3.75 (1 H, m), 3.82 (3 H, s), 3.95 - 4.35 (6 H, m), 4.52 (1 H, t, J = 5.5 Hz), 5.12 (2 H, q, J = 9.4 Hz), 6.44 (1 H, s), 7.16 - 7.35 (5 H, m), 7.39 (1 H, d, J = 7.6 Hz).

Ejemplo 662

Producción de 5-(3-clorobencil)-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 653, el compuesto del título (261 mg, 71%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 167 (281 mg, 0.635 mmol).

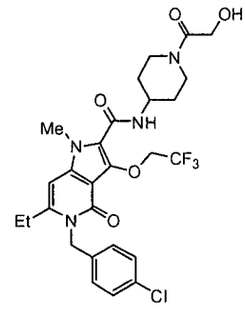
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.17 (3 H, t, J = 7.2 Hz),

1370

1.23 - 1.50 (2 H, m), 1.81 - 1.95 (2 H, m), 2.60 (2 H, q, *J* = 7.2 Hz), 2.76 - 2.92 (1 H, m), 3.02 - 3.17 (1 H, m), 3.64 - 3.76 (1 H, m), 3.85 (3 H, s), 3.95 - 4.15 (3 H, m), 4.19 - 4.36 (1 H, m), 4.52 (1 H, t, *J* = 5.4 Hz), 5.09 (2 H, q, *J* = 9.4 Hz), 5.35 (2 H, s amplio), 6. 55 (1 H, s), 6.95 - 7.03 (1 H, m), 7.07 - 7.15 (1 H, m), 7.25 - 7.30 (2 H, m), 7.55 (1 H, d, *J* = 7.6 Hz).

Ejemplo 663

Producción de 5-(4-clorobencil)-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida

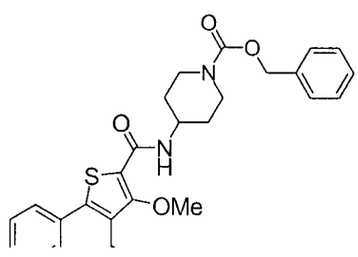


Del mismo modo que en el Ejemplo 653, el compuesto del título (160 mg, 65%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 169 (188 mg, 0.425 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.16 (3 H, t, *J* = 7.2 Hz), 1.23 - 1.49 (2 H, m), 1.82 - 1.95 (2 H, m), 2.59 (2 H, q, *J* = 7.2 Hz), 2.77 - 2.90 (1 H, m), 3.00 - 3.17 (1 H, m), 3.62 - 3.76 (1 H, m), 3.84 (3 H, s), 3.95 - 4.14 (3 H, m), 4.21 - 4.34 (1 H, m), 4.52 (1 H, t, *J* = 5.5 Hz), 5.09 (2 H, q, *J* = 9.4 Hz), 5.33 (2 H, s amplio), 6. 53 (1 H, s), 7.03 - 7.12 (2 H, m), 7.34 - 7.32 (2 H, m), 7.53 (1 H, d, *J* = 7.6 Hz).

Ejemplo 664

Producción de Bencil 4-({[3-metoxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato



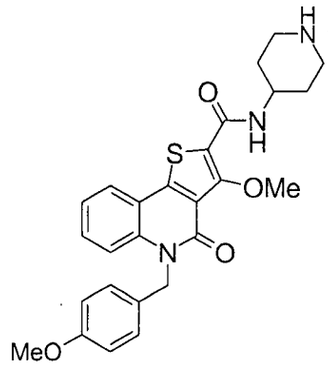
1371

Del mismo modo que en el Ejemplo 25, el compuesto del título (3.07 g, 79%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 13 (2.5 g, 6.31 mmol) y bencilo 4-aminopiperidina-1-carboxilato clorhidrato (2.56 g, 9.46 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.15 - 1.64 (2H, m), 1.87 (2H, amplio d, *J* = 9.6 Hz), 2.90 - 3.10 (2H, amplio), 3.69 (3H, s), 4.00 (2H, d, *J* = 11,4 Hz), 4.09 (4H, s), 5.10 (2H, s), 5.53 (2H, s amplio), 6.87 (2H, d, *J* = 8.7 Hz), 7.20 (2H, d, *J* = 8.7 Hz), 7.28 - 7.30 (6H, m), 7.39 - 7.56 (2H, m), 7.80 (1H, d, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 8.4 Hz).

Ejemplo 665

Producción de 3-metoxi-5-(4-metoxibencil)-4-oxo-N-piperidin-4-il-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



Una mezcla del compuesto del Ejemplo 664 (300 mg, 0.49 mmol), 10% Pd-C (60 mg) y THF (20 ml)-metanol (10 ml) se agitó a temperatura ambiente durante 24 hrs bajo una atmósfera de hidrógeno. El catalizador se eliminó por filtración, y el filtrado se concentró y se recristalizó a partir de metanol-dietil éter para dar el compuesto del título (154 mg, 66%) como cristales amarillo

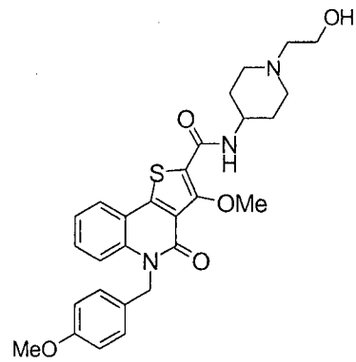
1372

pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.48 (2H, q, *J* = 11.0 Hz), 1.82 (2H, d, *J* = 9.6 Hz), 1.95 - 2.15 (1H, amplio), 2.56 (2H, t, *J* = 8.4 Hz), 2.93 (2H, d, *J* = 12.6 Hz), 3.33 (3H, s), 3.70 (3H, s), 3.80 - 4.00 (1H, amplio), 4.10 (3H, s), 5.53 (2H, s amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.20 (2H, d, *J* = 8.4 Hz), 7.30 (1H, t, *J* = 7.1 Hz), 7.39 - 7.58 (2H, m), 7.72 (1H, d, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 7.8 Hz).

Ejemplo 666

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-5-(4-metoxibencil)-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida



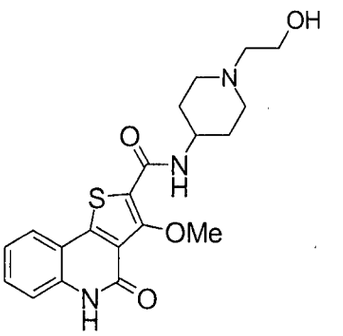
Del mismo modo que en el Ejemplo 79, el compuesto del título (110 mg, 68%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo 665 (150 mg, 0.31 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.55 - 1.74 (2H, m), 2.00 - 2.11 (2H, m), 2.36 (2H, t, *J* = 11.6 Hz), 2.58 (2H, t, *J* = 5.4 Hz), 2.84 (3H, s amplio), 3.65 (2H, t, *J* = 5.4 Hz), 3.75 (3H, s), 4.05 - 4.20 (1H, amplio), 4.20 (3H, s), 5.53 (2H, s amplio), 6.83 (2H, dd, *J* = 6.9, 1.8 Hz), 7.17 - 7.26 (3H, m), 7.35 (1H, d, *J* = 8.1 Hz), 7.31 - 7.36 (1H, m), 7.64 (1H, d, *J* = 7.8 Hz), 7.85 (1H, dd, *J* = 7.8, 1.5 Hz).

Ejemplo 667

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-4-oxo-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida

1373

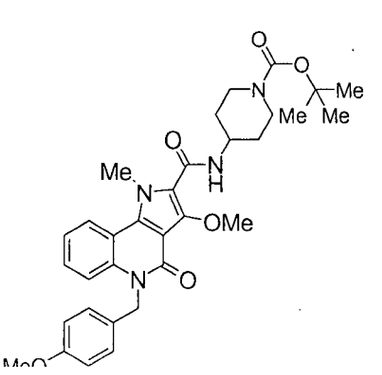


A una solución del compuesto del Ejemplo 666 (110 mg, 0.21 mmol), anisol (91 mg, 0.84 mmol) y ácido trifluorometansulfónico (0.5 ml) en ácido trifluoroacético (2 ml) se agitó a 8°C durante 1 hrs. Luego de enfriar, la mezcla de reacción se concentró, y el residuo se repartió entre acetato de etilo y solución saturada de hidrógeno carbonato de sodio. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de sílice (eluato; acetato de etilo/hexano=1/1 a 2/1) para dar el compuesto del título (60 mg, 71%) como un sólido blanco.

