Industria y Comercio

SUPERINTENDENCIA

CSA056720

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Organizacion y
Digitalizacion CSA Ltda

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 09-94461

54. **TÍTULO** COMPUESTOS ANULARES FUSIONADOS COMO AGONISTAS PARCIALES DE PPAR-GAMMA

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPON

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

22. **BOGOTÁ, D.C.,** 20 2099

Rb

In. 09-01-2009

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-094451- -00000-0000
Fecha: 2009-09-04 15:36:33 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1100

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,
Japón

Domicilio: Osaka,
Japón

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

3 REPRESENTANTE O APODERADO

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

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

4 INVENTOR (ES) (72)

1. Taisuke TAWARAISHI
c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
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Japón

2. Hiroshi IMOTO
1742 Sand Hill Road #206,
Palo Alto,
California 94304,
Estados Unidos de América

3. Nobuo CHO
c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED
17-85, Jusohonmachi 2-chome,
Yodogawa-ku, Osaka-shi,
Osaka 532-8686,
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2008/052217 Fecha: 05 de febrero de 2008
Publicación Internacional No. WO 2008/099794 A1 Fecha: 21 de agosto de 2008

6 Título (54)

COMPUESTOS ANULARES FUSIONADOS COMO AGONISTAS PARCIALES DE PPAR-GAMMA

7 Clasificación Internacional (51) C07D 231/012

8 Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	09 de febrero de 2007	2007-031221

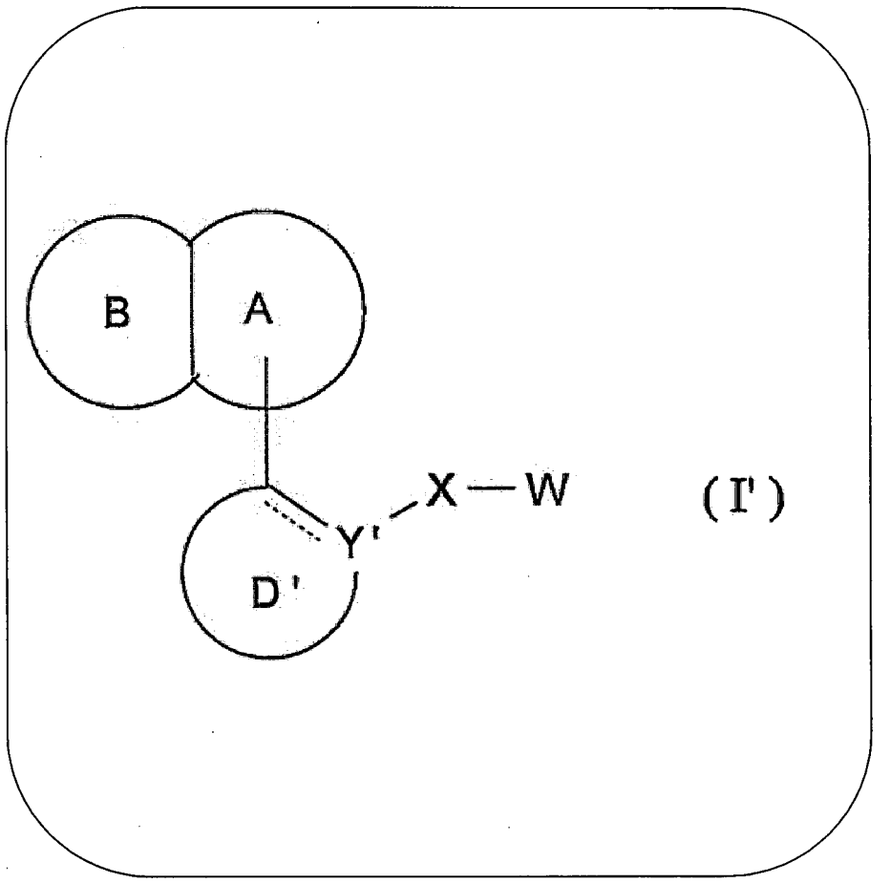
9 **Comprobante de pago No.:** 09-61,514 **Fecha:** 19 de agosto de 2009

10 **Anexos:**

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- [ ] Comprobante de pago por reivindicaciones adicionales después de la decimoquinta reivindicación por.
- [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



12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Paez

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

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/099794 A1

   Descripción:

   Páginas 401 en el idioma original

   Páginas 647 en español

   Reivindicaciones: Número (s) 15

   Figuras: Número (s)

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

3. ☒ 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

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 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 N° 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, injunctions, concession of licenses, writ of mandamus, the protection of trade secrets, general lawsuits, criminal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us) and also in the above matters they may substitute this Power of Attorney, compromise, conciliate, admit

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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

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

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

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

en/in Osaka, Japan

por/by

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

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
28 AGO. 2009
RAMIRO QUINTERO ARTURO
NOTARIA

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REGISTER NUMBER 334 / 2004

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

Dated this 14th day of December, 2004

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

Kiyoomi Fujita

Kiyoomi Fujita
Notary attached
to The Osaka Legal
Affairs Bureau

COMO NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPÚBLICA DE COLOMBIA
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

8.

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. 2009

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

8. No. 04149

9. Seal/stamp:

10. Signature:

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

ACOMO 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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

9

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 CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C., REPÚBLICA DE COLOMBIA
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

10.

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

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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

A №009149

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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

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: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

DE RELACIONES
ERIORES

085749

FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

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

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

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

COMO NOTARIA SEXTA DEL CÍRCULO DE BOGOTÁ D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPÚBLICA DE COLOMBIA
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

REGISTRO NÚMERO **334** / 2004

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

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

L3

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 Osaka

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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

APOSTILLA

(Convention de La Haye du 5 octubre 1961)

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

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

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

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

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

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
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

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 4 DE 1999
MINISTERIO DE JUSTICIA

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

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

SANTAFE DE BOGOTA, 08 FEB2005

CODEX JURIS CIVILIS

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

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -8 P 2:40

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

313395

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

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

28 AGO. 2009

MARO QUINTERO ARTURO
NOTARIA

LS

Certificado

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

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

8. **No. 04149**

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

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

MINISTERIO DE RELACIONES EXTERIORES • JAPÓN •

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

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

Noviembre 17 de 2004

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. REPÚBLICA DE COLOMBIA
28 AGO. 2009
AMPARO QUINTERO ARTURO
NOTARIA

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

Número de Membresía: KT-01-00080

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

Diego Fernando Cadena

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

SANTAFE DE BOGOTA, 08 FEB 2005

CODEX JURIS CIVILIS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES EXTERIORES

2005 FEB -8 P 2:39

JEFE DE LEGALIZACIONES BOGOTA D.C.

313391

ESTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

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

BOGOTA D.C. REPÚBLICA DE COLOMBIA

28 AGO. 2009

AMPARO QUINTERO ARTURO

NOTARIA

L6.

25

The State of Maryland

Office of the Secretary of State

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America
   This public document
2. has been signed by **Robert P. Duckworth**
3. acting in the capacity of **Clerk of the Circuit Court for Anne Arundel County**
4. bears the seal/stamp of the **Circuit Court for Anne Arundel County**

Certified

5. at Annapolis, Maryland
6. the **15th day of July, 2009**
7. by The Secretary of State of Maryland
8. Seal



9. Signature

Secretary of State

No. 241806

CONSULADO DE COLOMBIA
WASHINGTON, D.C.

EL CONSULADO DE COLOMBIA

CERTIFICA:

Que es auténtica la firma de ROBERT P. DUCKWORTH

quien el día 15 JULIO 2009

desempeñaba las funciones de JUEZ DEL CIRCUITO ANNE ARUNDEL COUNTY MARYLAND

la cual aparece al pie de los documentos anexos relacionados con DOCUMENTO COMERCIAL

JUL 17 2009

Dado en Washington, D.C. a los _____

Pagado Impuesto de Timbre US$10.oo
Pagado Derecho Consular US$20.oo
Total US$30.oo

(El Consulado no asume ninguna responsabilidad por el contenido de los documentos anexos)

JORGE CORREA RODRIGUEZ
VICECONSUL
CONSULADO GENERAL DE COLOMBIA

81285

State of Maryland, Anne Arundel County, Sct.

I, ROBERT P. DUCKWORTH, Clerk of the Circuit Court for Anne Arundel County, Maryland, a court of record, do hereby certify that **Ahmad Miski** was a commissioned appointed and qualified Notary Public commencing on the 5th day of May, 2009.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of the court this 15th day of July, 2009.

Robert P Duckworth

Robert P. Duckworth, Clerk
Circuit Court for Anne Arundel County, Maryland

17

25

To All To Whom These Presents Shall Come

Based upon available information

US Legalization

Authenticates the signature of

Hiroshi Imoto

Notarized by

Ajitha Reddy Kakloor

is true and correct.

Hanadi Ajami

Hanadi Ajami

Authoorized Signature

On this day of July 15th, 2009, I,Ahmad Miski, Notary Public, Anne Arundel County, State of Maryland, do hereby certify under the Oath of my Office and Seal that the signature of Hanadi Ajami is true and correct.

My commission expires on May 28, 2013

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

374

18

CESION

Yo, (nosotros) abajo firmado (s)

1.
2.
3.

domiciliado(s) en

de la invención:

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

constituida y existente de conformidad con las leyes de

domiciliada en

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

ASSIGNMENT

I (we), the undersigned

1. Taisuke TAWARAISHI
2. Hiroshi IMOTO
3. Nobuo CHO

of

1.& 3. c/o Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8686 Japan
2. 1742 Sand Hill Road #206, Palo Alto, CA 94304 USA

state(s) under oath to be sole and true inventor(s) of the invention:
FUSED RING COMPOUNDS AS PARTIAL AGONISTS OF PPAR-GAMMA

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

Takeda Pharmaceutical Company Limited

a corporation constituted and existing in conformity with the laws of

Japan

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

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

Dado y firmado hoy/Given and signed this

____ day of _____ 200___

en/in _____

Firma/Signature

1. Taisuke Tawaraishi Taisuke TAWARAISHI 2. Hiroshi Imoto Hiroshi IMOTO

3. Nobuo Cho Nobuo CHO

PLEASE SEE ATTACHED CURR...

© CAVELIER ABOGADOS

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大阪法務局所属　公証人役場

認証登簿　平成２１年 第　**255**　号

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. JUN. 24. 2009

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

8. No. **3444**

9. Seal/stamp:

10. Signature:

Noriko KAWAHITO

For the Minister for Foreign Affairs

20

REGISTER NUMBER **255** / 2009

I hereby certify that this document was signed before me and that the signatures appearing on the same are the true signatures of Messrs. Taisuke TAWARAISHI and Nobuo CHO.

Dated this 23rd day of June, 2009

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

総 第 2792 号

証 明

大阪法務局所属公証人 **見 満 正 治**

平成 21年 6月 23日付

平成21年 登簿 第 255 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21年6月24日
平成 年 月 日

大阪法務局長 白 石 研 二

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 JUN. 24. 2009

Director of the Osaka Legal Affairs Bureau

22

CALIFORNIA JURAT WITH AFFIANT STATEMENT

☐ See Attached Document (Notary to cross out lines 1–6 below)
☐ See Statement Below (Lines 1–5 to be completed only by document signer[s], *not* Notary)

Documents described the invention of "fused ring compounds as partial agonists of PPAR-gamma"

Hiroshi Imoto
Signature of Document Signer No. 1

Signature of Document Signer No. 2 (if any)

State of California

County of Santa Clara

Subscribed and sworn to (or affirmed) before me on this 10 (Date) day of July (Month), 2009 (Year), by

(1) Hiroshi Imoto (Name of Signer),

proved to me on the basis of satisfactory evidence to be the person who appeared before me (.) (,)

(and

(2) N/A (Name of Signer),

proved to me on the basis of satisfactory evidence to be the person who appeared before me.)

AJITHA REDDY KAKLOOR
COMM. # 1838244
NOTARY PUBLIC - CALIFORNIA
SANTA CLARA COUNTY
My Comm. Exp. Feb. 24, 2013

Signature _____ (Signature of Notary Public)

Place Notary Seal Above

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

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Document Date: _____ Number of Pages: _____

Signer(s) Other Than Named Above: _____

RIGHT THUMBPRINT OF SIGNER #1	RIGHT THUMBPRINT OF SIGNER #2
Top of thumb here	Top of thumb here

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TRADUCCIÓN OFICIAL No. 07.20/09a 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.

CESIÓN

Yo(nosotros) los suscritos, 1. Taisuke TAWARAISHI; 2. Hiroshi IMOTO; 3. Nobuo CHO, domiciliados en 1. & 3. c/o Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8686 Japón, 2. 1742 Sand Hill Road #206, Palo Alto, CA 94304, Estados Unidos de América, declaramos bajo juramento ser únicos y verdaderos inventores de la invención COMPUESTOS DE ANILLO FUSIONADO COMO AGONISTAS PARCIALES DE PPAR-GAMA y declaramos así mismo que cedemos y transferimos, sin limitación, a favor de la sociedad **Takeda Pharmaceutical Company Limited**, 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 quedan facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

1. *Firma Ilegible* Taisuke TAWARAISHI 2. *Firma Ilegible* Hiroshi IMOTO

3. *Firma Ilegible* Nobuo CHO

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

NÚMERO DE REGISTRO: 255 /2009

Por el presente certifico que este documento fue firmado ante mí y que las firmas que aparecen en el mismo son las firmas auténticas de los señores Taisuke TAWARAISHI y Nobou CHO.

Fechado hoy 23 de junio de 2009

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

Firma ilegible

Masaharu KEMMA

Notario adjunto a

La Oficina de Asuntos Legales de Osaka

Texto en Japonés

CERTIFICADO

El presente es para certificar que el anexo Certificado Notarial 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 JUN. 24. 2009

Director de la Oficina de Asuntos Legales de Osaka

APOSTILLA

(Convention de La Haye du 5 octubre 1961)

1. País: JAPÓN

   Este documento público

2. ha sido firmado por Masaharu KEMMA

3. actuando en calidad de Notario Público de la Oficina de Asuntos Legales de Osaka

4. lleva el sello/estampilla de Masaharu KEMMA, Notario Público

Certificado

5. en Osaka 6. JUN.24.2009

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

LS.

7. por el Ministerio de Relaciones Exteriores

8. **No. 3444**

9. Sello/estampilla

MINISTERIO DE RELACIONES EXTERIORES • JAPÓN •

10. Firma: *Diego F. Vargas Z.*

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

Firma Ilegible

Noriko KAWAHITO
Por el Ministro de Relaciones Exteriores

CERTIFICADO DE AUTENTICIDAD DE CALIFORNIA CON DECLARACIÓN DEL DEPONENTE

☐ Ver documento adjunto (Notario debe tachar las líneas 1-6 abajo)

☐ Ver Declaración a continuación (Líneas 1-5 deberán ser diligenciadas únicamente por el signatario(s) del documento no por el Notario)

Documentos que describen la invención como "compuestos de anillo fusionado como agonistas parciales de PPAR-gama"

Firma Ilegible
Firma del Signatario No. 1 del Documento

Firma del Signatario No. 2 del Documento

Estado de California

Condado de *Santa Clara*

Suscrito y juramentado (o ratificado) ante mí hoy

10 (Día) de *Julio* (Mes) de *2009* (Año) por parte de

(1) Hiroshi Imoto
Nombre del Signatario

comprobó ante mí con base en evidencia satisfactoria ser la persona que compareció ante mí (.)(,)

(y

(2) *N/A*
Nombre del Signatario

comprobó ante mí con base en evidencia satisfactoria ser la persona que compareció

AJITHA REDDY KAKLOOR
COMISIÓN # 1838244
NOTARIO PÚBLICO - CALIFORNIA
CONDADO DE SANTA CLARA
Mi Comisión Vence Feb. 24, 2013

ante mí.)

Firma *Firma Ilegible*

Fijar Sello Notarial Arriba

Firma del Notario Público

OPCIONAL

Aunque la siguiente información no es obligatoria por ley, esta podría tener valor para aquellas personas que admitan el documento y podría prevenir la remoción fraudulenta y anexión de este formato a otro documento.

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Punta del Pulgar	Punta del Pulgar

Descripción Complementaria de cualquier documento adjunto

Título o Tipo Documento:_____

Fecha del Documento:_____Número de Páginas:_____

Signatarios distintos a los nombrados anteriormente:_____

A TODOS AQUELLOS A QUIENES LOS PRESENTES LLEGAREN

Con fundamento en información disponible

Legalización de los Estados Unidos

por medio de la cual se autentica la firma de

Hiroshi Imoto

Notarizada por

Ajitha Reddy Kakloor

es auténtica y verdadera

Firma Ilegible

Hanadi Ajami

Firma Autorizada

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

Hoy 15 de julio de 2009, yo Ahmad Miski, Notario Público, del Condado de Anne Arundel, Estado de Maryland, por el presente certifico bajo el juramento de oficio y sello que la firma de Hanadi Ajami es verdadera y auténtica.

Firma Ilegible

Mí Comisión Vence 28 de mayo de 2013

27

81285

Estado de Maryland, Condado de Anne Arundel, Sct.

Yo, **ROBERT P. DUCKWORTH**, Secretario del Tribunal de Circuito para el Condado de Anne Arundel, Maryland, un tribunal de registro, por el presente certifico que **Ahmad Miski** es un Notario Público comisionado/nombrado y calificado a partir del 5 de mayo de 2009.

En Testimonio de lo Cual, he firmado y fijado el sello del tribunal al presente hoy 15 de julio de 2009.

Firma Ilegible

Robert P. Duckworth, Secretario
Secretario del Tribunal de Circuito para el Condado de Anne Arundel, Maryland

---

Certificación del Consulado de Colombia en Washington D.C., Colombia, por medio de la cual se certifica la firma de Robert P. Duckworth en el anterior documento. Dado el 15 de julio de 2009. Pagados el impuesto de timbre y el derecho consular.
Legalización de la firma anterior por parte del Jefe de Legalizaciones del Ministerio de Relaciones Exteriores el 24 de agosto de 2009 con el número **021648.**

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

SELLO FACSIMILAR

El Estado de Maryland

Oficina del Secretario de Estado

Apostilla

(Convention de La Haye du 5 Octubre 1961)

1. País: Estados Unidos de América

   Este documento público

2. ha sido firmado por **Robert P. Duckworth**

3. actuando en calidad de **Secretario del Tribunal de Circuito para el Condado de Anne Arundel**

4. lleva el sello/estampilla del **Tribunal de Circuito para el Condado de Anne Arundel**

Certificado:

5. en Annapolis, Maryland

6. el **15 de julio de 2009**

7. por el Secretario de Estado de Maryland

8. Sello:



10. Firma:

Firma ilegible

Secretario de Estado

No. 241806

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

DVZ\DVZ\ID-155924\WPCL002H\COLO 14656-841-052-7

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

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
21 August 2008 (21.08.2008)

(10) International Publication Number
WO 2008/099794 A1

(51) International Patent Classification:
C07D 231/12 (2006.01) *C07D 413/14* (2006.01)
C07D 401/14 (2006.01) *C07D 417/14* (2006.01)
C07D 403/04 (2006.01) *C07D 471/04* (2006.01)
C07D 405/14 (2006.01) *C07D 491/113* (2006.01)
C07D 409/04 (2006.01) *A61K 31/4155* (2006.01)
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(21) International Application Number:
PCT/JP2008/052217

(22) International Filing Date: 5 February 2008 (05.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2007-031221 9 February 2007 (09.02.2007) JP

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TAWARAISHI, Taisuke** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85,Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). **IMOTO, Hiroshi** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85,Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP). **CHO, Nobuo** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 17-85,Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka, 5328686 (JP).

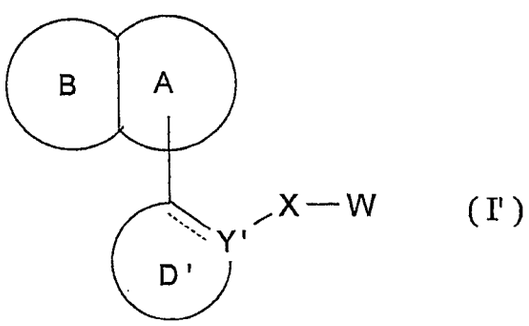
(74) Agent: **TAKASHIMA, Hajime**; Meiji Yasuda Seimei, Osaka Midosuji Bldg., 1-1, Fushimimachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410044 (JP).

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

(54) Title: FUSED RING COMPOUNDS AS PARTIAL AGONISTS OF PPAR-GAMMA



(I')

(57) Abstract: The present invention provides an agent for the prophylaxis or treatment of diabetes, which has a superior hypoglycemic action, and is associated with a fewer side effects such as body weight gain and the like. The resent invention relates an agent for the prophylaxis or treatment of diabetes, which comprises a compound represented by wherein each symbol is as defined in the description, or a salt thereof or a prodrug thereof.

WO 2008/099794 A1

DESCRIPTION

FUSED RING COMPOUNDS AS PARTIAL AGONISTS OF PPAR-GAMMA

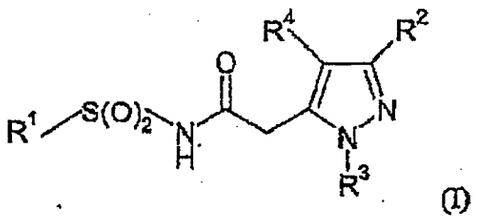
Technical Field

The present invention relates to a fused ring compound as an agent for the prophylaxis or treatment of diabetes.

Background of the Invention

As a fused ring compound, the compounds described in the following literatures are known.

(1) As a compound having endothelin-converting enzyme inhibitory action, WO2006/075955 discloses a compound represented by the formula:



(I)

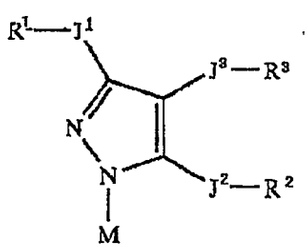
wherein

R^1 is an optionally substituted aryl group or an optionally substituted heteroaryl group;

R^2 and R^4 are independently a hydrogen atom, a halogen atom, a C_{1-6} alkyl group and the like; and

R^3 is an optionally substituted aryl group, an optionally substituted heteroaryl group or a C_{3-7} cycloalkyl group.

(2) As a compound having 15-lipoxygenase inhibitory action, US2005/0070589 discloses a compound represented by the formula:



wherein

J^1 is a bond, -C(O)-, -OC(O)-, -C(O)O-, $-NR^4-$, $-NR^4$-CO- or -$CONR^4$-;

J^2 is a bond, -CO-, -OC(O)-, -C(O)O-, $-NR^{4a}-$, $-NR^{4a}$-C(O)- or -C(O)NR^{4a}-;

J^3 is an alkylene group, an alkenylene group, an alkynylene group and the like, each of which is optionally substituted by an alkyl group and the like;

R^1 and R^2 are independently a hydrogen atom, a cycloalkyl group, a heterocyclic group, an aryl group, a heteroaryl group and the like, each of which is optionally substituted by an alkyl group and the like;

R^3 is $-NR^{3a}SO_2Z$, $-NR^{3a}C(O)OZ$, $-NR^{3a}C(O)Z$, $-NR^{3a}C(O)NR^{3b}Z$ and the like;

R^{3a}, R^{3b}, R^4 and R^{4a} are independently a hydrogen atom, an alkyl group and the like;

Z is $-NR^5R^6$, $-C(O)R^7$, $-C(O)OR^7$ and the like;

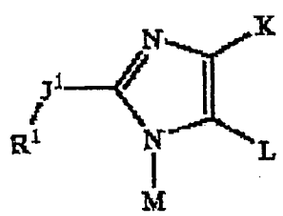
R^5 and R^6 are independently a hydrogen atom, an alkyl group and the like;

R^7 is a hydrogen atom, an alkyl group and the like; and

M is a hydrogen atom, an alkyl group and the like,

provided that a compound wherein R^1-J^1- and R^2-J^2- are both hydrogen atoms are excluded.

(3) As a compound having 15-lipoxygenase inhibitory action, US2005/0070588 discloses a compound represented by the formula:



wherein

one of K and L is $-J^2-R^2$ and the other is $-J^3-R^3$;

J^1 is a bond, -C(O)-, -OC(O)-, -C(O)O-, $-NR^4-$, $-NR^4$-CO- or -CONR^4-;

J^2 is a bond, -CO-, -OC(O)-, -C(O)O-, $-NR^{4a}-$, $-NR^{4a}$-C(O)- or -C(O)NR^{4a}-;

J^3 is an alkylene group, an alkenylene group, an alkynylene group and the like, each of which is optionally substituted by an alkyl group and the like;

R^1 and R^2 are independently a hydrogen atom, a cycloalkyl group, a heterocyclic group, an aryl group, a heteroaryl group and the like, each of which is optionally substituted by an alkyl group and the like;

R^3 is $-NR^{3a}SO_2Z$, $-NR^{3a}C(O)OZ$, $-NR^{3a}C(O)Z$, $-NR^{3a}C(O)NR^{3b}Z$ and the like;

R^{3a}, R^{3b}, R^4 and R^{4a} are independently a hydrogen atom, an alkyl group and the like;

Z is $-NR^5R^6$, $-C(O)R^7$, $-C(O)OR^7$ and the like;

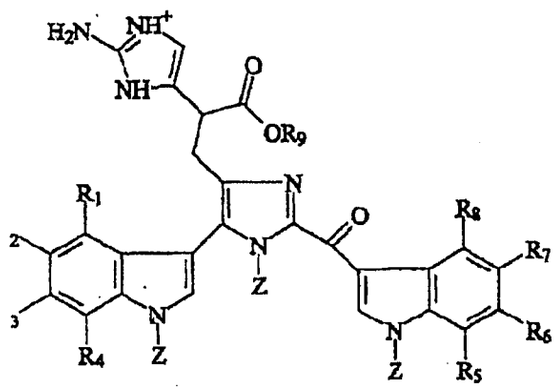
R^5 and R^6 are independently a hydrogen atom, an alkyl group and the like;

R^7 is a hydrogen atom, an alkyl group and the like; and

M is a hydrogen atom, an alkyl group and the like,

provided that a compound wherein R^1-J^1- and R^2-J^2- are both hydrogen atoms are excluded.

(4) As a therapeutic agent for neuritis, WO99/42092 discloses a compound represented by the formula:



(III)

wherein

R^1 to R^8 are independently a hydrogen atom, a hydroxy group, a halogen atom, -R, -OR, -OCOR, -OA or NZZ;

R^9 is a C_{1-8} alkyl group or an aryl group;

Z is a hydrogen atom, -R, a hydroxy group or -COR;

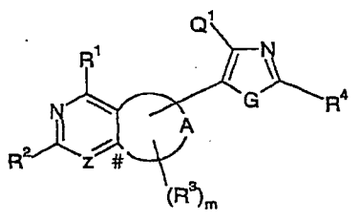
R is a C_{1-3} alkyl group, a C_{1-8} alkoxy group, a mesyl group or a

tosyl group; and

A is -R-phenyl.

Peroxisome proliferator-activated receptor gamma (PPARγ), which is one member of the nuclear hormone receptor superfamily represented by steroid hormone receptors and thyroid gland hormone receptors, shows an induced expression at the beginning of differentiation of adipocytes and plays an important role as a master regulator in the differentiation of adipocytes. PPARγ binds to a ligand to form a dimer with retinoid X receptor (RXR), and the dimer binds to a responsive element of a target gene in the nucleus to directly control (activate) the transcription efficiency.

(5) As a Tie2 receptor tyrosine kinase inhibitor, WO2004/013141 discloses a compound represented by the formula:



wherein

A is a 5-membered aromatic heterocycle;

G is O, S or NR^5;

Z is N or CR^6;

Q^1 is an aryl group or a heteroaryl group, each of which is optionally substituted;

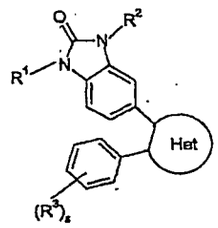
R^2 is H, an amino and the like;

R^3, R^4, R^5 and R^6 are independently H, OH, a halogen atom, Q^4-X^5- and the like;

Q^4 is an aryl group, an aryl-C_{1-6} alkyl group, a heteroaryl group, a heteroaryl-C_{1-6} alkyl group, a heterocyclyl group or a heterocyclyl-C_{1-6} alkyl group; and

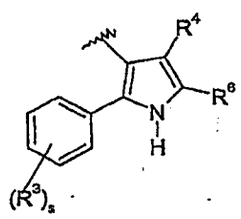
m is 0, 1 or 2.

(6) As an ERK/MAP inhibitor, WO2002/072576 discloses a compound represented by the formula:

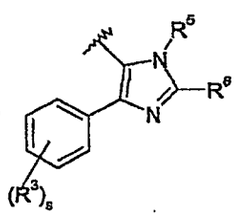


wherein

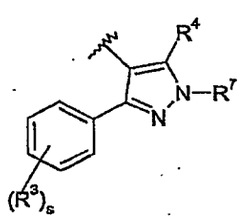
Het is any of



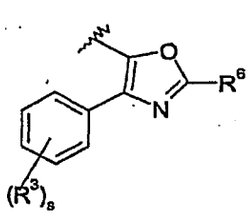
(a)



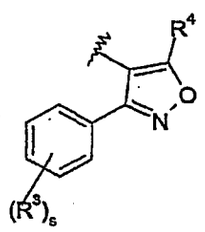
(b)



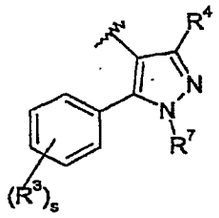
(c)



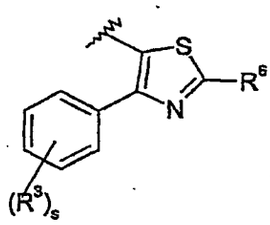
(d)



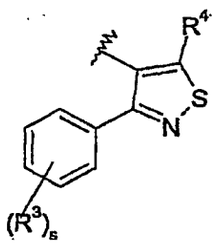
(e)



(f)



or



(g) (h)

R^1 and R^2 are independently H, a C_{1-6} alkyl and the like;

R^3 is a halogen atom, a C_{1-6} alkyl and the like;

R^4 and R^6 are independently H, a halogen atom or $-(CH_2)_n-B-R^9$;

B is a bond, -O-, -S-, -CO- and the like;

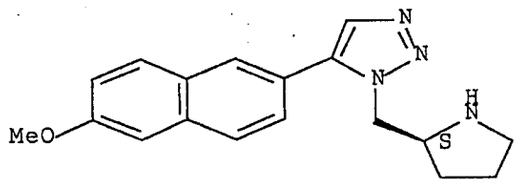
R^5 and R^7 are independently H, an optionally substituted phenyl, an optionally substituted C_{1-10} heteroaryl, an optionally substituted C_{1-10} heterocyclyl and the like;

R^9 is H, an optionally substituted phenyl, an optionally

substituted C_{1-10} heteroaryl, an optionally substituted C_{1-10} heterocyclyl and the like; and

s is an integer of 0 to 5.

(7) As a catalyst, Journal of Organic Chemistry, 2006, 71(24), pp.9244-9247 discloses the following compound:



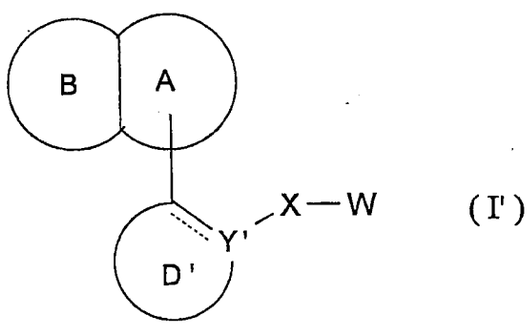
Disclosure of the Invention

There is a demand on the development of an agent for the prophylaxis or treatment of diabetes, which has a superior hypoglycemic action, and is associated with a fewer side effects such as body weight gain and the like.

The present inventors have found that a compound represented by the following formulas (I') and a compound represented by the following formulas (I) have a superior hypoglycemic action, and are useful for the prophylaxis or treatment of diabetes, which resulted in the completion of the present invention.

Accordingly, the present invention relates to

[1] a compound represented by the formula (I'):



(I')

wherein

ring A and ring B are the same or different and each is an optionally substituted 5- to 7-membered monocycle;

ring D' is an optionally substituted 5-membered monocyclic aromatic heterocycle wherein Y' is N or C;

X is a spacer having 1 to 4 atoms in the main chain; and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} and R^{1b} are the same or different and each is a hydrogen atom or a C_{1-6} alkyl group;

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

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

m and n are the same or different and each is an integer of 1 or 2, or

a 5- or 6-membered heterocyclic group containing NH, which is optionally substituted,

provided that

1) when ring D' is a substituted imidazole, then W should not be 2-amino-1H-imidazol-5-yl, 1H-imidazol-2-yl, 3,5-dimethyl-1H-pyrazol-4-yl and piperazin-1-yl;

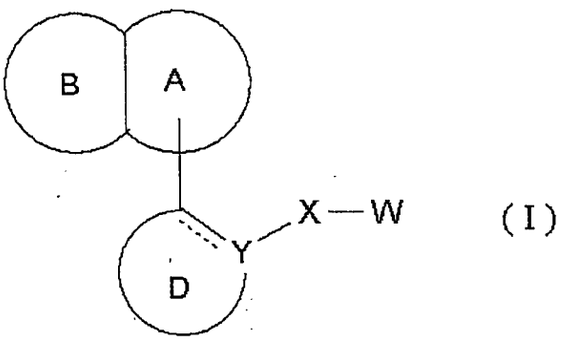
2) when ring D' is a substituted pyrazole, and X is -CH=, then W should not be 4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene, 5-oxo-2-thioxoimidazolidin-4-ylidene optionally substituted by phenyl group(s), 3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene, 2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene and

4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene; and

3) 5-(6-methoxy-2-naphthyl)-1-(pyrrolidin-2-ylmethyl)-1H-1,2,3-triazole is excluded,

or a salt thereof (hereinafter to be abbreviated as compound (I′));

[2] a compound represented by the formula (I):



(I)

wherein

ring A and ring B are the same or different and each is an optionally substituted 5- to 7-membered monocycle;

ring D is an optionally substituted 5-membered monocycle

wherein Y is N, C or CH;

X is a spacer having 1 to 4 atoms in the main chain; and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} and R^{1b} are the same or different and each is a hydrogen atom or a C_{1-6} alkyl group;

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

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and m and n are the same or different and each is an integer of 1 or 2, or

a 5- or 6-membered heterocyclic group containing NH, which is optionally substituted,

provided that

1) when ring D is a substituted imidazole, then W should not be an aminoimidazole; and

2) when ring D is a substituted pyrazole, and X is -CH=, then W should not be an oxothioxothiazolidinyl and an oxothioxoimidazolidinyl,

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

[3] the compound of the above-mentioned [1], wherein ring D' is an optionally substituted pyrazole;

[4] the compound of the above-mentioned [2], wherein ring D is an optionally substituted pyrazole;

[5] the compound of the above-mentioned [1] or [2], wherein X is a C_{1-4} alkylene group or a C_{2-4} alkenylene group;

[6] the compound of the above-mentioned [1] or [2], wherein W is a group represented by $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined in the above-mentioned [1];

[7] (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 9),
(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 27),
(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide (Example 33),
(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide (Example 62),
cyclopropylmethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 189),

butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 197),

(2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 232),

(2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide (Example 264),

N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide (Example 279),

(2E)-N-(butylsulfonyl)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide (Example 283),

N-[(butylamino)carbonyl]-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide (Example 294), or

butyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate (Example 295),

or a salt thereof;

[8] a prodrug of compound (I');

[9] a pharmaceutical agent comprising compound (I') or a prodrug thereof;

[10] the pharmaceutical agent of the above-mentioned [9], which is an insulin sensitizer;

[11] the pharmaceutical agent of the above-mentioned [9], which is an agent for the prophylaxis or treatment of diabetes;

[12] a method of improving insulin resistance in a mammal, which comprises administering compound (I') or a prodrug thereof to the mammal;

[13] a method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering compound (I') or a

prodrug thereof to the mammal;

[14] use of compound (I') or a prodrug thereof for the production of an insulin sensitizer;

[15] use of compound (I') or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes;

and the like.