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.60 - 1.76 (2H, m), 2.07 (2H, d, *J* = 14.4 Hz), 2.36 (2H, t, *J* = 10.1 Hz), 2.59 (2H, t, *J* = 5.4 Hz), 2.88 (2H, d, *J* = 11.4 Hz), 3.65 (2H, t, *J* = 5.4 Hz), 3.70 - 3.80 (2H, amplio), 4.00 - 4.15 (1H, m), 4.22 (3H, s), 6.76 - 6.85 (1H, m), 7.32 (1H, t, *J* = 8.1 Hz), 7.51 (1H, t, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.1 Hz), 10.20 - 10.50 (1H, amplio).

Ejemplo 668

Producción de *terc*-butil 4-({[3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato



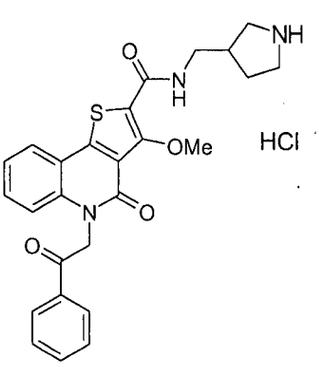
1374

Del mismo modo que en el Ejemplo 25, el compuesto del título (3.45 g, 95%) se obtuvo como un sólido beige a partir del compuesto del Ejemplo de Referencia 107 (2.49 g, 6.35 mmol) y *terc*-butil 4-aminopiperidin-1-carboxilato (2.54 g, 12.69 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.35 – 1.49 (11H, m), 1.85 (2H, dd, *J* = 12.6, 2.7 Hz), 2.89 - 2.96 (2H, m), 3.69 (3H, s), 3.88 (2H, d, *J* = 13.5 Hz), 3.96-4.09 (4H, m), 4.27 (3H, s), 5.40 -5.60 (2H, amplio), 6.83-6.88 (2H, m), 7.14 (2H, d, *J* = 8.7 Hz), 7.24 - 7.30 (1H, m), 7.31 - 7.39 (2H, m), 7.97 (1H, d, *J* = 8.1 Hz), 8.33 (1H, d, *J* = 8.1 Hz).

Ejemplo 669

Producción de 3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-N-(pirrolidin-3-ilmetil)-4,5-dihidrotieno[3,2-c]quinolin-2-carboxamida, clorhidrato



Del mismo modo que en el Ejemplo 25, *terc*-butilo 3-[({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)metil]pirrolidina-1-carboxilato (530 mg, 72%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (500 mg, 1.27 mmol) y 3-(aminometil)-1-boc-pirrolidina (381 mg, 1.90 mmol).

Del mismo modo que en el Ejemplo 500, el compuesto del

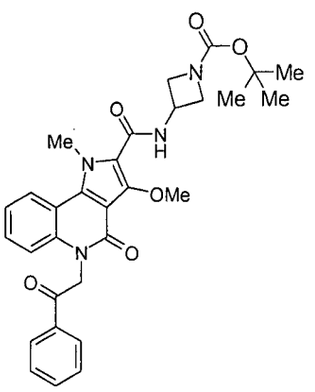
1375

título (456 mg, 97%) se obtuvo como un polvo blanco a partir de *terc*-butil 3-[({[3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)metil]pirrolidina-1-carboxilato (530 mg, 0.92 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.55 - 1.73 (1H, m), 1.90 - 2.10 (1H, m), 2.55 - 2.70 (1H, m), 2.85 - 3.00 (1H, amplio), 3.10 - 3.45 (5H, m), 4.05 (3H, s), 6.00 (2H, s), 7.35 (1H, t, *J* = 7.5 Hz), 7.39 - 7.67 (5H, m), 7.77 (1H, t, *J* = 7.3 Hz), 8.05 (1H, d, *J* = 7.8, Hz), 8.16 - 8.19 (2H, m), 8.25 (1H, t, *J* =5.9 Hz), 9.04 (2H, s amplio).

Ejemplo 670

Producción de *terc*-butilo 3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)azetidine-1-carboxilato



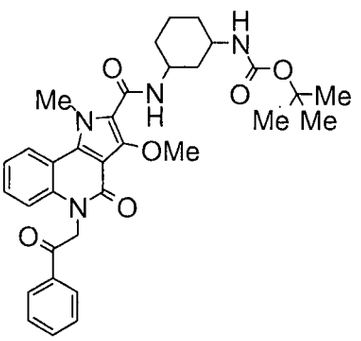
Del mismo modo que en el Ejemplo 25, el compuesto del título (610 mg, 88%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 28 (500 mg, 1.27 mmol) y 3-amino-1-boc-azetidine (330 mg, 1.92 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.40 (9H, m), 3.85 - 3.95 (2H, m), 3.99 (3H, s), 4.14 (2H, t, *J* = 7.8 Hz), 4.27 (3H, s), 4.62 - 4.74 (1H, m), 5.97 (2H, s), 7.31 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 8.1 Hz), 7.38 (1H, t, *J* = 7.5 Hz), 7.64 (2H, t, *J* = 7.5 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 8.16 - 8.19 (2H, m), 8.37 (1H, d, *J* = 8.1 Hz), 8.56 (1H, d, *J* = 7.2 Hz).

1376

Ejemplo 671

Producción de *terc*-butil [3-({[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)ciclohexil]carbamato

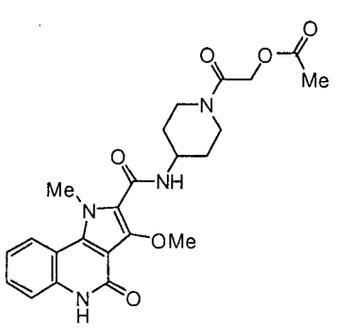


Del mismo modo que en el Ejemplo 25, el compuesto del título (395 mg, 66%) se obtuvo como un polvo blanco a partir del compuesto del Ejemplo de Referencia 7 (400 mg, 1.02 mmol) y *terc*-butilo (3-aminociclohexil)carbamato (285 mg, 1.33 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.98-1,46 (13 H, m), 1.65 - 1.90 (3 H, m), 2.00 - 2.12 (1 H, m), 3.23 - 3.42 (1 H, m), 3.73-3.88 (1 H, m), 3.96 (2 H, s), 4.04 (1 H, s), 4.30 (2 H, s), 4.35 (1 H, s), 5.97 (2 H, s), 6.76-6.94 (1 H, m), 7.24 - 7.32 (2 H, m), 7.33 - 7.53 (1 H, m), 7.63 (2 H, t, *J* = 7.6 Hz), 7.71 - 7.80 (1 H, m), 7.86 (1 H, d, *J* = 7.9 Hz), 8.12-8.22 (2 H, m), 8.31-8.42 (1 H, m).

Ejemplo 672

Producción de 2-(4-{[(3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il)carbonil]amino}piperidin-1-il)-2-oxoacetato de etilo



El compuesto del Ejemplo 558 (500 mg, 0.87 mmol), anisol (376 mg, 3.48 mmol) y ácido trifluorometansulfónico (2 ml) se

1377

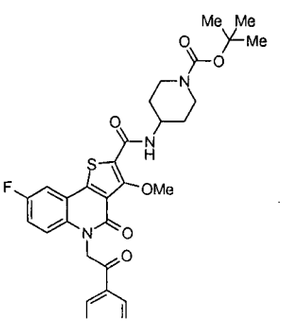
disolvieron en ácido trifluoroacético (9 ml), y la mezcla se agitó a 8°C durante 2 hrs. Luego de enfriar hasta la temperatura ambiente, la mezcla se concentró bajo presión reducida. El residuo se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con THF-acetato de etilo. El extracto se concentró para dar 3-metoxi-1-metil-4-oxo-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida (1.10 g) como un sólido beige.