Effect of the Invention

According to the present invention, an agent for the prophylaxis or treatment of diabetes, which has a superior hypoglycemic action, and is associated with a fewer side effects such as body weight gain and the like, can be provided.

[Detailed Description of the Invention]

The present invention is explained in detail in the following.

Unless otherwise specified, the "halogen atom" in the present specification means fluorine atom, chlorine atom, bromine atom or iodine atom.

Unless otherwise specified, the "C_{1-3} alkylenedioxy group" in the present specification means methylenedioxy, ethylenedioxy, trimethylenedioxy or the like.

Unless otherwise specified, the "C_{1-6} alkyl group" in the present specification means methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl or the like.

Unless otherwise specified, the "C_{1-6} alkoxy group" in the present specification means methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy or the like.

Unless otherwise specified, the "C_{1-6} alkoxy-carbonyl group" in the present specification means methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl or the

like.

Unless otherwise specified, the "C_{1-6} alkyl-carbonyl group" in the present specification means acetyl, propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, hexanoyl or the like.

The definition of each symbol in the formulas (I') and (I) is described in detail in the following.

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,
$-CONR^{1a}S(O)_mOR^2$,
$-CONR^{1a}CONR^{1c}R^2$,
$-CONR^{1a}S(O)_mNR^{1c}R^2$,
$-NR^{1b}CONR^{1a}S(O)_mR^2$,
$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,
$-S(O)_mNR^{1a}CO_nR^2$,
$-S(O)_mNR^{1a}CONR^{1c}R^2$,
$-OCONR^{1a}S(O)_mR^2$,
$-OCONR^{1a}S(O)_mNR^{1c}R^2$,
$-ONR^{1a}CO_nR^2$,
$-OCONR^{1c}R^2$, or
$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} and R^{1b} are the same or different and each is a hydrogen atom or a C_{1-6} alkyl group;

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

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

m and n are the same or different and each is an integer of 1 or 2, or

a 5- or 6-membered heterocyclic group containing NH, which is optionally substituted.

As the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2, for example, a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a C_{3-10} cycloalkyl

group, a C_{3-10} cycloalkenyl group, a C_{4-10} cycloalkadienyl group, a C_{6-14} aryl group, a C_{7-13} aralkyl group, a C_{8-13} arylalkenyl group and the like can be mentioned.

As the C_{1-10} alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like can be mentioned. Of these, a C_{1-6} alkyl group is preferable.

As the C_{2-10} alkenyl group, for example, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like can be mentioned. Of these, a C_{2-6} alkenyl group is preferable.

As the C_{2-10} alkynyl group, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl and the like can be mentioned. Of these, a C_{2-6} alkynyl group is preferable.

As the C_{3-10} cycloalkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like can be mentioned. Of these, a C_{3-6} cycloalkyl group is preferable.

As the C_{3-10} cycloalkenyl group, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like can be mentioned. Of these, a C_{3-6} cycloalkenyl group is preferable.

As the C_{4-10} cycloalkadienyl group, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like can be mentioned. Of these, a C_{4-6} cycloalkadienyl group is preferable.

The above-mentioned C_{3-10} cycloalkyl group, C_{3-10}

cycloalkenyl group and C_{4-10} cycloalkadienyl group are each optionally condensed with a benzene ring to form a fused cyclic group, and as the fused cyclic group, for example, indanyl, dihydronaphthyl, tetrahydronaphthyl, fluorenyl and the like can be mentioned.

In addition, the above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group may be each a C_{7-10} cross-linked hydrocarbon group. As the C_{7-10} cross-linked hydrocarbon group, bicyclo[2.2.1]heptyl (norbornyl), bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl, adamantyl and the like can be mentioned.

Moreover, the above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group each optionally form, together with a C_{3-10} cycloalkane, a C_{3-10} cycloalkene or a C_{4-10} cycloalkadiene, a spiro ring group. As the C_{3-10} cycloalkane, C_{3-10} cycloalkene and C_{4-10} cycloalkadiene, rings corresponding to the above-mentioned C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group can be mentioned. As the spiro ring groups, spiro[4.5]decan-8-yl and the like can be mentioned.

As the C_{6-14} aryl group, for example, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenylyl and the like can be mentioned. Of these, a C_{6-12} aryl group is preferable.

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

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

The C_{1-10} alkyl group, C_{2-10} alkenyl group and C_{2-10} alkynyl group exemplified as the aforementioned "hydrocarbon group" optionally has 1 to 3 substituents at substitutable positions.

As such substituents, for example,

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

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

substituted by 1 to 3 substituents selected from

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

(b) a hydroxy group,

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

(d) a halogen atom;

(3) an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, pyrazolyl, imidazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl) optionally substituted by 1 to 3 substituents selected from

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

(b) a hydroxy group,

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

(d) a halogen atom;

(4) a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperazinyl) optionally substituted by 1 to 3 substituents selected from

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

(b) a hydroxy group,

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

(d) a halogen atom;

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

(a) a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from a halogen atom and a C_{3-10} cycloalkyl group (e.g., cyclopropyl),

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

(c) a C_{1-6} alkoxy-carbonyl group optionally substituted by 1

to 3 halogen atoms;

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

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

(a) a halogen atom, and

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

(8) a C_{1-6} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, isopropylsulfonyl) optionally substituted by 1 to 3 halogen atoms;

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

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

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

(12) a carboxy group;

(13) a hydroxy group;

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

(a) a halogen atom,

(b) a carboxy group,

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

(d) a C_{1-6} alkyl-carbonyl group,

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

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

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

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

(15) a C_{2-6} alkenyloxy group (e.g., ethenyloxy) optionally substituted by 1 to 3 halogen atoms;

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

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

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

(a) a halogen atom, and

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

(19) a non-aromatic heterocyclylcarbonyl group (e.g., pyrrolidinylcarbonyl, morpholinylcarbonyl, 1,1-dioxidothiomorpholinylcarbonyl) optionally substituted by 1 to 3 substituents selected from a C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms;

(20) a mercapto group;

(21) a C_{1-6} alkylthio group (e.g., methylthio, ethylthio) optionally substituted by 1 to 3 halogen atoms;

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

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

(24) a cyano group;

(25) a nitro group;

(26) a halogen atom;

(27) a C_{1-3} alkylenedioxy group;

(28) an aromatic heterocyclylcarbonyl group (e.g., pyrazolylcarbonyl, pyrazinylcarbonyl, isoxazolylcarbonyl, pyridylcarbonyl, thiazolylcarbonyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups optionally substituted by 1 to 3 halogen atoms;

(29) a hydroxyimino group optionally substituted by a C_{1-6} alkyl group (e.g., methyl) optionally substituted by 1 to 3 C_{6-14} aryl groups (e.g., phenyl);

(30) a C_{1-6} alkylsulfonyloxy group (e.g., methylsulfonyloxy) and the like can be mentioned. When two or more substituents are used, the substituents may be the same or different.

The C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{4-10} cycloalkadienyl group, C_{6-14} aryl group, C_{7-13} aralkyl group and C_{8-13} arylalkenyl group exemplified as the aforementioned

"hydrocarbon group" optionally have 1 to 3 substituents at substitutable positions.

As such substituent, for example,

(1) the groups exemplified as the substituents for the aforementioned C_{1-10} alkyl group and the like;

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

(a) a halogen atom,

(b) a carboxy group,

(c) a hydroxy group,

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

(e) a C_{1-6} alkoxy group optionally substituted by silyl group(s) optionally substituted by 1 to 3 C_{1-6} alkyl groups (e.g., trimethylsilyl),

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

(g) a C_{6-14} aryl group (e.g., phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups;

(3) a C_{2-6} alkenyl group (e.g., ethenyl, 1-propenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) a carboxy group,

(c) a hydroxy group,

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

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

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

(4) a C_{7-13} aralkyl group (e.g., benzyl) optionally substituted by 1 to 3 substituents selected from

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

(b) a hydroxy group,

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

(d) a halogen atom;

and the like can be mentioned. When two or more substituents

are used, the substituents may be the same or different.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, an aromatic heterocyclic group and a non-aromatic heterocyclic group can be mentioned.

As the aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a fused aromatic heterocyclic group can be mentioned. As the fused aromatic heterocyclic group, for example, a group derived from a fused ring wherein a ring corresponding to the 5- to 7-membered monocyclic aromatic heterocyclic group and 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring are fused, and the like can be mentioned.

As preferable examples of the aromatic heterocyclic group,
monocyclic aromatic heterocyclic groups such as furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 4-isothiazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl,

1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl (e.g., 1,2,4-triazin-1-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-1-yl) and the like;

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

and the like can be mentioned.

As the non-aromatic heterocyclic group, for example, a 5- to 7-membered monocyclic non-aromatic heterocyclic group containing, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom (the sulfur atom is optionally oxidized) and a nitrogen atom, and a fused non-aromatic heterocyclic group can be mentioned. As the fused non-aromatic heterocyclic group, for example, a group derived from a fused ring wherein a ring corresponding to the 5- to 7-membered monocyclic non-aromatic heterocyclic

group and 1 or 2 rings selected from a 5- or 6-membered aromatic heterocycle containing 1 or 2 nitrogen atoms (e.g., pyrrole, imidazole, pyrazole, pyrazine, pyridine, pyrimidine), a 5-membered aromatic heterocycle containing one sulfur atom (e.g., thiophene) and a benzene ring are fused, a group wherein the above-mentioned group is partially saturated, and the like can be mentioned. In addition, as the non-aromatic heterocyclic group, a group wherein any of ring-constituting carbon atoms on the ring of the above-mentioned non-aromatic heterocyclic group is substituted by 1 to 3 oxo groups and/or thioxo groups, can be mentioned.

As preferable examples of the non-aromatic heterocyclic group,

monocyclic non-aromatic heterocyclic groups such as tetrahydrofuryl (e.g., 2-tetrahydrofuryl), dihydropyrrolyl (e.g., 2,3-dihydro-1H-pyrrol-1-yl), pyrrolidinyl (e.g., 1-pyrrolidinyl), 1,1-dioxidotetrahydrothienyl (e.g., 1,1-dioxidotetrahydro-3-thienyl), piperidinyl (e.g., piperidino), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), 1,1-dioxidothiomorpholinyl (e.g., 1,1-dioxidothiomorpholino), piperazinyl (e.g., 1-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolinyl (e.g., 2,5-dihydrooxazol-3-yl, 3,4-dihydrooxazol-3-yl), thiazolinyl (e.g., 2,5-dihydrothiazol-3-yl, 3,4-dihydrothiazol-3-yl), imidazolinyl (e.g., 2-imidazolin-3-yl), oxazolidinyl (e.g., oxazolidin-3-yl), thiazolidinyl (e.g., thiazolidin-3-yl), imidazolidinyl (e.g., imidazolidin-3-yl), dioxolyl (e.g., 1,3-dioxol-4-yl), dioxolanyl (e.g., 1,3-dioxolan-4-yl), dihydrooxadiazolyl (e.g., 4,5-dihydro-1,2,4-oxadiazol-3-yl), thioxooxazolidinyl (e.g., 2-thioxo-1,3-oxazolidin-5-yl), tetrahydropyranyl (e.g., 4-tetrahydropyranyl), tetrahydrothiopyranyl (e.g., 4-tetrahydrothiopyranyl), 1,1-dioxidotetrahydrothiopyranyl (e.g., 1,1-dioxidotetrahydrothiopyran-4-yl), pyrazolinyl (e.g., pyrazolin-3-yl), pyrazolidinyl (e.g., pyrazolidin-1-

yl), oxotetrahydropyridazinyl (e.g., 3-oxo-2,3,4,5-tetrahydropyridazin-4-yl) and the like;

fused non-aromatic heterocyclic groups such as dihydroisoindolyl (e.g., 1,3-dihydro-2H-isoindol-2-yl), dihydrobenzofuranyl (e.g., 2,3-dihydro-1-benzofuran-5-yl), dihydrobenzodioxinyl (e.g., 2,3-dihydro-1,4-benzodioxin-2-yl), dihydrobenzodioxepinyl (e.g., 3,4-dihydro-2H-1,5-benzodioxepin-2-yl), tetrahydrobenzofuranyl (e.g., 4,5,6,7-tetrahydro-1-benzofuran-3-yl), tetrahydrobenzothiazolyl (e.g., 4,5,6,7-tetrahydro-1-benzothiazol-2-yl), tetrahydrobenzoxazolyl (e.g., 4,5,6,7-tetrahydro-1-benzoxazol-2-yl), chromenyl (e.g., 4H-chromen-2-yl, 2H-chromen-3-yl), dihydroquinolinyl (e.g., 1,2-dihydroquinolin-2-yl), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydroquinolin-2-yl), dihydroisoquinolinyl (e.g., 1,2-dihydroisoquinolin-2-yl), tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydroisoquinolin-4-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl), dihydrophthalazinyl (e.g., 1,4-dihydrophthalazin-4-yl), tetrahydroindazolyl (e.g., 4,5,6,7-tetrahydro-2H-indazol-2-yl), tetrahydroquinazolinyl (e.g., 5,6,7,8-tetrahydroquinazolin-6-yl), tetrahydrothiazolopyridinyl (e.g., 4,5,6,7-tetrahydrothiazolo[5.4-c]pyridin-6-yl), tetrahydroimidazopyridinyl (e.g., 1,2,3,4-tetrahydroimidazo[4.5-c]pyridin-2-yl), tetrahydropyrazolopyridinyl (e.g., 1,2,3,4-tetrahydropyrazolo[3.4-c]pyridin-2-yl), tetrahydrotriazolopyrazinyl (e.g., 1,2,3,4-tetrahydrotriazolo[4.3-a]pyrazin-2-yl), tetrahydroimidazopyrazinyl (e.g., 1,2,3,4-tetrahydroimidazo[1.2-a]pyrazin-2-yl, 1,2,3,4-tetrahydroimidazo[3.4-a]pyrazin-2-yl), tetrahydropyridopyrimidinyl (e.g., 5,6,7,8-tetrahydropyrido[5.4-c]pyrimidin-6-yl) and the like;

can be mentioned.

The "heterocyclic group" of the "optionally substituted

heterocyclic group" for R^2 optionally has 1 to 3 substituents at substitutable positions. As such substituents, those similar to the substituents which the C_{3-10} cycloalkyl group and the like exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 optionally has, can be mentioned. When two or more substituents are used, the substituents may be the same or different.

R^{1a} is preferably a hydrogen atom.

R^{1b} is preferably a hydrogen atom.

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

R^2 is preferably

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl,

cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy).

m is preferably 2.

The "5- or 6-membered heterocyclic group containing NH" of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W is a 5- or 6-membered heterocyclic group containing, as a ring-constituting member, at least one non-substituted NH (i.e., -NH-), and further containing, as a ring-constituting atom, 4 or 5 atoms selected from a carbon atom (the carbon atom is optionally substituted by an oxo group or a thioxo group), an oxygen atom, a sulfur atom (the sulfur atom is optionally oxidized) and a nitrogen atom. For example, a 5- or 6-membered aromatic heterocyclic group and a 5- or 6-membered non-aromatic heterocyclic group, each of which contains NH, can be mentioned.

As specific preferable examples of the "5- or 6-membered aromatic heterocyclic group containing NH", pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl and the like can be mentioned.

As specific preferable examples of the "5- or 6-membered non-aromatic heterocyclic group containing NH", pyrrolinyl, 2,5-dioxopyrrolinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dioxopyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 2-oxoimidazolidinyl, 2,4-dioxoimidazolidinyl, triazolinyl, triazolidinyl, tetrazolinyl, tetrazolidinyl, piperidinyl, 2,6-dioxopiperidinyl, morpholinyl,

thiomorpholinyl, piperazinyl, 2-oxopiperazinyl, hexamethyleniminyl, oxazolinyl, oxooxazolinyl, oxazolidinyl, 2,4-dioxooxazolidinyl, thiazolinyl, thiazolidinyl, 2,4-dioxothiazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, 1,1-dioxidoisothiazolidinyl, 1,1-dioxido-3-oxoisothiazolidinyl, oxadiazolinyl, oxadiazolidinyl, oxooxadiazolinyl, oxooxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, 1,1-dioxido-3-oxothiadiazolidinyl, dihydropyridyl, tetrahydropyridyl, dihydropyrimidinyl, tetrahydropyrimidinyl, 2,6-dioxohexahydropyrimidinyl, dihydropyridazinyl, tetrahydropyridazinyl, dihydropyrazinyl, tetrahydropyrazinyl, 1,1-dioxido-1,2-thiazinanyl, 1,1-dioxido-3-oxo-1,2-thiazinanyl and the like can be mentioned.

The "5- or 6-membered heterocyclic group containing NH" of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W optionally has 1 to 3 substituents at substitutable positions. As such substituents, those similar to the substituents which the C_{3-10} cycloalkyl group and the like exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 optionally has, can be mentioned. When two or more substituents are used, the substituents may be the same or different.

As preferable substituents for "5- or 6-membered heterocyclic group containing NH", a C_{1-6} alkyl group (preferably propyl, isopropyl) and the like can be mentioned.

The "5- or 6-membered heterocyclic group containing NH" of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W is preferably a 5- or 6-membered non-aromatic heterocyclic group containing NH, more preferably oxooxadiazolinyl (preferably 5(4H)-oxo-1,2,4-oxadiazol-3-yl), 2,4-dioxothiazolidinyl (preferably 2,4-dioxothiazolidin-5-yl), 2,4-dioxoimidazolidinyl (preferably 2,4-dioxoimidazolidin-3-yl), 2-oxopiperazinyl (preferably 2-

oxopiperazin-1-yl) or 1,1-dioxido-3-oxothiadiazolidinyl (preferably 1,1-dioxido-3-oxo-1,2,5-thiadiazolidin-5-yl).

W is preferably a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein each symbol is as defined above, or a 5- or 6-membered non-aromatic heterocyclic group containing NH, which is optionally substituted. Of these, it is preferably a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, or

$-S(O)_mNR^{1a}CONR^{1c}R^2$

wherein each symbol is as defined above, particularly preferably a group represented by $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above.

As specific preferable examples of W,

(A) a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1b} is a hydrogen atom;

R^{1c} is a hydrogen atom, a C_{1-6} alkyl group (preferably methyl) or a C_{1-6} alkoxy group (preferably propoxy);

R^2 is

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl,

cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy);

m is 2; and

n is 1 or 2, and

(B) a 5- or 6-membered non-aromatic heterocyclic group containing NH [preferably oxooxadiazolinyl (preferably 5(4H)-oxo-1,2,4-oxadiazol-3-yl), 2,4-dioxothiazolidinyl (preferably 2,4-dioxothiazolidin-5-yl), 2,4-dioxoimidazolidinyl (preferably 2,4-dioxoimidazolidin-3-yl), 2-oxopiperazinyl (preferably 2-oxopiperazin-1-yl), 1,1-dioxido-3-oxothiadiazolidinyl (preferably 1,1-dioxido-3-oxo-1,2,5-thiadiazolidin-5-yl)] optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably propyl, isopropyl),

can be mentioned.

As specific more preferable examples of W, a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, or

$-S(O)_mNR^{1a}CONR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1c} is a hydrogen atom, a C_{1-6} alkyl group (preferably methyl) or a C_{1-6} alkoxy group (preferably propoxy);

R^2 is

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy);

m is 2; and

n is 1 or 2,

can be mentioned.

As specific particularly preferable examples of W, a group represented by

$-CONR^{1a}S(O)_mR^2$

wherein

R^{1a} is a hydrogen atom;

R^2 is

(1) a C_{1-10} alkyl group (preferably methyl, propyl, butyl, pentyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl), and

(b) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

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

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(4) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(5) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy); and

m is 2,

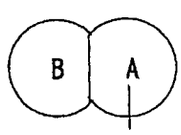
can be mentioned.

Ring A and ring B are the same or different and each is an optionally substituted 5- to 7-membered monocycle. As the "5- to 7-membered monocycle" of the "optionally substituted 5- to 7-membered monocycle" for ring A or ring B, a "5- to 7-membered monocyclic aromatic ring" and a "5- to 7-membered monocyclic non-aromatic ring" can be mentioned.

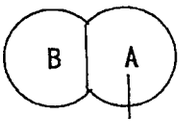
As the "5- to 7-membered monocyclic aromatic ring", benzene, a 5- to 7-membered ring (e.g., pyrrole, pyrazole, imidazole, thiophene, pyridine), from among the monocyclic aromatic heterocycle corresponding to the monocyclic aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, can be mentioned.

As the "5- to 7-membered monocyclic non-aromatic ring", a 5- to 7-membered ring (i.e., a C_{5-7} cycloalkane, a C_{5-7} cycloalkene and a C_{5-7} cycloalkadiene), from among a C_{3-10} cycloalkane, a C_{3-10} cycloalkene and a C_{4-10} cycloalkadiene corresponding to the C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group and C_{4-10} cycloalkadienyl group exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2, and a 5- to 7-membered ring (e.g., pyrroline), from among a monocyclic non-aromatic heterocycle corresponding to the monocyclic non-aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, can be mentioned.

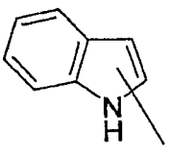
In the present specification, the moiety represented by



of the formula (I') and the formula (I) is a group derived from a bicycle wherein formed by ring A and ring B having one common bond (that is, they are condensed). The bond multiplicity for ring A and that for ring B, involved in the bicycle formation, are the same. For example, when the moiety represented by

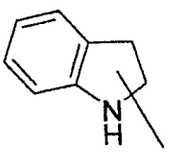


of the formula (I') and the formula (I) is a group represented by (A)



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then ring A should be "pyrrole", and ring B should be "benzene". When the moiety is



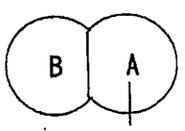
,

then ring A should be "pyrroline", and ring B should be "benzene".

As specific preferable examples of the "5- to 7-membered monocycle" of the "optionally substituted 5- to 7-membered monocycle" for ring A, benzene, a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyrrole, pyrazole, imidazole, thiophene), a 5- to 7-membered monocyclic non-aromatic heterocycle (preferably pyrroline) and the like can be mentioned.

As specific preferable examples of the "5- to 7-membered monocycle" of the "optionally substituted 5- to 7-membered monocycle" for ring B, benzene, a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyridine) and the like can be mentioned.

As specific preferable examples of the moiety represented by



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1H-indol-1-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indazol-1-yl,

1H-indazol-3-yl, 2H-indazol-2-yl, 1H-benzimidazol-1-yl, 1H-benzimidazol-2-yl, 1-benzothiophen-2-yl, 1-benzothiophen-3-yl, 2-benzothiophen-1-yl, 1-benzofuran-2-yl, 1-benzofuran-3-yl, 2-benzofuran-1-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 1H-pyrrolo[2,3-b]pyridin-2-yl, 1H-pyrrolo[2,3-b]pyridin-3-yl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-2-yl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl, 1H-pyrrolo[3,2-c]pyridin-1-yl, 1H-pyrrolo[3,2-c]pyridin-2-yl, 1H-pyrrolo[3,2-c]pyridin-3-yl, 1H-pyrrolo[2,3-c]pyridin-1-yl, 1H-pyrrolo[2,3-c]pyridin-2-yl, 1H-pyrrolo[2,3-c]pyridin-3-yl, 1-naphthyl, 2-naphthyl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, quinolin-8-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl, isoquinolin-8-yl and the like can be mentioned.

The "5- to 7-membered monocycle" of the "optionally substituted 5- to 7-membered monocycle" for ring A or ring B optionally has 1 to 3 substituents at substitutable positions. As such substituents, those similar to the substituents which the C_{3-10} cycloalkyl group and the like exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 optionally has, can be mentioned. When two or more substituents are used, the substituents may be the same or different.

As preferable substituents for ring A and ring B,

(1) a halogen atom (preferably chlorine atom, fluorine atom, bromine atom),

(2) a hydroxy group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(5) a C_{1-6} alkoxy group (preferably methoxy, ethoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably methoxy),

(c) a C_{3-10} cycloalkyl group (preferably cyclopropyl), and

(d) a C_{1-6} alkyl-carbonyl group (preferably acetyl),

(6) a C_{3-10} cycloalkyl group (preferably cyclopropyl),

(7) a C_{1-6} alkylsulfonyloxy group (preferably methylsulfonyloxy),

(8) a C_{6-14} aryl group (preferably phenyl),

(9) an aromatic heterocyclic group (preferably furyl, thienyl),

(10) a non-aromatic heterocyclic group (preferably pyrrolidinyl),

(11) an amino group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (preferably methyl, ethyl) optionally substituted by 1 to 3 C_{3-10} cycloalkyl groups (preferably cyclopropyl)

and the like can be mentioned.

Ring A is preferably optionally substituted benzene, an optionally substituted 5- to 7-membered monocyclic aromatic heterocycle (preferably pyrrole, pyrazole, imidazole, thiophene) or an optionally substituted 5- to 7-membered monocyclic non-aromatic heterocycle (preferably pyrroline).

As specific preferable examples of ring A, benzene, a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyrrole, pyrazole, imidazole, thiophene) and a 5- to 7-membered monocyclic non-aromatic heterocycle (preferably pyrroline), each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably chlorine atom) and a C_{1-6} alkyl group (preferably methyl), can be mentioned.

Ring B is preferably an optionally substituted benzene or an optionally substituted 5- to 7-membered monocyclic aromatic heterocycle (preferably pyridine).

As specific preferable examples of ring B, benzene and a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyridine), each of which is optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably chlorine atom, fluorine atom, bromine atom),

(2) a hydroxy group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(5) a C_{1-6} alkoxy group (preferably methoxy, ethoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably methoxy),

(c) a C_{3-10} cycloalkyl group (preferably cyclopropyl), and

(d) a C_{1-6} alkyl-carbonyl group (preferably acetyl),

(6) a C_{3-10} cycloalkyl group (preferably cyclopropyl),

(7) a C_{1-6} alkylsulfonyloxy group (preferably methylsulfonyloxy),

(8) a C_{6-14} aryl group (preferably phenyl),

(9) an aromatic heterocyclic group (preferably furyl, thienyl),

(10) a non-aromatic heterocyclic group (preferably pyrrolidinyl), and

(11) an amino group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (preferably methyl, ethyl) optionally substituted by 1 to 3 C_{3-10} cycloalkyl groups (preferably cyclopropyl)

can be mentioned.

Ring D is an optionally substituted 5-membered monocycle wherein Y is N, C or CH, which is a ring D-constituting atom in the formula (I). As the "5-membered monocycle" of the "optionally substituted 5-membered monocycle" for ring D, a "5-membered monocyclic aromatic ring" and a "5-membered monocyclic non-aromatic ring" can be mentioned.

As the "5-membered monocyclic aromatic ring", a 5-membered ring (e.g., pyrazole), from among a monocyclic aromatic heterocycle corresponding to the monocyclic aromatic

heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, can be mentioned.

As the "5-membered monocyclic non-aromatic ring", cyclopentane, cyclopentene, cyclopentadiene, and a 5-membered ring (e.g., pyrazolidine, pyrazoline, imidazoline, imidazolidine), from among a monocyclic non-aromatic heterocycle corresponding to the monocyclic non-aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, can be mentioned.

In ring D, Y (a ring D-constituting atom) and the carbon atom on the ring D (bonded to ring A) are adjacent each other via a single bond or a double bond.

The "5-membered monocycle" of the "optionally substituted 5-membered monocycle" for ring D is preferably a 5-membered monocyclic aromatic heterocycle (preferably pyrazole) and the like.

The "5-membered monocycle" of the "optionally substituted 5-membered monocycle" for ring D optionally has 1 to 3 substituents at substitutable positions. As such substituents, those similar to the substituents which the C_{3-10} cycloalkyl group and the like exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 optionally has, can be mentioned. When two or more substituents are used, the substituents may be the same or different.

As preferable substituents for ring D,

(1) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably fluorine atom) and a C_{1-6} alkoxy group (preferably methoxy)

and the like can be mentioned.

Ring D is preferably an optionally substituted 5-membered monocyclic aromatic heterocycle, more preferably an optionally

substituted pyrazole.

As specific preferable examples of ring D, pyrazole optionally substituted by 1 to 3 substituents selected from (1) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably fluorine atom) and a C_{1-6} alkoxy group (preferably methoxy)
can be mentioned.

Ring D' is an optionally substituted 5-membered monocyclic aromatic heterocycle wherein Y' is N or C, which is a ring D'-constituting atom in the formula (I'). As the "5-membered monocyclic aromatic heterocycle" of the "optionally substituted 5-membered monocyclic aromatic heterocycle" for ring D', a 5-membered ring (e.g., pyrazole, imidazole, pyrrole, triazole, tetrazole, thiophene, furan, oxazole, thiazole, isoxazole, isothiazole, oxadiazole, thiadiazole), from among a monocyclic aromatic heterocycle corresponding to the monocyclic aromatic heterocyclic group exemplified as the "heterocyclic group" of the "optionally substituted heterocyclic group" for R^2, can be mentioned. Of these, it is preferably pyrazole, thiophene, imidazole or pyrrole, particularly preferable pyrazole (it is (i) bonded to ring A at the 5-position and bonded to X at the 4-position, (ii) bonded to ring A at the 3-position and bonded to X at the 4-position, or (iii) bonded to ring A at the 5-position and bonded to X at the 1-position, preferably (i) bonded to ring A at the 5-position and bonded to X at the 4-position).

In ring D', Y' (a ring D'-constituting atom) and the carbon atom on the ring D' (bonded to ring A) are adjacent each other via a single bond or a double bond.

The "5-membered monocyclic aromatic heterocycle" of the "optionally substituted 5-membered monocyclic aromatic heterocycle" for ring D' has 1 to 3 substituents at substitutable positions. As such substituents, those similar to the substituents which the C_{3-10} cycloalkyl group and the

like exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" for R^2 optionally has, can be mentioned. When two or more substituents are used, the substituents may be the same or different.

As preferable substituents for ring D',

(1) a C_{1-6} alkyl group (preferably methyl, ethyl, butyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably fluorine atom),

(b) a C_{1-6} alkoxy group (preferably methoxy), and

(c) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(2) a C_{1-6} alkoxy-carbonyl group (preferably t-butoxycarbonyl),

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl)

and the like can be mentioned.

Ring D' is preferably pyrazole, thiophene, imidazole or pyrrole, each of which is optionally substituted, more preferably an optionally substituted pyrazole (it is (i) bonded to ring A at the 5-position and bonded to X at the 4-position, (ii) bonded to ring A at the 3-position and bonded to X at the 4-position, or (iii) bonded to ring A at the 5-position and bonded to X at the 1-position, preferably (i) bonded to ring A at the 5-position and bonded to X at the 4-position).

As specific preferable examples of ring D', a 5-membered monocyclic aromatic heterocycle (preferably pyrazole, thiophene, imidazole, pyrrole, more preferably pyrazole (it is (i) bonded to ring A at the 5-position and bonded to X at the 4-position, (ii) bonded to ring A at the 3-position and bonded to X at the 4-position, or (iii) bonded to ring A at the 5-position and bonded to X at the 1-position, preferably (i) bonded to ring A at the 5-position and bonded to X at the 4-position)) optionally substituted by 1 to 3 substituents selected from

(1) a C_{1-6} alkyl group (preferably methyl, ethyl, butyl)

optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably fluorine atom),

(b) a C_{1-6} alkoxy group (preferably methoxy), and

(c) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(2) a C_{1-6} alkoxy-carbonyl group (preferably t-butoxycarbonyl), and

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl) can be mentioned.

X is a spacer having 1 to 4 atoms in the main chain.

The "main chain" of the "spacer having 1 to 4 atoms in the main chain" for X is a straight chain connecting Y' (a ring D'-constituting atom) or Y (a ring D-constituting atom) and group W, and the atom number of the main chain is counted such that the number of atoms in the main chain will be minimum. The total atom number in the spacer is not particularly limited as long as the main chain consists of 1 to 4 atoms, and the spacer optionally has 4 or more atoms. The "main chain" consists of 1 to 4 atoms selected from a carbon atom (the carbon atom is optionally substituted by oxo group(s)) and a hetero atom (e.g., O, S, N), and may be saturated or unsaturated. In addition, when group W is a "5- or 6-membered non-aromatic heterocyclic group containing NH, which is optionally substituted", and the non-aromatic heterocyclic group is bonded to X at the ring-constituting saturated carbon atom, the group W-side terminal of the "spacer having 1 to 4 atoms in the main chain" for X may be double bond (e.g., -CH=).

As the "spacer having 1 to 4 atoms in the main chain", for example, a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group, a C_{3-6} cycloalkylene group, $-X^{1a}-Z-X^{2a}-$ wherein Z is NH, O or S, X^{1a} and X^{2a} are the same or different and each is a straight chain C_{1-3} alkylene group, and the total carbon number of X^{1a} and X^{2a} is 3 or less, $-X^{3a}-CH=$ wherein X^{3a}

is a bond or a straight chain C_{1-3} alkylene group, and the like can be mentioned.

As specific examples of the "spacer having 1 to 4 atoms in the main chain",

(1) a C_{1-4} alkylene group (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-CH(C_2H_5)-$, $-CH(C_3H_7)-$, $-CH(i-C_3H_7)-$, $-CH(CH_3)-CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)(CH_2)_2-$, $-(CH_2)_2CH(CH_3)-$, $-CH_2-CH(CH_3)-CH_2-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-CH(CH_3)-CH(CH_3)-$, $-CH_2-C(CH_3)_2-$);

(2) a C_{2-4} alkenylene group (e.g., $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-C(CH_3)=CH-$, $-CH=C(CH_3)-$, $-CH=C(C_2H_5)-$);

(3) a C_{2-4} alkynylene group (e.g., $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-$);

(4) a C_{3-6} cycloalkylene group (e.g., 1,2-cyclopropylene, 1,2-cyclobutylene, 1,3-cyclobutylene, 1,2-cyclopentylene, 1,3-cyclopentylene, 1,2-cyclohexylene, 1,3-cyclohexylene, 1,4-cyclohexylene);

(5) $-X^{1a}-Z-X^{2a}-$ wherein Z is NH, O or S, X^{1a} and X^{2a} are the same or different and each is a straight chain C_{1-3} alkylene group, and the total carbon number of X^{1a} and X^{2a} is 3 or less (e.g., $-CH_2-NH-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-S-CH_2-$);

(6) $-X^{3a}-CH=$ wherein X^{3a} is a bond or a straight chain C_{1-3} alkylene group (e.g., $-CH=$, $-CH_2-CH_2-CH=$, $-CH_2-CH_2-CH_2-CH=$);

and the like can be mentioned.