A una solución de 3-metoxi-1-metil-4-oxo-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida (300 mg, 0.87 mmol) y trietilamina (88 mg, 0.87 mmol) en THF (30 ml) se agregó cloruro de acetoxiacetilo (119 mg, 0.87 mmol) enfrió con hielo, y la mezcla se agitó durante 2 hrs. La mezcla de reacción se diluyó con solución de hidrógeno carbonato de sodio, y se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio y se concentró. El sólido obtenido se lavó con dietil éter-hexano para dar el compuesto del título (221 mg, 56%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.30 - 1.65 (2H, m), 1.80 - 2.00 (2H, m), 2.09 (3H, s), 2.90 (2H, t, *J* = 11.4 Hz), 3.19 (2H, t, *J* = 11.4 Hz), 3.70 (2H, d, *J* = 13.5 Hz), 4.02 - 4.19 (4H, m), 4.28 (3H, s), 7.22 (1H, t, *J* = 7.5 Hz), 7.40 - 7.48 (2H, m), 7.93 (1H, d, *J* = 7.5 Hz), 8.24 (1H, d, *J* = 8.4 Hz), 11.34 (1H, s).

Ejemplo 673

Producción de *terc*-butil 4-({[8-fluoro-3-metoxi-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidrotieno[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato



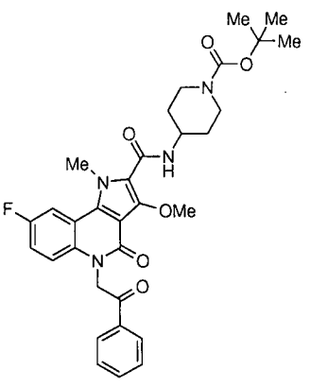
1378

Del mismo modo que en el Ejemplo 25, el compuesto del título (486 mg, 84%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 116 (400 mg, 0.97 mmol), y *terc*-butil 4-aminopiperidina-1-carboxilato (234 mg, 1.2 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.40 - 1.53 (11H, m), 1.96 - 2.11 (2H, m), 2.92-3.10 (2H, m), 3.95 - 4.08 (2H, m), 4.10 - 4.24 (4H, m), 5.85 (2H, s), 6.99 (1H, dd, *J* = 9.3, 4.3 Hz), 7.15 - 7.25 (1H, m), 7.50 - 7.62 (4H, m), 7.65 - 7.74 (1H, m), 8.05 - 8.16 (2H, m).

Ejemplo 674

Producción de *terc*-butil 4-({[8-fluoro-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidina-1-carboxilato



Del mismo modo que en el Ejemplo 25, el compuesto del título (2.5 g, 87%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 119 (2.0 g, 4.9 mmol), y *terc*-butil 4-aminopiperidina-1-carboxilato (1.2 g, 5.9 mmol).

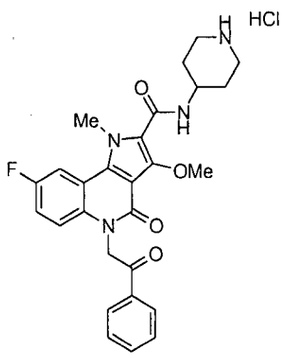
^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.34 -1.53 (11H, m), 1.89 - 2.13 (2H, m), 2.94 - 3.14 (2H, m), 3.89-4.07 (2H, m), 4.08 - 4.24 (4H, m), 4.46 (3H, s), 5.87 (2H, s), 6.93 - 7.04 (1H, m), 7.08 - 7.21 (1H, m), 7.38 - 7.60 (2H, m), 7.62 - 7.75 (2H, m), 7.94 (1H,

1379

dd, J = 10.0, 2.8 Hz), 8.04-8.20 (2H, m).

Ejemplo 675

Producción de 8-fluoro-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato

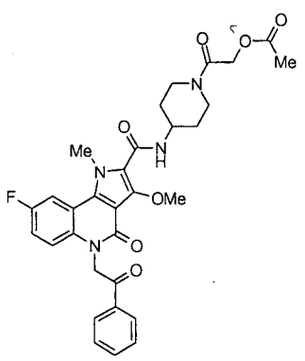


Del mismo modo que en el Ejemplo 542, el compuesto del título (1.6 g, 72%) se obtuvo como un sólido amarillo pálido a partir del compuesto del Ejemplo 674 (2.5 g, 4.3 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.62 - 1.86 (2H, m), 1.96 - 2.13 (2H, m), 2.95 - 3.14 (2H, m), 3.21-3.47 (2H, m), 3.95 (3H, s), 4.02 - 4.18 (1H, m), 4.27 (3H, s), 5.98 (2H, s), 7.23 - 7.51 (2H, m), 7.57 - 7.68 (2H, m), 7.71 - 7.84 (1H, m), 8.04-8.26 (4H, m), 8.64 (2H, s amplio).

Ejemplo 676

Producción de 2-[4-({[8-fluoro-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}amino)piperidin-1-il]-2-oxoacetato de etilo



Del mismo modo que en el Ejemplo 544, el compuesto del título (293 mg, 87%) se obtuvo como un sólido blanco a partir del

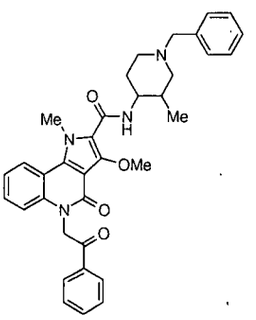
1380

compuesto del Ejemplo 675 (300 mg, 0.57 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.30 - 1.65 (2H, m), 1.82-1.96 (2H, m), 2.08 (3H, s), 2.80 - 2.96 (1H, m), 3.08-3,26 (1H, m), 3.65 - 3.78 (1H, m), 3.96 (3H, s), 4.02 - 4.22 (2H, m), 4.30 (3H, s), 4.74-4.85 (2H, m), 5.97 (2H, s), 7.29 -7.50 (2H, m), 7.57 - 7.68 (2H, m), 7.72 - 7.81 (1H, m), 7.98-8.06 (1H, m), 8.07-8.21 (3H, m).

Ejemplo 677

Producción de N-(1-bencil-3-metilpiperidin-4-il)-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



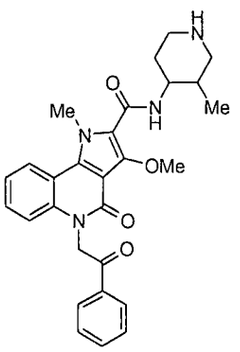
A una solución de 1-bencil-3-metilpiperidin-4-ona (227 mg, 1.1 mmol) y acetato de amonio (861 mg, 11 mmol) en metanol (9.0 ml) se agregó triacetoxiborohidruro de sodio (750 mg, 3.5 mol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 2 hrs. La mezcla de reacción se diluyó con acetato de etilo, se lavó con solución acuosa 1N de hidróxido de sodio, y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos se combinaron, se secaron sobre sulfato de magnesio, y se concentró bajo presión reducida. A una solución de el residuo, el compuesto del Ejemplo de Referencia 28 (396 mg, 1.0 mmol) y HOBt (151 mg, 1.1 mol) en DMF (7.0 ml) se agregó WSCD (215 mg, 1.1 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 15 hrs. La mezcla de reacción se diluyó con solución saturada de hidrógeno carbonato de sodio, y se extrajo

dos veces con acetato de etilo. El extracto se combinó, se lavó con salmuera, se secó sobre sulfato de magnesio, y se pasó a través de un gel de aminosílice. El filtrado se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; acetato de etilo/hexano=30/70 - 100/0) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (373 mg, 64%) como un sólido blanco.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.83 - 1.01 (3H, m), 1.49 - 2.40 (5H, m), 2.56 - 2.89 (1H, m), 3.22-3.59 (3H, m), 3.94-4.04 (3H, m), 4.07-4.20 (1H, m), 4.25 - 4.41 (3H, m), 5.98 (2H, s), 7.16 - 7.32 (7H, m), 7.33 - 7.54 (1H, m), 7.58 - 7.69 (2H, m), 7.72 - 7.81 (1H, m), 7.82 - 7.94 (1H, m), 8.10 - 8.23 (2H, m), 8.28-8.45 (1H, m).