X is preferably a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{3-6} cycloalkylene group, $-X^{1a}-Z-X^{2a}-$ or $-X^{3a}-CH=$ wherein each symbol is as defined above, more preferably a C_{1-4} alkylene group or a C_{2-4} alkenylene group.

As specific preferable examples of X,

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$);

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) a C_{3-6} cycloalkylene group (preferably 1,2-cyclopropylene);

(4) $-X^{1a}-Z-X^{2a}-$ wherein each symbol is as defined above (preferably $-CH_2-O-CH_2-$); and

(5) $-X^{3a}-CH=$ wherein each symbol is as defined above (preferably $-CH=$, $-CH_2-CH_2-CH=$);

more preferably

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$; and

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$),

can be mentioned.

In compound (I),

1) when ring D is a substituted imidazole, then W should not be an aminoimidazole; and

2) when ring D is a substituted pyrazole, and X is -CH=, then W should not be an oxothioxothiazolidinyl and an oxothioxoimidazolidinyl.

In compound (I'),

1) when ring D' is a substituted imidazole, then W should not be 2-amino-1H-imidazol-5-yl, 1H-imidazol-2-yl, 3,5-dimethyl-1H-pyrazol-4-yl and piperazin-1-yl;

2) when ring D' is a substituted pyrazole, and X is -CH=, then W should not be 4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene, 5-oxo-2-thioxoimidazolidin-4-ylidene optionally substituted by phenyl group(s), 3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene, 2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene and 4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene; and

3) 5-(6-methoxy-2-naphthyl)-1-(pyrrolidin-2-ylmethyl)-1H-1,2,3-triazole is excluded.

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

[Compound A]

Compound (I) wherein

ring D is an optionally substituted pyrazole;

X is a C_{1-4} alkylene group or a C_{2-4} alkenylene group; and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$

wherein each symbol is as defined above.

[Compound B]

Compound (I) wherein

ring A is benzene, a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyrrole, pyrazole, imidazole, thiophene) or a 5- to 7-membered monocyclic non-aromatic heterocycle (preferably pyrroline), each of which is optionally substituted by 1 to 3 halogen atoms (preferably chlorine atom);

ring B is benzene or a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyridine), each of which is optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably chlorine atom, fluorine atom),

(2) a hydroxy group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom), and

(5) a C_{1-6} alkoxy group (preferably methoxy) optionally substituted by 1 to 3 C_{6-14} aryl groups (preferably phenyl);

ring D is pyrazole optionally substituted by 1 to 3 substituents selected from

(1) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably fluorine atom) and a C_{1-6} alkoxy group (preferably methoxy);

X is

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$);

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) $-X^{1a}-Z-X^{2a}-$ wherein each symbol is as defined above (preferably $-CH_2-O-CH_2-$); or

(4) $-X^{3a}-CH=$ wherein each symbol is as defined above

(preferably -CH=, $-CH_2-CH_2-CH=$); and

W is

(A) a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mR^2$, or

$-OCONR^{1a}S(O)_mNR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1b} is a hydrogen atom;

R^{1c} is a hydrogen atom or a C_{1-6} alkyl group (preferably methyl);

R^2 is

(1) a C_{1-10} alkyl group (preferably methyl, ethyl, butyl, pentyl, 1-ethylpropyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl), and

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

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

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom), and

(c) a C_{1-6} alkoxy group (preferably methoxy);

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl);

(4) an aromatic heterocyclic group (preferably furyl, thienyl); or

(5) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl); and

m is 2, or

(B) oxooxadiazolinyl (preferably 5(4H)-oxo-1,2,4-oxadiazol-3-yl) or 2,4-dioxothiazolidinyl (preferably 2,4-dioxothiazolidin-5-yl).

[Compound C]

Compound B wherein

X is

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$); or

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$); and

W is a group represented by $-CONR^{1a}S(O)_mR^2$

wherein

R^{1a} is a hydrogen atom;

R^2 is

(1) a C_{1-10} alkyl group (preferably methyl, pentyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl), and

(b) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

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

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom), and

(c) a C_{1-6} alkoxy group (preferably methoxy);

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(4) an aromatic heterocyclic group (preferably furyl, thienyl); or

(5) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl); and

m is 2.

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

[Compound BB-1]

Compound (I') wherein

ring A is benzene, a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyrrole, pyrazole, imidazole, thiophene) or a 5- to 7-membered monocyclic non-aromatic heterocycle (preferably pyrroline), each of which is optionally substituted by 1 to 3 substituents selected from a halogen atom (preferably chlorine atom) and a C_{1-6} alkyl group (preferably methyl);

ring B is benzene or a 5- to 7-membered monocyclic aromatic heterocycle (preferably pyridine), each of which is optionally substituted by 1 to 3 substituents selected from

(1) a halogen atom (preferably chlorine atom, fluorine atom, bromine atom),

(2) a hydroxy group,

(3) a cyano group,

(4) a C_{1-6} alkyl group (preferably methyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(5) a C_{1-6} alkoxy group (preferably methoxy, ethoxy, isopropoxy) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably methoxy),

(c) a C_{3-10} cycloalkyl group (preferably cyclopropyl), and

(d) a C_{1-6} alkyl-carbonyl group (preferably acetyl),

(6) a C_{3-10} cycloalkyl group (preferably cyclopropyl),

(7) a C_{1-6} alkylsulfonyloxy group (preferably methylsulfonyloxy),

(8) a C_{6-14} aryl group (preferably phenyl),

(9) an aromatic heterocyclic group (preferably furyl, thienyl),

(10) a non-aromatic heterocyclic group (preferably pyrrolidinyl), and

(11) an amino group optionally mono- or di-substituted by C_{1-6} alkyl group(s) (preferably methyl, ethyl) optionally substituted by 1 to 3 C_{3-10} cycloalkyl groups (preferably cyclopropyl);

ring D' is a 5-membered monocyclic aromatic heterocycle (preferably pyrazole, thiophene, imidazole, pyrrole, more preferably pyrazole (it is (i) bonded to ring A at the 5-position and bonded to X at the 4-position, (ii) bonded to ring A at the 3-position and bonded to X at the 4-position, or (iii) bonded to ring A at the 5-position and bonded to X at the 1-position, preferably (i) bonded to ring A at the 5-position and bonded to X at the 4-position)) optionally substituted by 1 to 3 substituents selected from

(1) a C_{1-6} alkyl group (preferably methyl, ethyl, butyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably fluorine atom),

(b) a C_{1-6} alkoxy group (preferably methoxy), and

(c) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(2) a C_{1-6} alkoxy-carbonyl group (preferably t-butoxycarbonyl), and

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

X is

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$;

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) a C_{3-6} cycloalkylene group (preferably 1,2-cyclopropylene);

(4) $-X^{1a}-Z-X^{2a}-$ wherein each symbol is as defined above (preferably $-CH_2-O-CH_2-$); or

(5) $-X^{3a}-CH=$ wherein each symbol is as defined above (preferably $-CH=$, $-CH_2-CH_2-CH=$); and

W is

(A) a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1b} is a hydrogen atom;

R^{1c} is a hydrogen atom, a C_{1-6} alkyl group (preferably methyl) or a C_{1-6} alkoxy group (preferably propoxy);

R^2 is

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 C_{1-6} alkoxy groups (preferably methoxy),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy);

m is 2; and

n is 1 or 2, or

(B) a 5- or 6-membered non-aromatic heterocyclic group containing NH [preferably oxooxadiazolinyl (preferably 5(4H)-oxo-1,2,4-oxadiazol-3-yl), 2,4-dioxothiazolidinyl (preferably 2,4-dioxothiazolidin-5-yl), 2,4-dioxoimidazolidinyl (preferably 2,4-dioxoimidazolidin-3-yl), 2-oxopiperazinyl (preferably 2-oxopiperazin-1-yl), 1,1-dioxido-3-oxothiadiazolidinyl (preferably 1,1-dioxido-3-oxo-1,2,5-thiadiazolidin-5-yl)] optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably propyl, isopropyl).

[Compound BB-2]

Compound BB-1 wherein

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, or

$-S(O)_mNR^{1a}CONR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1c} is a hydrogen atom, a C_{1-6} alkyl group (preferably methyl) or a C_{1-6} alkoxy group (preferably propoxy);

R^2 is

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally

substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy);

m is 2; and

n is 1 or 2.

[Compound BB-3]

Compound BB-1 wherein

X is

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$; or

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$); and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, or

$-S(O)_mNR^{1a}CONR^{1c}R^2$

wherein

R^{1a} is a hydrogen atom;

R^{1c} is a hydrogen atom, a C_{1-6} alkyl group (preferably methyl) or a C_{1-6} alkoxy group (preferably propoxy);

R^2 is

(1) a hydrogen atom,

(2) a C_{1-10} alkyl group (preferably methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, 1-propylbutyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl),

(b) a C_{1-6} alkoxy group (preferably isopropoxy),

(c) a C_{1-6} alkoxy-carbonyl group (preferably ethoxycarbonyl),

(d) a C_{3-10} cycloalkyl group (preferably cyclopropyl,

cyclohexyl),

(e) a hydroxy group, and

(f) a halogen atom (preferably fluorine atom);

(3) a C_{6-14} aryl group (preferably phenyl) optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(4) a C_{3-10} cycloalkyl group (preferably cyclopropyl, cyclohexyl);

(5) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(6) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy);

m is 2; and

n is 1 or 2.

[Compound CC]

Compound BB-1 wherein

X is

(1) a C_{1-4} alkylene group (preferably $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$); or

(2) a C_{2-4} alkenylene group (preferably $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$); and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$

wherein

R^{1a} is a hydrogen atom;

R^2 is

(1) a C_{1-10} alkyl group (preferably methyl, propyl, butyl, pentyl, 4-methylpentyl) optionally substituted by 1 to 3 substituents selected from

(a) a C_{6-14} aryl group (preferably phenyl), and

(b) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

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

(a) a halogen atom (preferably chlorine atom),

(b) a C_{1-6} alkyl group (preferably methyl, butyl) optionally substituted by 1 to 3 halogen atoms (preferably fluorine atom),

(c) a C_{1-6} alkoxy group (preferably methoxy), and

(d) a hydroxy group;

(3) a C_{3-10} cycloalkyl group (preferably cyclopropyl);

(4) an aromatic heterocyclic group (preferably furyl, thienyl, imidazolyl) optionally substituted by 1 to 3 C_{1-6} alkyl groups (preferably methyl); or

(5) a non-aromatic heterocyclic group (preferably dihydrobenzofuranyl, morpholinyl, piperidinyl) optionally substituted by 1 to 3 substituents selected from

(a) an oxo group,

(b) a hydroxy group,

(c) a C_{1-6} alkyl group (preferably methyl), and

(d) a C_{1-3} alkylenedioxy group (preferably ethylenedioxy); and

m is 2.

[Compound D]

(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 9),

(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 27),

(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-

pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide (Example 33),

(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide (Example 62),

cyclopropylmethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 189),

butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 197),

(2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 232),

(2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide (Example 264),

N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide (Example 279),

(2E)-N-(butylsulfonyl)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide (Example 283),

N-[(butylamino)carbonyl]-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide (Example 294), or

butyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate (Example 295),

or a salt thereof.

The salts of a compound represented by the formula (I') and a compound represented by the formula (I) are preferably pharmacologically acceptable salts and, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids and the like can be mentioned.

Preferable examples of the salts with inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; aluminum salt, ammonium salt and the like.

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

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

Preferable examples of the salt with organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and the like.

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

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

The prodrug of the compounds (I') and (I) (hereinafter, to be referred to as compound (I)) is a compound which is converted to the compound (I) with a reaction due to an enzyme, gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to the compound (I) by enzymatic oxidation, reduction, hydrolysis, etc.; a compound which is converted to the compound (I) by hydrolysis etc. due to gastric acid, and the like. A prodrug of the compound (I) may be a compound obtained by subjecting an amino group in the compound (I) to an acylation, alkylation or phosphorylation (e.g., a compound

obtained by subjecting an amino group in the compound (I) to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, tetrahydropyranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy group in the compound (I) to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy group in the compound (I) to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, dimethylaminomethylcarbonylation, or tetrahydropyranylation); a compound obtained by subjecting a carboxyl group in the compound (I) to an esterification or amidation (e.g., a compound obtained by subjecting a carboxyl group in the compound (I) to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Any of these compounds can be produced from the compound (I) by a method known *per se*.

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

The compound (I) may be in the form of a crystal, and the crystal form of the crystal may be single or plural. The crystal can be produced by a crystallization method known *per se*. In the present specification, the melting point means that measured using, for example, a micromelting point apparatus (Yanaco, MP-500D or Buchi, B-545) or a DSC (differential scanning calorimetry) device (SEIKO, EXSTAR6000) [heating

rate : 5°C/min] and the like.

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

The crystal of the compound (I) is superior in physicochemical properties (melting point, solubility, stability etc.) and biological properties (pharmacokinetics (absorption, distribution, metabolism, excretion), efficacy expression, etc.), and thus it is extremely useful as a medicament.

The compound (I) may be a solvate (e.g., hydrate) or a non-solvate, both of which are encompassed in the compound (I).

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

Deuterium-converted compound wherein ^{1}H has been converted to $^{2}H(D)$ are also encompassed in the compound (I).

The compound (I) or a prodrug thereof (hereinafter sometimes to be simply abbreviated as the compound of the present invention) shows low toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, drug interaction, carcinogenicity), and can be used as it is or as a pharmaceutical composition in admixture with a commonly known pharmaceutically acceptable carrier etc., as an agent for the prophylaxis or treatment of the below-mentioned various disease, an insulin sensitizer and the like, in mammals (e.g., humans, mice, rats, rabbits, dogs, cats, bovines, horses, pigs, monkeys).

Here, as the pharmacologically acceptable carrier, various organic or inorganic carrier substances conventionally used as a preparation material can be used. They are

incorporated as excipient, lubricant, binder and disintegrant for solid preparations; solvent, dissolution aids, suspending agent, isotonicity agent, buffer and soothing agent for liquid preparations and the like. Where necessary, preparation additives such as preservatives, antioxidants, coloring agents, sweetening agents and the like can be used.

As preferable examples of the excipient, lactose, sucrose, D-mannitol, D-sorbitol, starch, α-starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose, gum arabic, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, magnesium alumino metasilicate and the like can be mentioned.

As preferable examples of the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned.

As preferable examples of the binder, α-starch, saccharose, gelatin, gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like can be mentioned.

As preferable examples of the disintegrant, lactose, sucrose, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, light anhydrous silicic acid, low-substituted hydroxypropylcellulose and the like can be mentioned.

As preferable examples of the solvent, water for injection, physiological brine, Ringer solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, cottonseed oil and the like can be mentioned.

As preferable examples of the dissolution aids, polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol,

triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like can be mentioned.

As preferable examples of the suspending agent, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, polyoxyethylene hydrogenated castor oil, and the like can be mentioned.

As preferable examples of the isotonicity agent, sodium chloride, glycerin, D-mannitol, D-sorbitol, glucose and the like can be mentioned.

As preferable examples of the buffer, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned.

As preferable examples of the soothing agent, benzyl alcohol and the like can be mentioned.

As preferable examples of the preservative, p-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned.

As preferable examples of the antioxidant, sulfite, ascorbate and the like can be mentioned.

As preferable examples of the coloring agent, water-soluble food tar colors (e.g., food colors such as Food Red Nos. 2 and 3, Food Yellow Nos. 4 and 5, Food Blue Nos. 1 and 2 and the like), water insoluble lake dye (e.g., aluminum salts of the aforementioned water-soluble food tar colors), natural dyes (e.g., β-carotene, chlorophyll, red iron oxide) and the like can be mentioned.

As preferable examples of the sweetening agent, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the

like can be mentioned.

The dosage form of the aforementioned pharmaceutical composition is, for example, an oral agent such as tablets (inclusive of sugar-coated tablets, film-coated tablets, sublingual tablets and orally disintegrable tablets), capsules (inclusive of soft capsules and microcapsules), granules, powders, troches, syrups, emulsions, suspensions, films (e.g., orally disintegrable film) and the like; a parenteral agent such as injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, drip infusions), external agents (e.g., transdermal preparations, ointments), suppositories (e.g., rectal suppositories, vaginal suppositories), pellets, nasal preparations, pulmonary preparations (inhalations), ophthalmic preparations and the like, and the like. These may be administered safely via an oral or parenteral (e.g., topical, rectal, intravenous administrations etc.) route.

These preparations may be controlled-release preparations (e.g., sustained-release microcapsule) such as immediate-release preparation, sustained-release preparation and the like.

The pharmaceutical composition can be produced by a method conventionally used in the preparation technical field, such as a method described in the Japanese Pharmacopoeia and the like.

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

The compound of the present invention has a hypoglycemic action, a hypolipidemic action, an insulin sensitizing action, an insulin sensitivity enhancing action and a peroxisome growth responsive receptor (PPAR)γ (GenBank Accession No. L40904) agonist (activation) action. Here, PPARγ may form a

heterodimer receptor with any of retinoid X receptor (RXR)α (GenBank Accession No. X52773), RXRβ (GenBank Accession No. M84820) and RXRγ (GenBank Accession No. U38480).

The compound of the present invention particularly has a selective partial agonist (partial agonist) action on PPARγ.

A selective partial agonist for PPARγ has been reported to be unaccompanied by side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like, as compared to a full agonist for PPARγ (e.g., thiazolidinedione compound) (Molecular Endocrinology, vol. 17, NO. 4, page 662, 2003). Therefore, the compound of the present invention is useful as a hypoglycemic agent unaccompanied by side effects such as body weight gain, adipocyte accumulation, cardiac hypertrophy and the like, as compared to a full agonist for PPARγ.

The compound of the present invention can be used, for example, as an agent for the prophylaxis or treatment of diabetes (e.g., type-1 diabetes, type-2 diabetes, gestational diabetes, obesity diabetes); an agent for the prophylaxis or treatment of hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-HDL-emia, postprandial hyperlipidemia); insulin sensitizer; an agent for enhancing insulin sensitivity; an agent for the prophylaxis or treatment of impaired glucose tolerance [IGT (Impaired Glucose Tolerance)]; and an agent for preventing progress of impaired glucose tolerance into diabetes.

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

According to this report, diabetes is a condition showing any of a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 126 mg/dl, a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of not less than 200 mg/dl, and a non-fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 200

mg/dl. A condition not falling under the above-mentioned diabetes and different from "a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of less than 110 mg/dl or a 75 g oral glucose tolerance test (75 g OGTT) 2 h level (glucose concentration of intravenous plasma) of less than 140 mg/dl" (normal type) is called a "borderline type".

In addition, ADA (American Diabetes Association) and WHO reported new diagnostic criteria of diabetes.

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

According to the above-mentioned reports of ADA and WHO, impaired glucose tolerance is a condition showing a 75 g oral glucose tolerance test 2 h level (glucose concentration of intravenous plasma) of not less than 140 mg/dl and less than 200 mg/dl. According to the report of ADA, a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 100 mg/dl and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). On the other hand, WHO defines the IFG (Impaired Fasting Glucose) to be a condition showing a fasting blood glucose level (glucose concentration of intravenous plasma) of not less than 110 mg/dl and less than 126 mg/dl, and calls it IFG (Impaired Fasting Glycaemia).

The compound of the present invention can be also used as an agent for the prophylaxis or treatment of diabetes, borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycaemia), as determined according to the above-mentioned new diagnostic criteria. Moreover, the compound of the present invention can prevent progress of borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired

Fasting Glycaemia) into diabetes.

The compound of the present invention can also be used as an agent for the prophylaxis or treatment of, for example, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder], obesity, osteoporosis, cachexia (e.g., cancerous cachexia, tuberculous cachexia, diabetic cachexia, blood disease cachexia, endocrine disease cachexia, infectious disease cachexia or cachexia due to acquired immunodeficiency syndrome), fatty liver, hypertension, polycystic ovary syndrome, kidney disease (e.g., diabetic nephropathy, glomerular nephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage kidney disease), muscular dystrophy, myocardial infarction, angina pectoris, cerebrovascular accident (e.g., cerebral infarction, cerebral apoplexy), insulin resistance syndrome, Syndrome X, metabolic syndrome (pathology having three or more selected from hypertriglyceridemia (TG), hypoHDL cholesterolemia (HDL-C), hypertension, abdomen overweight and impaired glucose tolerance), hyperinsulinemia, hyperinsulinemia-induced sensory disorder, tumor (e.g., leukemia, breast cancer, prostate cancer, skin cancer), irritable bowel syndrome, acute or chronic diarrhea, inflammatory diseases (e.g., arteriosclerosis (e.g., atherosclerosis), chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis (inclusive of nonalcoholic steatohepatitis), pneumonia, pancreatitis, inflammatory bowel disease, ulcerative colitis, chronic obstructive pulmonary disease (COPD)), visceral obesity

syndrome, leg ulcer, sepsis, psoriasis and the like.

In addition, the compound of the present invention can also be used for ameliorating the conditions such as abdominal pain, nausea, vomiting, discomfort in the upper abdomen and the like, which are associated with peptic ulcer, acute or chronic gastritis, biliary dyskinesia, cholecystitis and the like, and the like.

The compound of the present invention can also be used as an agent for the prophylaxis or treatment of inflammatory disease involving TNF-α. Here, the inflammatory disease involving TNF-α is an inflammatory disease developed by the presence of TNF-α, which can be treated via a TNF-α inhibitory effect. As such inflammatory disease, for example, diabetic complications (e.g., retinopathy, nephropathy, neuropathy, macroangiopathy), chronic rheumatoid arthritis, spondylitis deformans, osteoarthritis, lumbago, gout, postoperative or traumatic inflammation, swelling, neuralgia, pharyngolaryngitis, cystitis, hepatitis, pneumonia, stomach mucous membrane injury (including stomach mucous membrane injury caused by aspirin) and the like can be mentioned.

The compound of the present invention has an apoptosis inhibitory action and can also be used as an agent for the prophylaxis or treatment of diseases involving promotion of apoptosis. As the disease involving promotion of apoptosis, for example, viral diseases (e.g., AIDS, fulminant hepatitis), neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's syndrome, amyotrophic lateral sclerosis, pigmentosa, cerebellar degeneration), myelodysplasia (e.g., aplastic anemia), ischemic diseases (e.g., cardiac infarction, cerebral apoplexy), hepatic diseases (e.g., alcoholic hepatitis, hepatitis B, hepatitis C), joint-diseases (e.g., osteoarthritis), atherosclerosis and the like can be mentioned.

The compound of the present invention can also be used for reduction of visceral fat, inhibition of visceral fat

accumulation, glycometabolism improvement, lipometabolism improvement, insulin resistance improvement, oxidized LDL production inhibition, lipoprotein metabolism improvement, coronary metabolism improvement, prophylaxis or treatment of cardiovascular complications, prophylaxis or treatment of heart failure complications, decrease of blood remnant, prophylaxis or treatment of anovulation, prophylaxis or treatment of hirsutism, prophylaxis or treatment of hyperandrogenemia and the like.

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

While the dose of the compound of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, for example, it is generally about 0.005 to 50 mg/kg body weight, preferably 0.01 to 2 mg/kg body weight, more preferably 0.025 to 0.5 mg/kg body weight, for oral administration to adult diabetic patients, which is desirably administered in one to three portions a day.

The compound of the present invention can be used in combination with pharmaceutical agents (hereinafter to be abbreviated as combination drug) such as therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, antiobesity agents, diuretics, chemotherapeutic agents, immunotherapeutic agents, antithrombotic agents, therapeutic agents for osteoporosis, antidementia agents, erectile dysfunction ameliorating agents, therapeutic agents for urinary incontinence or pollakiuria, therapeutic agents for dysuria and the like. These combination drugs may be low-molecular-weight compounds, high-molecular-weight proteins, polypeptides, antibodies or nucleic acids (including antisense nucleic acid, siRNA, shRNA), vaccines and the like.

The administration time of the compound of the present invention and the combination drug is not restricted, and these can be administered to an administration subject simultaneously, or may be administered at staggered times.

As the administration mode of the compound of the present invention and the combination drug, the following methods can be mentioned: (1) The compound of the present invention and the combination drug are simultaneously formulated to give a single preparation which is administered. (2) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered by the same administration route at staggered times. (4) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered simultaneously by the different administration routes. (5) The compound of the present invention and the combination drug are separately formulated to give two kinds of preparations which are administered by the different administration routes at staggered times (for example, the compound of the present invention and the combination drug are administered in this order, or in the reverse order), and the like.

The dose of the combination drug can be appropriately determined based on the dose employed clinically. The mixing ratio of the compound of the present invention and a combination drug can be appropriately determined depending on the administration subject, administration route, target disease, symptom, combination and the like. When the administration subject is human, for example, a combination drug can be used in 0.01 to 100 parts by weight relative to 1 part by weight of the compound of the present invention.

Examples of the therapeutic agents for diabetes include

insulin preparations (e.g., animal insulin preparations extracted from pancreas of bovine or swine; human insulin preparations genetically synthesized using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1), oral insulin preparation), insulin sensitizers (e.g., pioglitazone or a salt thereof (preferably hydrochloride), rosiglitazone or a salt thereof (preferably maleate), Tesaglitazar, Ragaglitazar, Muraglitazar, Edaglitazone, Metaglidasen, Naveglitazar, AMG-131, THR-0921), α-glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), biguanides (e.g., metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)), insulin secretagogues [sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or a calcium salt hydrate thereof], dipeptidyl peptidase IV inhibitors (e.g., Alogliptin or a salt thereof (preferably benzoate), Vildagliptin, Sitagliptin, Saxagliptin, T-6666, TS-021), β3 agonists (e.g., AJ-9677), GPR40 agonists, GLP-1 receptor agonists [e.g., GLP-1, GLP-1MR agent, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH_2, CJC-1131], amylin agonists (e.g., pramlintide), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists), SGLUT (sodium-glucose cotransporter) inhibitors (e.g., T-1095), 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists, glucokinase activators (e.g., Ro-28-1675), GIP (Glucose-dependent insulinotropic peptide) and the like.

Examples of the therapeutic agents for diabetic complications include aldose reductase inhibitors (e.g.,

Examples of the antiobesity agents include antiobesity agents acting on the central nervous system (e.g., dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex; MCH receptor antagonists (e.g., SB-568849; SNAP-7941; compounds described in WO01/82925 and WO01/87834); neuropeptide Y antagonists (e.g., CP-422935); cannabinoid receptor antagonists (e.g., SR-141716, SR-147778); ghrelin antagonists; 11β-hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498)), pancreatic lipase inhibitors (e.g., orlistat, cetilistat (ATL-962)), β3 agonists (e.g., AJ-9677), peptide anorexiants (e.g., leptin, CNTF (Ciliary Neurotropic Factor)), cholecystokinin agonists (e.g., lintitript, FPL-15849), feeding deterrents (e.g., P-57) and the like.

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

Examples of the chemotherapeutic agents include alkylating agents (e.g., cyclophosphamide, ifosfamide), metabolic antagonists (e.g., methotrexate, 5-fluorouracil and a derivative thereof), antitumor antibiotics (e.g., mitomycin, adriamycin), plant-derived antitumor agent (e.g., vincristine, vindesine, Taxol), cisplatin, carboplatin, etoposide and the like. Of these, Furtulon or NeoFurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

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

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

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

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

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

Examples of the erectile dysfunction ameliorating agents include apomorphine, sildenafil citrate and the like.

Examples of the therapeutic agents for urinary incontinence or pollakiuria include flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like.

Examples of the therapeutic agents for dysuria include acetylcholine esterase inhibitors (e.g., distigmine) and the like.

Examples of the combination drugs include drugs having a cachexia-ameliorating action established in animal models and clinical situations, such as cyclooxygenase inhibitors (e.g., indomethacin), progesterone derivatives (e.g., megestrol

acetate), glucosteroids (e.g., dexamethasone), metoclopramide agents, tetrahydrocannabinol agents, fat metabolism improving agents (e.g., eicosapentanoic acid), growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF-α, LIF, IL-6, oncostatin M and the like.

As the combination drugs, nerve regeneration promoting drugs (e.g., Y-128, VX853, prosaptide), antidepressants (e.g., desipramine, amitriptyline, imipramine), antiepileptics (e.g., lamotrigine), antiarrhythmic agents (e.g., mexiletine), acetylcholine receptor ligands (e.g., ABT-594), endothelin receptor antagonists (e.g., ABT-627), monoamine uptake inhibitors (e.g., tramadol), narcotic analgesics (e.g., morphine), GABA receptor agonists (e.g., gabapentin), α2 receptor agonists (e.g., clonidine), local analgesics (e.g., capsaicin), antianxiety drugs (e.g., benzothiazepines), dopamine receptor agonists (e.g., apomorphine), midazolam, ketoconazole and the like can also be mentioned.

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

The above-mentioned combination drugs may be used in a mixture of two or more kinds thereof at an appropriate ratio.

When the compound of the present invention is used in combination with a combination drug, the dose of each agent can be reduced within a safe range in consideration of the side effects thereof. Particularly, the doses of insulin sensitizers, insulin secretagogues and biguanides can be reduced from generally dose levels. Therefore, the side effects possibly caused by these agents can be safely prevented. In addition, the doses of the therapeutic agents for diabetic complications, the therapeutic agents for hyperlipidemia and the antihypertensive agents can be reduced, and as a result, the side effects possibly caused by these agents can be effectively prevented.

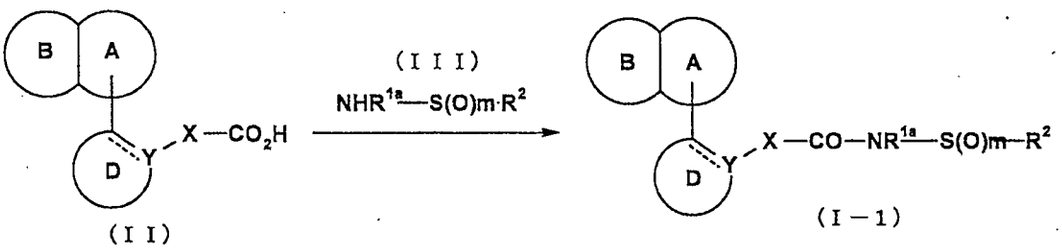
The production method of the compound of the present invention is explained in the following.

Compound (I) can be produced according to a method known per se, for example, according to the following Method A1, Method A2, Method B to Method G, Method H1, Method H2, Method I to Method N, Method O1, Method O2, Method P to Method R, Method S1, Method S2, Method AA to Method AL, Method AU and Method AW or a method analogous thereto.

In each production method, starting material compounds may be used in the form of a salt. As such salts, those similar to the salts of a compound represented by the formula (I) can be used.

Compound (I-1), which is compound (I) wherein W is $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined, is produced, for example, according to the following Method A1.

[Method A1]



wherein each symbol is as defined above.

In this method, compound (I-1) can be produced by subjecting compound (II) to a condensation reaction. This reaction is carried out according a method known per se, for example, method of directly condensing compound (II) with compound (III), or method of reacting a reactive derivative of compound (II) with compound (III), and the like. As the reactive derivative of compound (II), for example, acid halides (e.g., acid chlorides, acid bromides), imidazolide, mixed acid anhydrides (e.g., anhydrides with methyl carbonate, ethyl carbonate or isobutyl carbonate, etc.) and the like can be mentioned.

The method of directly condensing compound (II) with

compound (III) is carried out in the presence of a condensing agent, in a solvent that does not adversely influence the reaction.

As the condensing agent, a condensing agent known in the field, for example, carbodiimide condensing reagents such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide and a hydrochloride thereof and the like; phosphoric acid condensing reagents such as diethyl cyanophosphate, diphenyl azidophosphate and the like; 2-methyl-6-nitrobenzoic anhydride, N,N'-carbonyldiimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, propionitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (III) to be used is generally 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (II).

The amount of the condensing agent to be used is generally 0.1 to 10 mol, preferably 0.3 to 5 mol, per 1 mol of compound (II).

When a carbodiimide condensing reagent or 2-methyl-6-nitrobenzoic anhydride is used as a condensing agent, if necessary, the reaction efficiency can be improved by using a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide, 4-

dimethylaminopyridine etc.). When a phosphoric acid condensing reagent or 2-methyl-6-nitrobenzoic anhydride is used as a condensing agent, generally, the reaction efficiency can be improved by adding an organic amine base such as triethylamine, diisopropylethylamine and the like.

The amount of the condensation promoter and organic amine base to be used is generally 0.1 to 10 mol, preferably 0.3 to 5 mol, per 1 mol of compound (II), respectively.

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.1 to 100 hr.

When an acid halide is used as a reactive derivative of compound (II), the reaction is carried out by reacting compound (II) with a halogenating agent in a solvent that does not adversely influence the reaction, and reacting the resulting compound with compound (III) in the presence of a base.

As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; acetonitrile, ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

As the halogenating agent, for example, thionyl chloride, oxalyl chloride, phosphoryl chloride and the like can be mentioned.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

The amount of compound (III) to be used is generally 0.1

to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (II).

The amount of the halogenating agent to be used is generally 1 to 50 mol, preferably 1 to 10 mol, per 1 mol of compound (II).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.1 to 30 hr.

When a mixed acid anhydride is used as a reactive derivative of compound (II), the reaction is carried out by reacting compound (II) with a chlorocarbonate in the presence of a base, and reacting the resulting compound with compound (III).

As the chlorocarbonate, for example, methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like can be mentioned.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

The amount of compound (III) to be used is generally 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (II).

The amount of the chlorocarbonate to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.1 to 30 hr.

When an imidazolide is used as a reactive derivative of compound (II), the reaction is carried out by reacting compound (II) with N,N'-carbonyldiimidazole, and reacting the

resulting compound with compound (III) in the presence of a base.

As the base, those similar to the base used for the aforementioned reaction using an acid halide can be mentioned.

The amount of the compound (III) to be used is generally 0.1 to 10 mol, preferably 0.3 to 3 mol, per 1 mol of compound (II).

The amount of the N,N'-carbonyldiimidazole to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

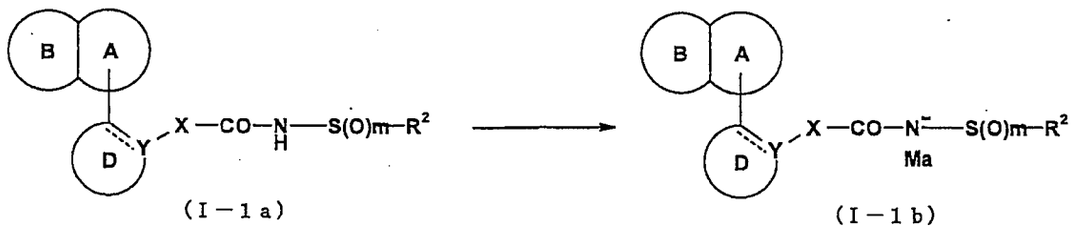
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.1 to 30 hr.