Ejemplo 678

Producción de 3-metoxi-1-metil-N-(3-metilpiperidin-4-il)-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



A una solución del compuesto del Ejemplo 677 (373 mg, 0.65 mmol) en THF (40 ml) se agregó cloroformiato de 1-cloroetilo (0.67 ml, 6.5 mol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 3 hrs. Se agregaron cloroformiato de 1-cloroetilo (0.67 ml, 6.5 mol) y diisopropiletilamina (0.30 ml, 3.2 mmol) enfrió con hielo, y la mezcla se agitó a temperatura ambiente durante 20 hrs. La mezcla de reacción se concentró

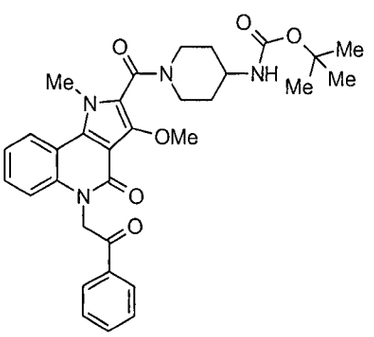
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bajo presión reducida, y el residuo se lavó con dietil éter. El residuo se disolvió en metanol (50 ml), y la mezcla se agitó a temperatura ambiente durante 7 hrs y se concentró bajo presión reducida. El residuo se purificó por cromatografía con gel de aminosílice (eluato; metanol/acetato de etilo=0/100 - 10/90) y se recristalizó a partir de acetato de etilo-hexano para dar el compuesto del título (90 mg, 29%) como un sólido marrón pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 0.83-0.95 (3H, m), 1.21-2.35 (5H, m), 2.60 - 3.01 (3H, m), 3.94-4.08 (3H, m), 4.11-4.22 (1H, m), 4.26-4.41 (3H, m), 5.98 (2H, s), 7.22- 7.32 (2H, m), 7.33 - 7.53 (1H, m), 7.59 - 7.69 (2H, m), 7.71-8.00 (2H, m), 8.12-8.22 (2H, m), 8.32-8.45 (1H, m).

Ejemplo 679

Producción de *terc*-butilo (1-{[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}piperidin-4-il)carbamato



Del mismo modo que en el Ejemplo 25, el compuesto del título (440 mg, 86%) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (350 mg, 0.90 mmol), *terc*-butilo piperidin-4-ilcarbamato (198 mg, 0.99 mmol).

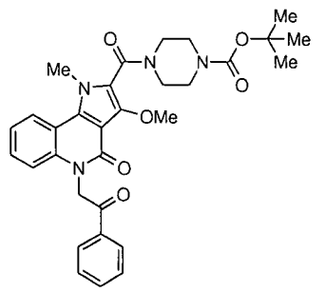
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.25 - 1.51 (11H, m), 1.68-1.94 (2H, m), 2.91-3.07 (1H, m), 3.10 - 3.27 (1H, m), 3.47 - 3.65 (1H, m), 3.67- 3.82 (1H, m), 3.88 (3H, s), 3.95- 4.06 (3H, m),

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4.29 -4.48 (1H, m), 5.97 (2H, s), 6.93 (1H, d, *J* = 6.2 Hz), 7.24 - 7.51 (3H, m), 7.57 - 7.69 (2H, m), 7.70 - 7.83 (1H, m), 8.11-8.23 (2H, m), 8.32 (1H, dd, *J* = 8.3, 1.1 Hz).

Ejemplo 680

Producción de *terc*-butil 4-{[3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-il]carbonil}piperazina-1-carboxilato

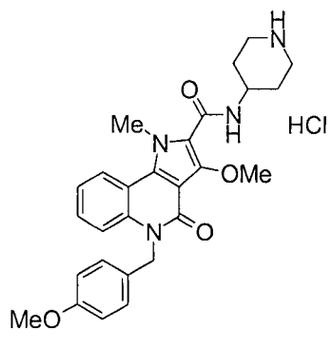


Del mismo modo que en el Ejemplo 25, el compuesto del título (571 mg, cuant.) se obtuvo como un sólido blanco a partir del compuesto del Ejemplo de Referencia 28 (400 mg, 1.0 mmol), *terc*-butilo piperazina-1-carboxilato (210 mg, 1.1 mmol).

^{1}H RMN (300 MHz, $CDCl_3$) δ: 1.49 (9H, s), 3.43- 3.88 (8H, m), 4.05 (3H, s), 4.08 - 4.12 (3H, m), 5.89 (2H, s), 7.01 - 7.10 (1H, m), 7.20 - 7.31 (1H, m), 7.35 - 7.34 (1H, m), 7.50 - 7.59 (2H, m), 7.62 - 7.71 (1H, m), 8.07-8.14 (2H, m), 8.20 (1H, dd, *J* = 8.2, 1.2 Hz).

Ejemplo 681

Producción de 3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-N-piperidin-4-il-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida, clorhidrato



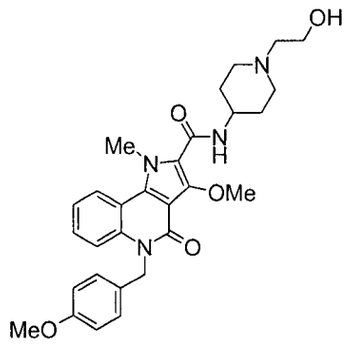
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A una solución del compuesto del Ejemplo 558 (500 mg, 0.87 mmol) en acetato de etilo (15 ml) se agregó solución 4N de hidrógeno cloruro de acetato de etilo (5 ml), y la mezcla se agitó a temperatura ambiente durante 4 hrs. El precipitado se recolectó por filtración, se lavó con dietil éter, y se secó bajo presión reducida para dar el compuesto del título (440 mg, 99%) como un polvo rosa pálido.

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.78 (2H, q, *J* = 10.3 Hz), 2.05 (2H, d, *J* = 10.8 Hz), 3.06 (2H, t, *J* = 10.7 Hz), 3.26-3.33 (2H, m), 3.63 (3H, s), 4.02 (3H, s), 4.09-4.13 (1H, m), 4.24 (3H, s), 5.40 -5.60 (2H, amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.7 Hz), 7.25 - 7.30 (1H, m), 7.32 - 7.39 (2H, m), 8.15 (1H, d, *J* = 7.5 Hz), 8.33 (1H, d, *J* = 7.8 Hz), 8.60 - 8.90 (2H, amplio).

Ejemplo 682

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-5-(4-metoxibencil)-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida



Del mismo modo que en el Ejemplo 79, el compuesto del título (1.91 g, 75%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 681 (2.50 g, 4.89 mmol).

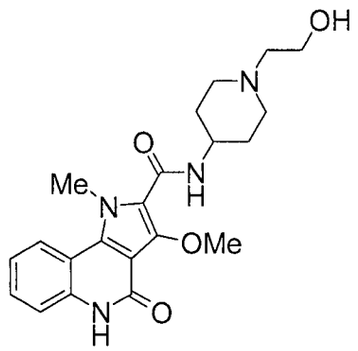
^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.58 (2H, q, *J* = 9.9 Hz), 1.85 (2H, d, *J* = 9.6 Hz), 2.18 (2H, t, *J* = 9.9 Hz), 2.40 (2H, t, *J* = 6.3 Hz), 2.78 (2H, d, *J* = 11.4 Hz), 3.50 (2H, q, *J* = 6.0 Hz), 3.69 (3H, s), 3.70 - 3.85 (1H, amplio), 4.04 (3H, s), 4.29 (3H, s), 4.35 -

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4.40 (1H, m), 5.40 -5.65 (2H, amplio), 6.86 (2H, d, *J* = 8.7 Hz), 7.14 (2H, d, *J* = 8.4 Hz), 7.24 - 7.30 (1H, m), 7.32 - 7.39 (2H, m), 7.91 (1H, d, *J* = 7.8 Hz), 8.33 (1H, d, *J* = 8.1 Hz).

Ejemplo 683

Producción de N-[1-(2-hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida

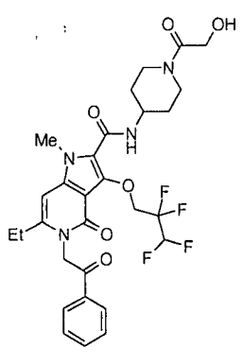


Del mismo modo que en el Ejemplo 672, el compuesto del título (457 mg, 33%) se obtuvo como cristales blancos a partir del compuesto del Ejemplo 682 (1.79 g, 3.45 mmol).

^{1}H RMN (300 MHz, DEMO-d_6) δ: 1.50 - 1.60 (2H, m), 1.83 (2H, d, *J* = 10.2 Hz), 2.18 (2H, t, *J* = 10.4 Hz), 2.40 (2H, t, *J* = 6.3 Hz), 2.65 - 2.85 (2H, m), 3.50 (2H, q, *J* = 6.0 Hz), 3.75 - 3.90 (1H, m), 4.03 (3H, s), 4.29 (3H, s), 4.38 (1H, t, *J* = 5.4 Hz), 7.22 (1H, t, *J* = 7.5 Hz), 7.30 - 7.35 (2H, m), 7.84 (1H, d, *J* = 7.8 Hz), 8.24 (1H, d, *J* = 8.1 Hz), 11,33 (1H, s).

Ejemplo 684

Producción de 6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,3.3-tetrafluoropropoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



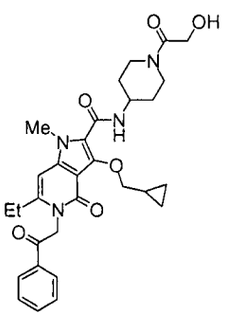
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Del mismo modo que en el Ejemplo 140, el compuesto del título(224 mg, 74%) se obtuvo como polvo blanco a partir del compuesto del Ejemplo de Referencia 175 (234 mg, 0.50 mmol).

1H-NMR (300 MHz, DEMO-d_6) δ: 1.19 (3H, t, *J* = 7.3 Hz), 1.24 - 1.48 (2H, m), 1.82-1.95 (2H, m), 2.58 (2H, q, *J* = 7.3 Hz), 2.70 - 2.89 (1H, m), 3.00 - 3.16 (1H, m), 3.62-3.78 (1H, m), 3.87 (3H, s), 3.96-4.15 (3H, m), 4.23-4.38 (1H, m), 4.53 (1H, t, *J* = 5.4 Hz), 4.94 (2H, t, *J* = 14.7 Hz), 5.63 (2H, s), 6.53 (1H, s), 6.66 (1H, tt, *J* = 52.0, 5.2 Hz), 7.52 (1H, d, *J* = 7.7 Hz), 7.57 - 7.66 (2H, m), 7.70 - 7.78 (1H, m), 8.08-8.16 (2H, m).

Ejemplo 685

Producción de 3-(ciclopropilmethoxi)-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida



Del mismo modo que en el Ejemplo 140, el compuesto del título(100 mg, 76%) se obtuvo como un polvo incoloro a partir del compuesto del Ejemplo de Referencia 177 (98 mg, 0.24 mmol).

1H-NMR (300MHz, DEMO-d_6) δ□ 0.19-0.27 (2H, m), 0.46-0.55 (2H, m), 1.06-1,20 (1H, m), 1.18 (3H, t, *J* = 7.3 Hz), 1.25 - 1.56 (2H, m), 1.84 - 2.00 (2H, m), 2.57 (2H, q, *J* = 7.3 Hz), 2.77-2.94 (1H, m), 3.04 - 3.20 (1H, m), 3.60 - 3.75 (1H, m), 3.91 (3H, s), 3.96-4.13 (3H, m), 4.17 (2H, d, *J* = 7.2 Hz), 4.20 - 4.32 (1H, m), 4.51 (1H, t, *J* = 5.5 Hz), 5.59 (2H, s), 6.48 (1H, s), 7.56 - 7.66 (2H, m), 7.69 - 7.81 (2H, m), 8.07-8.15 (2H, m).

Formulación Ejemplo 1

Un agente farmacéutico que contiene el compuesto de la

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presente invención como principio activo puede producirse, por ejemplo, en base a la siguiente composición.

1. cápsula

(1) compuesto obtenido en el Ejemplo 25	40 mg
(2) lactosa	70 mg
(3) celulosa microcristalina	9 mg
(4) estearato de magnesio	1 mg
1 cápsula	120 mg

(1), (2), (3) y 1/2 de (4) se mezclan y se granulan. A éstos se agrega el resto de (4) y la cantidad total se envasa en una cápsula de gelatina.

2. comprimido

(1) compuesto obtenido en el Ejemplo 25	40 mg
(2) lactosa	58 mg
(3) almidón de maíz	18 mg
(4) celulosa microcristalina	3.5 mg
(5) estearato de magnesio	0.5 mg
1 comprimido	120 mg

(1), (2), (3), 2/3 de (4) y 1/2 de (5) se mezclan y se granulan. A éstos se agrega el resto de (4) y (5) y la mezcla se forma por compresión para dar a comprimido.

Formulación Ejemplo 2

El compuesto obtenido en el Ejemplo 25 (50 mg) se disuelve en el agua para inyección de la Farmacopea Japonesa (50 ml), y el agua destilada para inyección de la Farmacopea Japonesa se agrega hasta 100 ml. LA una solución se filtra en condiciones estériles, y se envasa 1 ml de la solución en un vial de inyección en condiciones estériles y se liofiliza y precinta.

Ejemplos Experimentales

Los métodos de operación genética descritos en los Ejemplos Experimentales que siguen, se basan en los métodos

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descritos en un libro (Maniatis et al., Molecular Cloning, Cold Spanillo Harbor Laboratory, 1989), y el protocolo anexo del reactivo.

Ejemplo Experimental 1. Construcción del plásmido informante Gli

El plásmido informante Gli se construyó insertyo 8 x sitio de unión Gli y promotor δ-cristalino de pollo en el caudal ascendente de luc+ de pGL3 (Promega).

El promotor δ-cristalino se clonó por el método de PCR usando, como conjunto cebador, ADNs sintéticos

5'-GAAGATCTGCCAGCCCAGGCTCCGGGGC-3' (*SEC* ID NO: 1)

5'-CCCAAGCTTCTGCCCGCACAGCCCTGCTC-3' (*SEC* ID NO: 2)

preparados con referencia a la *sec*uencia base descrita en el No. de acceso al GenBank; X02187, y ADN de genoma de pollo como (Clontech) como patrón. La reacción por PCR se realizó usando Pfu Turbo (Stratagene) y siguiendo el protocolo adjunto. El fragmento obtenido de 108 pb se digirió con las enzimas de restricción BglII y HindIII, y se insertó en el sitio BglII-HindIII de pGL3 para dar el plásmido pGL3/promotor δ-cry.

Como 8 x Gli-sitio de unión, una *sec*uencia que contiene ocho *sec*uencias de consenso unidas a Gli de 9 pb (GACCACCCA) descritas en Yoon et al., J. Biol. Chem., vol. 273, páginas 3496-3501 (1998) se preparó a partir de ADN sintético. Es decir, dos ADNs sintéticos,

5'-GGGGTACCGACCACCCAGACCACCCAGACCACCCACACCACCCAGACCACCCAGACCACCCAGACCACCCAGACCACCCAAGATCTTC-3' (*SEC* ID NO: 3)

5'-GAAGATCTTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTCTGGGTGGTGTGGGTGGTCTGGGTGGTCTGGGTGGTCGG

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TACCCC-3' (*SEC* ID NO: 4)

se trataron por calor a 95°C durante 2 minutos, y se incubaron 37°C durante 1 hrs para templado para dar un ADN de hebra doble de los dos ADNs sintéticos mencionados con anterioridad. El ADN de doble hebra obtenido se digirió con enzimas de restricción BglII y KpnI, y el fragmento de ADN obtenido se insertó en el sitio BglII-KpnI del promotor pGL3/δ-cry para construir el plásmido promotor pGL3/δ-cry, 8 x sitio de unión Gli, es decir, plásmido informante Gli.