Compound (II) can be produced, for example, according to the below-mentioned Method T1 to Method T5, Step 1 of Method N or a method analogous thereto. Compound (III) can be produced according to a method known per se.

The alkali metal salt (I-1b) of compound (I-1a), which is compound (I) wherein W is $-CONR^{1a}S(O)_mR^2$ wherein R^{1a} is a hydrogen atom and the other symbols are as defined above, is produced, for example, according to the following Method A2.

[Method A2]



wherein Ma is an alkali metal, and the other symbols are as defined above.

As the alkali metal for Ma, sodium, potassium and the like can be mentioned.

In this method, compound (I-1b) can be produced by reacting compound (I-1a) with a base. This reaction is carried out in the presence of a base, in a water-containing solvent,

according to a method known per se.

As the base, for example, alkali metal carbonates such as potassium hydrogencarbonate, sodium hydrogencarbonate and the like, and the like can be mentioned.

The amount of the base to be used is generally 1 to 2 mol, per 1 mol of compound (I-1a).

As the water-containing solvent, for example, a mixed solvent of water and 1 or more solvents selected from alcohols such as methanol, ethanol and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; dimethyl sulfoxide, acetone and the like, and the like can be mentioned.

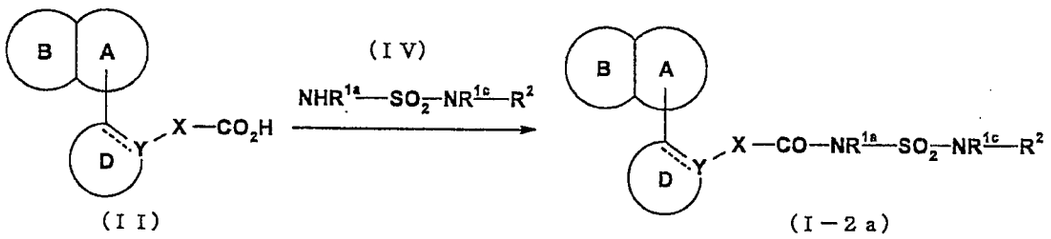
The reaction temperature is generally -30 to 150°C, preferably -10 to 50°C.

The reaction time is generally 0.1 to 20 hr.

Compound (I-1a) can be produced, for example, according to the above-mentioned Method A1, the below-mentioned Method AI, Method AJ, Method AL or a method analogous thereto.

Compound (I-2a), which is compound (I) wherein W is -$CONR^{1a}S(O)_mNR^{1c}R^2$ wherein m is 2 and the other symbols are as defined above, is produced, for example, according to the following Method B.

[Method B]



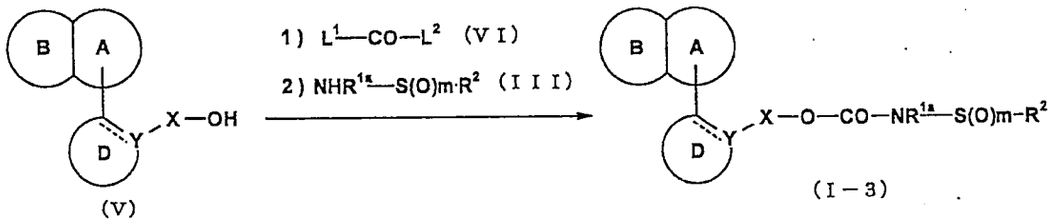
wherein each symbol is as defined above.

In this method, compound (I-2a) can be produced by reacting compound (II) with compound (IV). This reaction is carried out in the same manner as in the condensation reaction described in the aforementioned Method A1.

Compound (IV) can be produced, for example, according to the below-mentioned Method AT or a method analogous thereto.

Compound (I-3), which is compound (I) wherein W is -$OCONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above, is produced, for example, according to the following Method C or Method D.

[Method C]



wherein L^1 and L^2 are independently a leaving group, and the other symbols are as defined above.

As the leaving group L^1 or L^2, for example, a hydroxy group, a halogen atom, a imidazolyl group, a succinimidooxy group, $-OSO_2R^3$ wherein R^3 is a C_{1-4} alkyl group (preferably methyl), a C_{6-10} aryl group optionally substituted by C_{1-4} alkyl group(s) (preferably tolyl), and the like can be mentioned.

As compound (VI), for example, N,N'-carbonyldiimidazole, diphosgene, triphosgene and the like can be mentioned.

In this method, compound (I-3) can be produced from compound (V). This reaction is carried out according to a method known per se, for example, by reacting compound (V) with compound (VI) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 10 hr, and reacting the obtained compound with compound (III) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 50 hr.

This reaction may be carried out in the presence of 1 to 5 mol of a base, per 1 mol of compound (V).

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned. These

bases may be used in a mixture at an appropriate ratio.

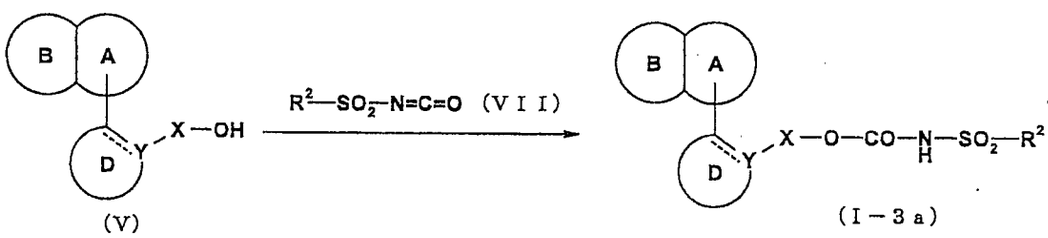
As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (VI) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

The amount of compound (III) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

Compound (V) can be produced, for example, according to the below-mentioned Method U1 or Method U2 or a method analogous thereto. Compound (VI) can be produced according to a method known per se.

[Method D]



wherein each symbol is as defined above.

In this method, compound (I-3a), which is compound (I-3) wherein R^{1a} is a hydrogen atom and m is 2, can be produced by reacting compound (V) with compound (VII). This reaction is carried out in a solvent that does not adversely influence the reaction.

This reaction may be carried out in the presence of 1 to 5 mol of a base, per 1 mol of compound (V).

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine,

4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned. These bases may be used in a mixture at an appropriate ratio.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (VII) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

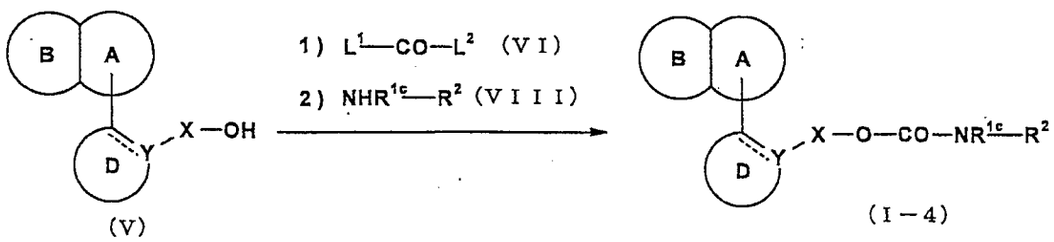
The reaction temperature is generally -30°C to 100°C.

The reaction time is generally 0.5 to 30 hr.

Compound (VII) can be produced according to a method known per se.

Compound (I-4), which is compound (I) wherein W is $-OCONR^{1c}R^2$ wherein each symbol is as defined above, is produced, for example, according to the following Method E or Method F.

[Method E]



wherein each symbol is as defined above.

In this method, compound (I-4) can be produced from compound (V). This reaction is carried out according to a method known per se, for example, by reacting compound (V) with compound (VI) in a solvent that does not adversely influence the reaction at -10°C to 100°C for 0.5 to 10 hr, and reacting the obtained compound with compound (VIII) in a

solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 30 hr.

This reaction may be carried out in the presence of 1 to 5 mol of a base, per 1 mol of compound (V).

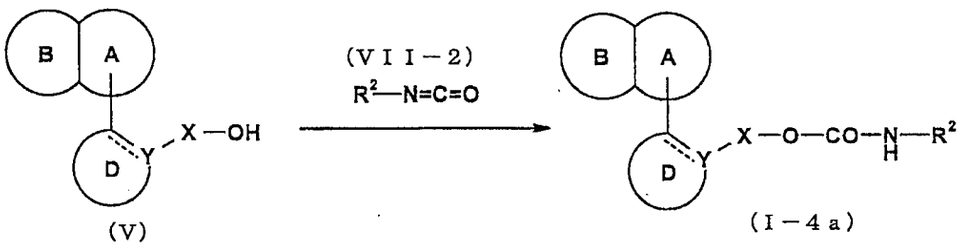
As the base and solvent that does not adversely influence the reaction, those exemplified in the aforementioned Method C can be mentioned.

The amount of compound (VI) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

The amount of compound (VIII) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

Compound (VIII) can be produced according to a method known per se.

[Method F]



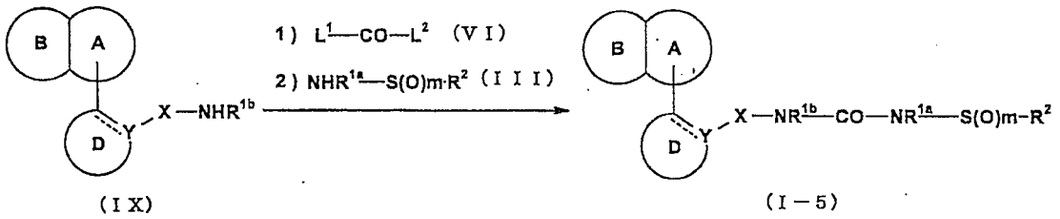
wherein each symbol is as defined above.

In this method, compound (I-4a), which is compound (I-4) wherein R^{1c} is a hydrogen atom, can be produced by reacting compound (V) with compound (VII-2). This reaction is carried out in the same manner as in the reaction described in the aforementioned Method D.

Compound (VII-2) can be produced according to a method known per se.

Compound (I-5), which is compound (I) wherein W is -$NR^{1b}CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above, is produced, for example, according to the following Method G, Method H1 or Method H2.

[Method G]



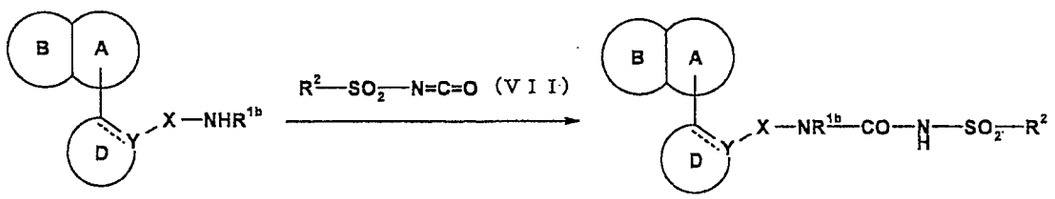
(IX) (I-5)

wherein each symbol is as defined above.

In this method, compound (I-5) can be produced by reacting compound (IX) with compound (VI) and (III) successively. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method C.

Compound (IX) can be produced, for example, according to the below-mentioned Method V1 or Method V2 or a method analogous thereto.

[Method H1]

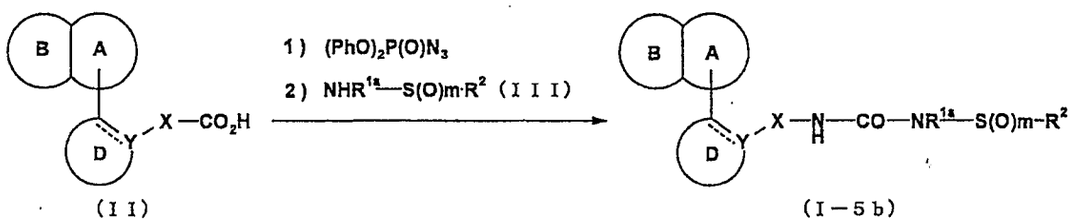


(IX) (I-5a)

wherein each symbol is as defined above.

In this method, compound (I-5a), which is compound (I-5) wherein R^{1a} is a hydrogen atom and m is 2, can be produced by reacting compound (IX) with compound (VII). This reaction is carried out in the same manner as in the reaction described in the aforementioned Method D.

[Method H2]



(II) (I-5b)

wherein each symbol is as defined above.

In this method, compound (I-5b), which is compound (I-5) wherein R^{1b} is a hydrogen atom, can be produced from compound (II). This reaction is carried out by reacting compound (II)

with diphenyl azidophosphate in the presence of a base, in a solvent that does not adversely influence the reaction, at -10°C to 40°C for 0.5 to 10 hr, and reacting an isocyanate generated by thermal decomposition of the obtained acylazide with compound (III) in the presence of a base, in a solvent that does not adversely influence the reaction, at 60°C to 150°C for 0.5 to 30 hr.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the diphenyl azidophosphate to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

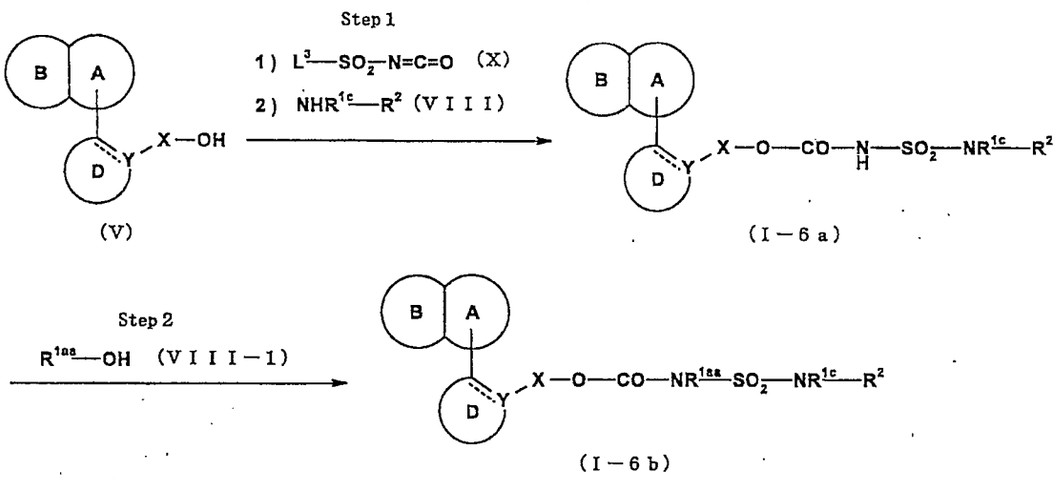
The amount of the base to be used is generally 1 to 10 mol, per 1 mol of compound (II).

The amount of compound (III) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (II).

Compound (I-6a), which is compound (I) wherein W is $-OCONR^{1a}S(O)_mNR^{1c}R^2$ wherein R^{1a} is a hydrogen atom, m is 2 and the other symbols are as defined above, and compound (I-6b), which is compound (I) wherein W is $-OCONR^{1a}S(O)_mNR^{1c}R^2$ wherein R^{1a} is a C_{1-6} alkyl group, m is 2 and the other symbols are as defined above, are produced, for example, according to the following

Method I.

[Method I]



wherein L^3 is a leaving group, R^{1aa} is a C_{1-6} alkyl group, and the other symbols are as defined above.

As the leaving group for L^3, those exemplified for the aforementioned L^1 or L^2 can be mentioned. Of these, it is preferably a halogen atom, particularly preferably a chlorine atom.

[Step 1]

In this step, compound (I-6a) can be produced from compound (V). This reaction is carried out according to a method known per se, for example, by reacting compound (V) with compound (X) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.1 to 10 hr, and reacting the obtained compound with compound (VIII) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 50 hr.

This reaction may be carried out in the presence of 1 to 10 mol of a base, per 1 mol of compound (V).

As specific examples of compound (X), chlorosulfonyl isocyanate and the like can be mentioned.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such

as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, propionitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (X) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

The amount of compound (VIII) to be used is generally 1 to 30 mol, preferably 1 to 10 mol, per 1 mol of compound (V).

[Step 2]

In this step, compound (I-6b) can be produced by reacting compound (I-6a) with compound (VIII-1). This reaction is carried out according to a method known per se, for example, the method described in Synthesis, page 1, (1981) or a method analogous thereto. That is, this reaction is generally carried out in the presence of an organic phosphorus compound and an electrophilic agent, in a solvent that does not adversely influence the reaction.

As the organic phosphorus compound, for example, triphenylphosphine, tributylphosphine and the like can be mentioned.

As the electrophilic agent, for example, diethyl azodicarboxylate, diisopropyl azodicarboxylate, azodicarbonyldipiperizine and the like can be mentioned.

The amount of the organic phosphorus compound and electrophilic agent to be used is generally 1 to 20 mol, per 1 mol of compound (I-6a), respectively.

The amount of compound (VIII-1) to be used is generally 1 to 10 mol, per 1 mol of compound (I-6a).

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

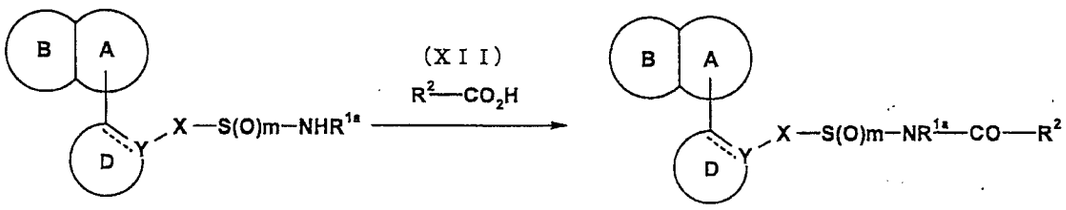
The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 50 hr.

Compound (X) and compound (VIII-1) can be produced according to a method known per se.

Compound (I-7a), which is compound (I) wherein W is $-S(O)_mNR^{1a}CO_nR^2$ wherein n is 1 and the other symbols are as defined above, is produced, for example, according to the following Method J.