Ejemplo Experimental 2. Construcción del plásmido para la expresión de fragmento terminal Shh-N de ratones

Como material para la construcción del plásmido para la expresión del fragmento terminal Shh-N, primero se clonó ADNc de Shh de ratones.

El ADN Shh de los se clonó por el método de PCR en Canasta usando ADNc de feto de ratones de 11 días (Clontech) como patrón. La *sec*uencia cebadora se preparó con referencia a la *sec*uencia base descrita en el No. de Acceso al GenBank; NM_009170.

Como el conjunto de cebador para la 1° PCR, se usaron

5'-CTGGGTGGGGATCGGAGACA-3' (*SEC* ID NO: 5)

5'-GCGCTTTCCCATCAGTTCCTTATT-3' (*SEC* ID NO: 6),

y como el conjunto de cebador para la 2° PCR, se usaron

5'-GGGGTACCATGCTGCTGCTGCTGGCCA-3' (*SEC* ID NO: 7)

5'-GCTCTAGATCAGCTGGACTTGACCGCCA-3' (*SEC* ID NO: 8)

La reacción por PCR se realizó usando Pfu Turbo (Stratagene) y siguiendo el protocolo anexo. El producto de PCR resultante se clonó por pcDNA3.1 (+) (Invitrogen), y la *sec*uencia base insertada se confirmó.

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Usando la *secuencia* de ADNc Shh de ratones obtenida como se mencionó con anterioridad como patrón, se agregó una *secuencia* de ADNc parcial la cual se agregó el codón de interrupción (TGA) en el extremo terminal 3' de la *secuencia* de ADNc que codifica la 1ra. a 198va. *secuencia* de aminoácidos de Shh de ratones obtenida por el método de PCR. Como el conjunto cebador, se usaron

5'-ATGCTGCTGCTGCTGGCCAG-3' (*SEC* ID NO: 9)

5'-TCAGCCGCCGGATTTGGCCG-3' (*SEC* ID NO: 10)

La reacción por PCR se realizó usando Pfu Turbo (Stratagene) y siguiendo el protocolo anexo. El producto de PCR obtenido se clonó por pcDNA3.1 (+) (Invitrogen), y la *secuencia* de base insertada se confirmó.

Del modo descrito anteriormente, se construyó un plásmido para la expresión de fragmento terminal Shh-N de ratones, pcDNA3.1/EMhh-N.

Ejemplo Experimental 3. Producción de fragmento de extremo Shh-N de ratones tipo recombinante

Se cultivaron células HEK293 en medio D-MEM (Invitrogen) que contenía 10% suero de feto de bovino en un recipiente de 10 cm y se introdujo pcDNA3.1/EMhh-N en las células usando FuGENE6 (Roche Applied Science). De ahí en adelante, las células HEK293 se cultivaron en un incubador de gas de dióxido de carbono a 37°C durante 24 horas, y el medio se cambió con medio D-MEM (Invitrogen) que contenía 2% suero de feto de bovino. Luego de cultivar durante 48 hrs, se obtuvo un sobrenadante de cultivo que contenía fragmento de extremo Shh-N de ratones de tipo recombinante por filtración usando un filtro (0.22 μM).

Ejemplo Experimental 4. Introducción del plásmido para el plásmido informante y de expresión Gli-1 en células NIH-3T3 y

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producción de células de expresión

Usando D-MEM (Invitrogen) que contenía 10% suero de feto de bocino, el plásmido de expresión pcDNA3.1 y el plásmido informante Gli (promotor pGL3/δ-cry, 8 x sitio de unión Gli) producido por el método del Ejemplo Experimental 1 se introdujeron en células NIH-3T3 cultivadas en un recipiente de 10 cm con el uso de FuGENE6 (Roche Applied Science).

Luego de cultivar durante 24 hrs, las células se recuperaron, se suspendieron en medio D-MEM que contenía 10% suero de feto de bovino y suplementado con Geneticin (Life Technologies Oriental, Inc.) hasta una concentración final de 500 μg/ml, diluido a 104 células/ml, se colocaron en placas en una placa de 96 pocillos, y se cultivaron en un incubador de gas de dióxido de carbono a 37°C para dar la línea celular transformada resistente a Geneticin.

La línea celular transformada obtenida se cultivó en una placa de 96 pocillos, el fragmento terminal Shh-N de ratones obtenido en el Ejemplo Experimental 3 se agregó, y se seleccionó la célula informante NIH-3T3/Gli, que es una línea celular capaz de inducción de expresión de luciferasa.

Ejemplo Experimental 5. Evaluación del compuesto

Las células informantes NIH-3T3/Gli cultivadas en D-MEM (Invitrogen) que contenía 10% suero de feto de bovino se colocaron en una placa blanca de 96 pocillos a 1x104 células/pocillo, y se cultivaron hasta la mañana siguiente en un incubador de gas de dióxido de carbono a 37°C. Se eliminó el medio, un Compuesto (50 μl) y sobrenadante de cultivo del fragmento de extremo Shh-N de ratones que expresa HEK293 (medio D-MEM que contiene 2% suero de feto de bovino, 50 μl) se agregaron, y las células se cultivaron durante 48 hrs en un incubador de gas de dióxido de carbono a 37°C. Se agregó

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Bright-Glo (Promega, 50 µl), y la mezcla se agitó, luego de lo cual se midió la actividad de luciferasa por EnVision (PerkinElmer). Se calculó el índice de inhibición en base a la actividad de luciferasa del control sin el agregado del compuesto como 100. Los resultados se muestran en las Tablas que siguen. La concentración del compuesto y el índice de inhibición se analizaron por PRISM3.00 (software de GraphPad), en base lo cual se calculó el valor IC50 (concentración de compuesto necesaria para lograr el 50% de valor máximo de índice de inhibición) del compuesto.

Los valores de IC50 de los compuestos de Ejemplos 2, 3. 9, 13, 16, 17, 22, 27, 32, 41, 43, 45, 48, 50, 51, 52, 53, 56, 69, 71, 73, 74, 79, 92, 102, 109 y 115 no fueron de más de 1 µM.

Tabla 3

Ejemplo	Índice de inhibición (%) a 1 µM
2	100
3	100
9	100
13	100
16	100
17	99
22	91
27	100
32	95
41	100
43	100
45	100
48	10
50	100
51	100
52	95
53	95
56	100
69	100
71	100
73	100
74	100
79	100
92	100
102	80

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Ejemplo	Índice de inhibición (%) a 1 μM
109	100
115	100
118	100
124	100
131	100
132	100
135	100
136	100
137	100
138	100
139-1)	100
140	100
141	100
142	100
143 - 1)	100
510	100
517	100
522	100
562	100
563	100
583	100
584	100
643	100
644	100
650	100
654	100
656	100
657	100
658	100
660	100
661	100

Ejemplo Experimental 6. Análisis anti-tumor *in vivo*

De acuerdo con la descripción de Sasaki, K. et al., (2006) Cáncer Res. 66: 4215 - 4222, se evaluó un efecto anti tumoral de un compuesto usando un modelo de trasplantación alogénica de meduloblastoma de ratones. Para ser precisos, se adquirieron

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ratones mutantes con el gen Patched 1 (nombre de la especie: Ptch1tm1Mps/J) de The Jackson Laboratory y se adquirieron ratones mutantes con gen p53 (nombre de la especie: P53N4-M, Nomenclatura: B6.129 -Trp53tm/BrdN4) de Taconic, y un fenotipo de ratones de Patched 1(+/-), p53(-/-) se preparó por apareamiento. El tejido tumoral de meduloblastoma ocurrió espontáneamente en el cerebelo de ratones con Patched 1(+/-), de seis a nueve semanas de vida, p53(-/-) y se trasplantó en forma subcutánea en ratones lampiños (nombre de la especie: CAnN.Cg-Foxn1<nu>/CrlCrlj).

El análisis anti-tumoral se realizó usando un tumor que se pasó por trasplante subcutáneo. Se aisló una masa tumoral por un separador de cepas celulares 40 μm (BD Biosciences, Cat. No. 352340), se preparó una suspensión tumoral con medio de Leibovitz L-15 (GIBCO, Cat. No. 11415 - 114) en una cantidad del doble con relación al peso de la masa tumoral, se mezcló con una cantidad equivalente de matrigel (BD Biosciences, Cat. No. 356237), y se trasplantó por vía subcutánea a los ratones a 100 μl por sitio de trasplante. El diámetro del tumor luego del trasplante se midió y, cuando el tamaño del tumor alcanzó 150 - 250 mm3, se inició la prueba anti-tumoral usando 5 ratones por grupo.

El compuesto de prueba se preparó para lograr una dosis de 6.25 mg/kg con una suspensión al 0.5 % de metilcelulosa (Shin-Etsu Chemical Co., Ltd., Cat. No. SM-100), y por vía oral administrado dos veces al día durante 2 semanas. El tamaño del tumor se calculó en base al diámetro más grande y el diámetro más corto del tumor medido con un calibre electrónico de vernier. Luego del inicio de la prueba, el tamaño del tumor se midió cada 2 ó 3 días y se calculó el índice de crecimiento. Se confirmó un efecto inhibidor del crecimiento de tumor del 95% o superior en

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cada grupo de administración del compuesto. El índice de crecimiento del tamaño del tumor por cada compuesto experimental al final de la prueba se muestra en la siguiente Tabla.

El índice de crecimiento del tumor y los resultados de un análisis de diferencia significativa por la administración de cada compuesto experimental se muestran en la Tabla. El índice de crecimiento del tamaño del tumor (T/C) se calculó de acuerdo con:

índice de crecimiento (T/C) = ((tamaño del tumor del grupo de administración del compuesto al final de la administración)-(tamaño del tumor del grupo de administración del compuesto al inicio de la administración))/((tamaño del tumor del grupo de control al final de la administración)-(tamaño del tumor del grupo de control al inicio de la administración))X100.

Tabla 4

Ejemplo	T/C (%)	Valor P (Prueba de Dunnett)
79	0.8	≤0.001
124	2.0	≤0.001
139-1)	0.4	≤0.001
140	5.3	≤0.001
143 - 1)	0.0	≤0.001

Los resultados antes mencionados confirman que el compuesto de la presente invención muestra un efecto anti-tumoral.

Aplicabilidad en la Industria

Dado que el compuesto de la presente invención muestra una acción superior como inhibidor de Smo, puede proporcionarse un agente clínicamente útil para la profilaxis o el tratamiento de enfermedades relacionadas con Smo (por ejemplo, cáncer etc.). Además, dado que el compuesto de la presente invención también

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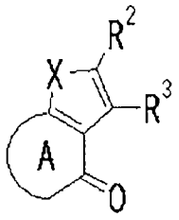
es superior en la expresión de eficacia, la farmacocinética, solubilidad, interacción con otros productos farmacéuticos, seguridad y estabilidad, es útil como un agente farmacéutico.

Esta solicitud se basa en las solicitudes Nos. 2008-045134 y 2008 - 256755 presentadas en Japón, cuyos contenidos se incorporan aquí a modo de referencia.

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REIVINDICACIONES

1. Un compuesto caracterizado por la fórmula



(I)

en donde

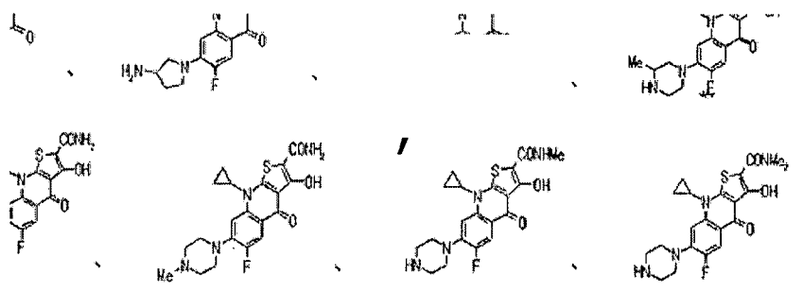
el anillo A es un anillo de 5 a 7 miembros que esta opcionalmente sustituido, donde los sustituyentes están unidos opcionalmente entre sí para formar un anillo;

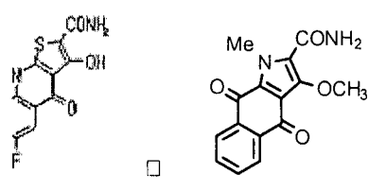
X es O, S o NR^1 (R^1 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido);

R^2 es carbamoilo que esta opcionalmente sustituido; y

R^3 es hidroxi que esta opcionalmente sustituido,

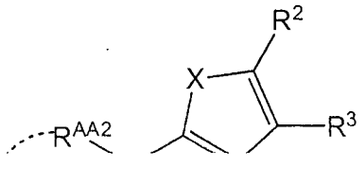
excepto los siguientes compuestos;





o una sal de lo mismo.

2. El compuesto de la reivindicación 1, caracterizado porque está



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representado por la fórmula

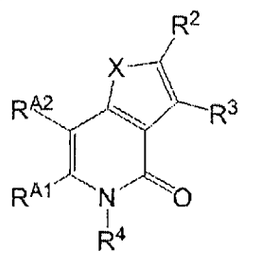
en donde

X, R^2 y R^3 son como se los define en la reivindicación 1,

R^{AA1} y R^{AA2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, o R^{AA1} y R^{AA2} están unidos opcionalmente entre sí para formar un anillo de 5 a 7 miembros que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido.

3. El compuesto de la reivindicación 2, caracterizado porque está representado por la fórmula



(I")

en donde

X, R^2 y R^3 son como se los define en la reivindicación 1,

R^{A1} y R^{A2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido.

4. El compuesto de la reivindicación 3. caracterizado porque X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido,

R^{A1} es un átomo de hidrógeno o un grupo alquilo de 1 a 6

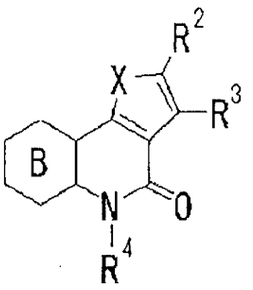
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átomos de carbono,

R^{A2} es un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono, y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido.

5. El compuesto de la reivindicación 1, caracterizado porque está representado por la fórmula



(I')

en donde

X, R^2 y R^3 son como se definen en la reivindicación 1,

el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido.

6. El compuesto de la reivindicación 5, caracterizado porque el anillo B es un anillo de 6 miembros que esta opcionalmente sustituido,

X es O, S o N(alquilo de 1 a 6 átomos de carbono),

R^2 es carbamoilo que esta opcionalmente sustituido,

R^3 es hidroxi que tiene opcionalmente alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido, y

R^4 es un átomo de hidrógeno o alquilo de 1 a 6 átomos de carbono que esta opcionalmente sustituido.

7. N-[1-(2-Hidroxietil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida o una sal del mismo.

8. N-[1-(Hidroxiacetil)piperidin-4-il]-3-metoxi-1-metil-4-oxo-5-(2-

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oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]quinolin-2-carboxamida o una sal del mismo.

9. 3-Etoxi-6-etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal del mismo.

10. N-[1-(Hidroxiacetil)piperidin-4-il]-1,6-dimetil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal del mismo.

11. 6-Etil-N-[1-(hidroxiacetil)piperidin-4-il]-1-metil-4-oxo-5-(2-oxo-2-feniletil)-3-(2,2,2-trifluoroetoxi)-4,5-dihidro-1H-pirrolo[3,2-c]piridin-2-carboxamida o una sal del mismo.

12. Un profármaco del compuesto de la reivindicación 1.

13. Un agente farmacéutico caracterizado porque comprende el compuesto de la reivindicación 1 o uno de sus profármacos.

14. El agente farmacéutico de la reivindicación 13, caracterizado porque es un inhibidor de Smo.

15. El agente farmacéutico de la reivindicación 13, caracterizado porque es un agente para la profilaxis o el tratamiento del cáncer.

16. Un método de inhibición de Smo en un mamífero, caracterizado porque comprende administrar una cantidad efectiva del compuesto de la reivindicación 1 o uno de sus profármacos al mamífero.

17. Un método para prevenir o tratar el cáncer en un mamífero, caracterizado porque comprende administrar una cantidad efectiva del compuesto de la reivindicación 1 o uno de sus profármacos al mamífero.

18. El uso del compuesto de la reivindicación 1 o uno de sus profármacos para la producción de un inhibidor de Smo.

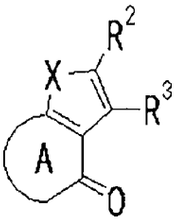
19. El uso del compuesto de la reivindicación 1 o uno de sus profármacos para la producción de un agente para la profilaxis o el tratamiento del cáncer.

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RESUMEN

La presente invención proporciona un compuesto que tiene una actividad inhibidora de Smo superior y baja toxicidad, que es suficientemente satisfactoria como producto farmacéutico.

La presente invención proporciona un compuesto representado por la fórmula



(I)

en donde anillo A es anillo de 5 a 7 miembros que esta opcionalmente sustituido, donde los sustituyentes están unidos opcionalmente entre sí para formar un anillo; X es O, S o NR^1 (R^1 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido); R^2 es carbamoilo que esta opcionalmente sustituido; y R^3 es hidroxi que esta opcionalmente sustituido, o una sal del mismo.

1402

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<130> 091350

<150> JP2008-045134

<151> 26-02-2008

<150> JP2008-256755

<151> 01-10-2008

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2009/054007

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D498/04 C07D513/04 C07D471/14 A61P35/00
A61K31/4355 A61K31/4365 A61K31/437

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 587 473 A (SANOFI ELF [FR] SANOFI SA [FR]) 16 March 1994 (1994-03-16) page 6, line 54 - page 7, line 25; claims; tables	1-19
A	WO 2004/058772 A (DAIICHI SUNTORY PHARMA CO LTD [JP]; DAIICHI SUNTORY BIOMEDICAL RES [JP]) 15 July 2004 (2004-07-15) page 55, compound 1 - page 61, compound 22; abstract	1
A	WO 2007/022268 A (IRM LLC [US]; SCRIPPS RESEARCH INST [US]; OKRAM BARUN [US]; REN PINGDA) 22 February 2007 (2007-02-22) paragraph [0003]; claim 1; examples	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2009	03/12/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2009/054007

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		JP 2006151810 A	15-06-2006
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		KR 20080035698 A	23-04-2008
		US 2008287432 A1	20-11-2008

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *Prioridad*	(32) *Fecha*	(33) *País*
2008-045134	26/02/2008	JP
2008-256755	01/10/2008	JP

(51) Int Cl: **C07D 471/004**

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

(72) Inventor(es) **NOBUHIRO FUJII Y OTROS**

(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**

(85) Fecha limite inicio fase nacional: 26/09/2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 25/02/2009
No. de solicitud PCT/JP2009/054007

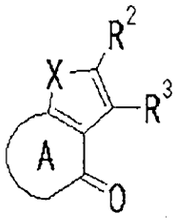
(87) Publicación internacional
Fecha: 03/09/2009
N° publicación: ***WO 2009/107850 A3***

(54) Titulo: **DERIVADO HETEROCICLICO FUSIONADO Y SU USO**

Reivindicación(es):

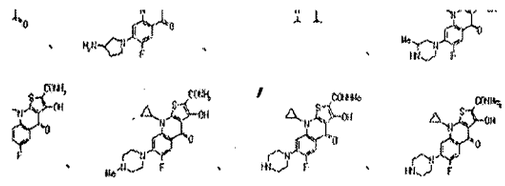
1. Un compuesto caracterizado por la fórmula

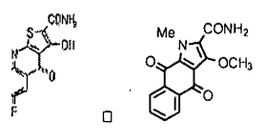
en donde



(I)

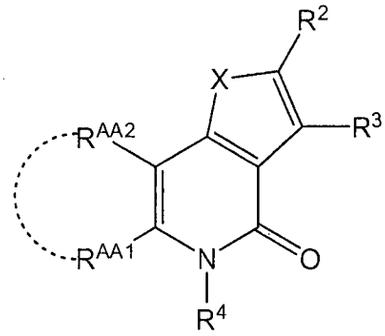
el anillo A es un anillo de 5 a 7 miembros que esta opcionalmente sustituido, donde los sustituyentes están unidos opcionalmente entre sí para formar un anillo;
X es O, S o NR^1 (R^1 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido);
R^2 es carbamoilo que esta opcionalmente sustituido; y
R^3 es hidroxi que esta opcionalmente sustituido,
excepto los siguientes compuestos;





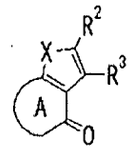
o una sal de lo mismo.

2. El compuesto de la reivindicación 1, caracterizado porque está representado por la fórmula

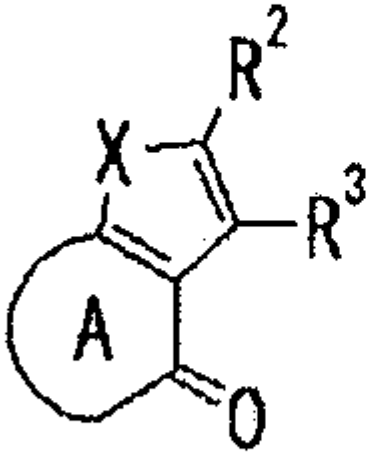


(I'")

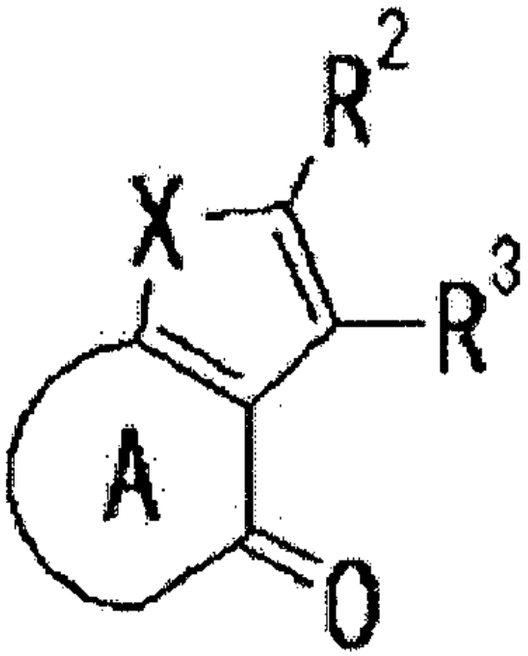
en donde
X, R^2 y R^3 son como se los define en la reivindicación 1,
R^{AA1} y R^{AA2} son iguales o diferentes y cada uno es un átomo de hidrógeno o un sustituyente, o R^{AA1} y R^{AA2} están unidos opcionalmente entre sí para formar un anillo de 5 a 7 miembros que esta opcionalmente sustituido, y
R^4 es un átomo de hidrógeno o un grupo hidrocarburo que esta opcionalmente sustituido.



(I)



(I)



(I)

1410

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 75,703
FECHA : SEPTIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-117653- -00000-0000

Fecha: 2010-09-23 11:05:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1408

***** 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	156794820	13/09/2010	45,370,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	*** N.CREACION PRORROGA DE TERMINOS 0	83,000.00
		TOTAL : $	83,000.00

SON: OCHENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 14656 - 841 - 061-8

1411

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 75,753
FECHA : SEPTIEMBRE 13 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-117653- -00000-0000

Fecha: 2010-09-23 11:05:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1408

***** 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	156794820	13/09/2010	45,370,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	3 PROC. REGISTRO DE MARCAS Y LEMAS	706,000.00
		TOTAL : $	706,000.00

SON: SETECIENTOS SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 34656-841-061-8

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-117653- -00000-0000

Fecha: 2010-09-23 11:05:03 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1408

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Folio 1411

2020
Bogotá D.C.,

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	10 117653
	Solicitud internacional	PCT/JP2009/054007
	Fecha inicio fase nacional	26/09/2010
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	13520
	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.

21 JUN. 2010

Cúmplase
Dado en Bogotá DC,

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

jfernand

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	10 117653
	Solicitud internacional	PCT/JP2009/054007
	Fecha inicio fase nacional	26/09/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13145

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

08 OCT. 2010

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11