[Method J]



(XI) (I-7a)

wherein each symbol is as defined above.

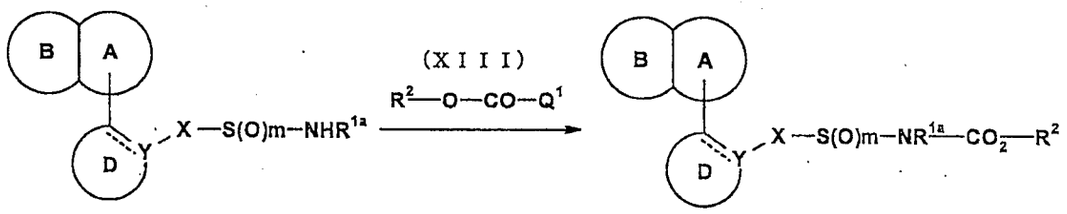
In this method, compound (I-7a) can be produced by reacting compound (XI) with compound (XII). This reaction is carried out in the same manner as the condensation reaction in described in the aforementioned Method A1.

Compound (XI) can be produced, for example, according to the below-mentioned Method W or a method analogous thereto. Compound (XII) can be produced according to a method known per se.

Compound (I-7b), which is compound (I) wherein W is $-S(O)_mNR^{1a}CO_nR^2$ wherein n is 2 and the other symbols are as

defined above, is produced, for example, according to the following Method K or the below-mentioned Method AU.

[Method K]



(XI) (I-7b)

wherein Q^1 is a halogen atom, and the other symbols are as defined above.

The halogen atom for Q^1 is preferably a chlorine atom.

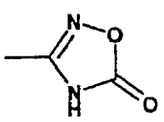
In this method, compound (I-7b) can be produced by reacting compound (XI) with compound (XIII).

The amount of compound (XIII) to be used is generally 0.5 to 200 mol, per 1 mol of compound (XI).

This reaction is carried out in the same manner as in the condensation reaction in described in the aforementioned Method A1.

Compound (XIII) can be produced according to a method known per se.

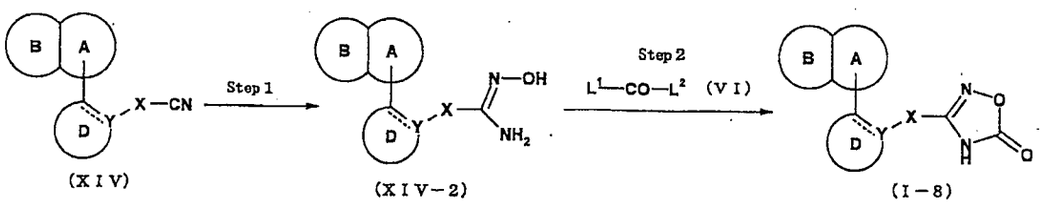
Compound (I-8), which is compound (I) wherein W is



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is produced, for example, according to the following Method L.

[Method L]



(XIV) (XIV-2) (I-8)

wherein each symbol is as defined above.

[Step 1]

In this step, compound (XIV-2) can be produced by reacting compound (XIV) with hydroxylamine (or hydroxylammonium chloride). This reaction is carried out in

the presence of a base, in a solvent that does not adversely influence the reaction.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and the like; aromatic hydrocarbons such as benzene, toluene, nitrobenzene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethylsulfoxide and the like; ketones such as acetone and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the hydroxylamine to be used is generally 1 to 10 mol, per 1 mol of compound (XIV).

The amount of the base to be used is generally 1 to 10 mol, per 1 mol of compound (XIV).

The reaction temperature is generally -30 to 180°C, preferably -10 to 120°C.

The reaction time is generally 0.5 to 30 hr.

Compound (XIV) can be produced, for example, according to the below-mentioned Method X or a method analogous thereto.

[Step 2]

In this step, compound (I-8) can be produced by reacting compound (XIV-2) with compound (VI). This reaction is carried out in the presence of a base, in a solvent that does not adversely influence the reaction.

As compound (VI), for example, N,N'-carbonyldiimidazole, diphosgene, triphosgene and the like can be mentioned.

The amount of compound (VI) to be used is generally 1 to 50 mol, preferably 1 to 5 mol, per 1 mol of compound (XIV-2).

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like, and the like can be mentioned.

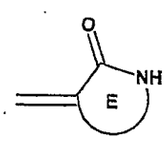
The amount of the base to be used is generally 1 to 50 mol, preferably 1 to 10 mol, per 1 mol of compound (XIV-2).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; ketones such as acetone and the like; acetonitrile and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

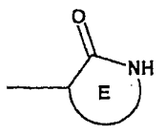
The reaction time is generally 0.5 to 30 hr.

Compound (I-9a), which is compound (I) wherein W is a group represented by the formula:



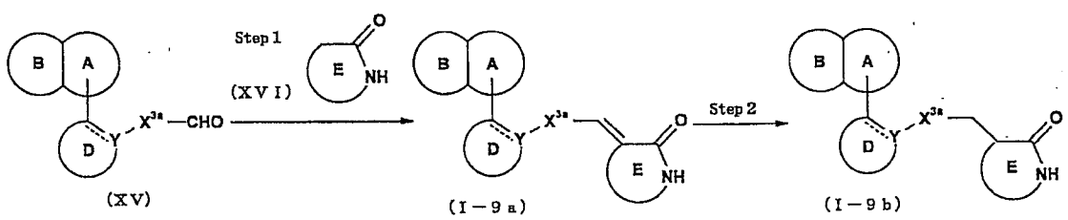
wherein ring E is a 5- or 6-membered heterocycle containing C-CO-NH, which is optionally substituted, and X is $-X^{3a}-CH=$

wherein X^{3a} is as defined above, and compound (I-9b), which is compound (I) wherein W is a group represented by the formula:



wherein ring E is a 5- or 6-membered heterocycle containing C-CO-NH, which is optionally substituted, and X is $-X^{3a}-CH_2-$ wherein X^{3a} is as defined above, are produced, for example, according to the following Method M.

[Method M]



wherein each symbol is as defined above.

As the "5- or 6-membered heterocycle containing C-CO-NH" of the "5- or 6-membered heterocycle containing C-CO-NH, which is optionally substituted" for ring E, rings containing C-CO-NH as a ring-constituting member (e.g., 2,5-dioxopyrroline, 2-oxopyrrolidine, 2,5-dioxopyrrolidine, 2,4-dioxoimidazolidine, 2,6-dioxopiperidine, 2,4-dioxothiazolidine, 1,1-dioxido-3-oxoisothiazolidine, 2,6-dioxohexahydropyrimidine, 1,1-dioxido-3-oxo-1,2-thiazinane), from among rings corresponding to the "5- or 6-membered heterocyclic group containing NH" of the aforementioned "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W, can be mentioned. As the substituents of the "5- or 6-membered heterocycle containing C-CO-NH, which is optionally substituted" for ring E, those similar to the substituents of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W can be mentioned.

[Step 1]

In this step, compound (I-9a) can be produced by reacting compound (XV) with compound (XVI). This reaction is carried

out in the presence of a base, in a solvent that does not adversely influence the reaction.

The amount of compound (XVI) to be used is generally 1 to 10 mol, per 1 mol of compound (XV).

As the base, for example, amines such as piperidine, pyrrolidine, morpholine, pyridine, diethylamine and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide and the like; alkali metal hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like, and the like can be mentioned.

The amount of the base to be used is generally 0.01 to 10 mol, preferably 0.05 to 5 mol, per 1 mol of compound (XV).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; acetic acid and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 150°C, preferably 20 to 120°C.

The reaction time is generally 0.5 to 50 hr.

Compound (XV) can be produced, for example, according to the below-mentioned Method Z1 - Method Z3, Step 2 of Method T4, Method AO, Method AQ, Method AV or a method analogous thereto. Compound (XVI) can be produced according to a method known per se.

[Step 2]

In this step, compound (I-9b) can be produced by subjecting compound (I-9a) to a hydrogenation reaction. This reaction can be carried out, for example, in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, palladium black, platinum-palladium, Raney-nickel, Raney-cobalt and the like and a hydrogen source, in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 to 1000 mol, preferably 0.01 to 100 mol, per 1 mol of compound (I-9a).

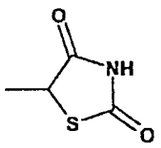
As the hydrogen source, for example, hydrogen gas, formic acid, an amine salt of formic acid, phosphinate, hydrazine and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; ethyl acetate, acetic acid and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 10 to 80°C.

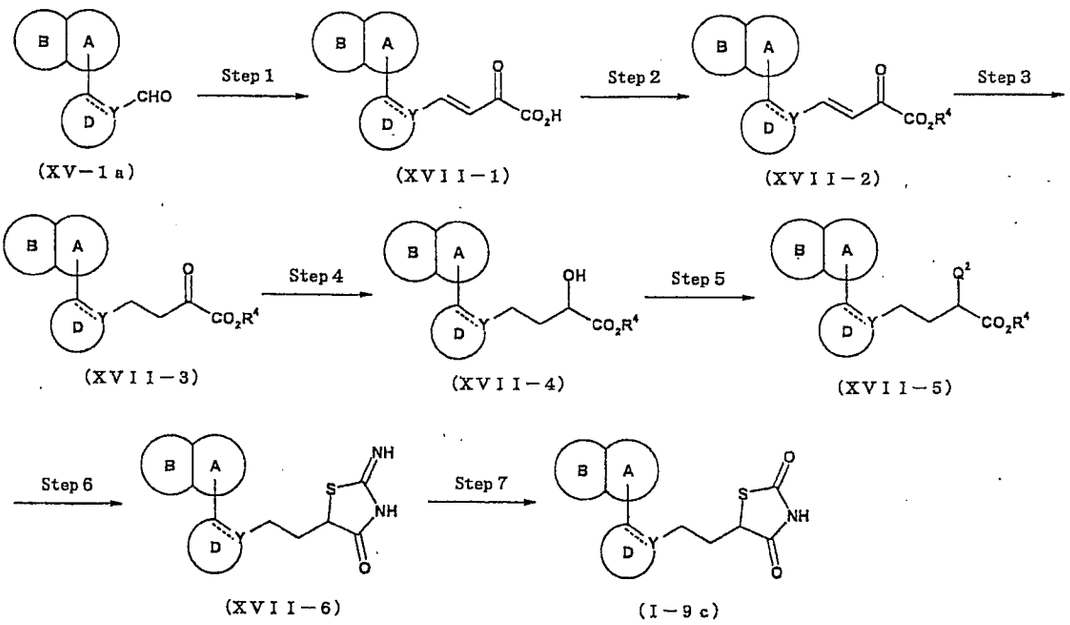
The reaction time is generally 0.5 to 200 hr.

Compound (I-9c), which is compound (I) wherein W is



and X is $-CH_2CH_2-$, is produced, for example, according to the following Method N.

[Method N]



wherein R^4 is a C_{1-6} alkyl group, Q^2 is a halogen atom, and the other symbols are as defined above.

The "C_{1-6} alkyl group" for R^4 is preferably methyl, ethyl, tert-butyl or the like. "

The "halogen atom" for Q^2 is preferably a chlorine atom or a bromine atom.

[Step 1]

In this step, compound (XVII-1) can be produced by reacting compound (XV-1a) with pyruvic acid. This reaction is carried out in the presence of a base, in a water-containing solvent.

The amount of the pyruvic acid to be used is generally 1 to 10 mol, per 1 mol of compound (XV-1a).

As the base, for example, amines such as piperidine, pyrrolidine, morpholine, pyridine, diethylamine and the like;

alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide and the like; alkali metal hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like, and the like can be mentioned.

The amount of the base to be used is generally 0.01 to 10 mol, preferably 0.05 to 5 mol, per 1 mol of compound (XV-1a).

As the water-containing solvent, for example, a mixed solvent of 1 or more solvents selected from alcohols (e.g., methanol, ethanol and the like) and the like and water, and the like can be mentioned.

The reaction temperature is generally 0 to 150°C, preferably 20 to 120°C.

The reaction time is generally 0.5 to 50 hr.

Compound (XV-1a) can be produced, for example, according to the below-mentioned Method Z1, Method Z2, Method AO, Method AQ, Method AV or a method analogous thereto.

[Step 2]

In this step, compound (XVII-2) can be produced by subjecting compound (XVII-1) to an esterification reaction. This reaction is carried out according to a method known per se, for example, by reacting compound (XVII-1) or a reactive derivative of compound (XVII-1) with an alcohol. As the reactive derivative of compound (XVII-1), for example, acid halides (e.g., acid chlorides, acid bromides), imidazolide, mixed acid anhydrides (e.g., anhydrides with methyl carbonate, ethyl carbonate or isobutyl carbonate, etc.) and the like can be mentioned.

The reaction of compound (XVII-1) with an alcohol is carried out in the presence of an acid.

As the alcohol, methanol, ethanol and the like can be mentioned.

The large excess amount of the alcohol is used as a reaction solvent.

As the acid, mineral acids such as hydrochloric acid,

sulfuric acid and the like, and the like can be mentioned.

The amount of the acid to be used is generally 0.05 to 1000 mol, per 1 mol of compound (XVII-1).

The reaction temperature is generally 0 to 200°C, preferably 20 to 120°C.

The reaction time is generally 0.1 to 200 hr.

The method using a reactive derivative of compound (XVII-1) is carried out in the same manner as in the method using a reactive derivative of compound (II) in the aforementioned Method A1 or a method analogous thereto.

[Step 3]

In this step, compound (XVII-3) can be produced by subjecting compound (XVII-2) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

[Step 4]

In this method, compound (XVII-4) can be produced by subjecting compound (XVII-3) to a reduction reaction. This reaction is generally carried out in the presence of a reducing agent, in a solvent that does not adversely influence the reaction.

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

The amount of the reducing agent to be used is generally 0.5 to 20 mol, per 1 mol of compound (XVII-3).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl

ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 100 hr.

[Step 5]

In this step, compound (XVII-5) can be produced by subjecting compound (XVII-4) to halogenation. This reaction is carried out in the presence of a halogenating agent, in a solvent that does not adversely influence the reaction.

As the halogenating agent, for example, thionyl chloride, oxalyl chloride, phosphoryl chloride, phosphorus trichloride, phosphorus tribromide and the like can be mentioned.

The amount of the halogenating agent to be used is generally 1 to 20 mol, per 1 mol of compound (XVII-4).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 50 hr.

[Step 6]

In this step, compound (XVII-6) can be produced by reacting compound (XVII-5) with thiourea. This reaction is carried out in the presence of sodium acetate or potassium acetate, in a solvent that does not adversely influence the reaction. In addition, the reaction efficiency can be improved by adding 1 to 1.5 mol of sodium iodide or potassium iodide, per 1 mol of compound (XVII-5).

The amount of the thiourea to be used is generally 1 to 10 mol, per 1 mol of compound (XVII-5).

The amount of the sodium acetate or potassium acetate to be used is generally 1 to 10 mol, per 1 mol of compound (XVII-5).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide, sulforan and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 180°C, preferably 50 to 150°C.

The reaction time is generally 0.5 to 100 hr.

[Step 7]

In this step, compound (I-9c) can be produced by subjecting compound (XVII-6) to hydrolysis. This reaction is carried out in the presence of an acid, in a solvent that does not adversely influence the reaction.

As the acid, mineral acids such as hydrochloric acid, sulfuric acid and the like, and the like can be mentioned.

The amount of the acid to be used is generally 0.01 to 1000 mol, per 1 mol of compound (XVII-6).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol,

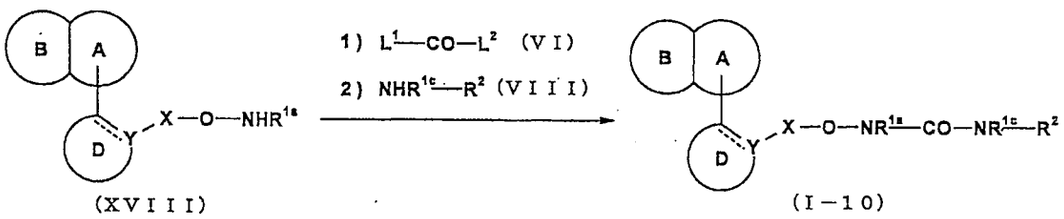
propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide, sulforan and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 20 to 150°C, preferably 50 to 120°C.

The reaction time is generally 0.5 to 50 hr.

Compound (I-10), which is compound (I) wherein W is $-ONR^{1a}CONR^{1c}R^2$ wherein each symbol is as defined above, is produced, for example, according to the following Method O1 or Method O2.

[Method O1]



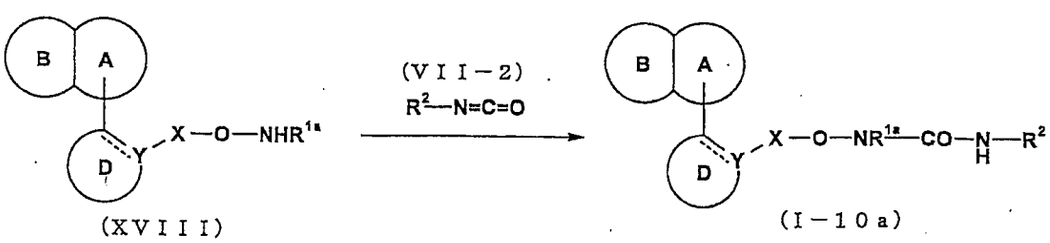
(XVIII) (I-10)

wherein each symbol is as defined above.

In this method, compound (I-10) can be produced by reacting compound (XVIII) with compound (VI) and (VIII) successively. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method E.

Compound (XVIII) can be produced, for example, according to the below-mentioned Method Y or a method analogous thereto.

[Method O2]



(XVIII) (I-10a)

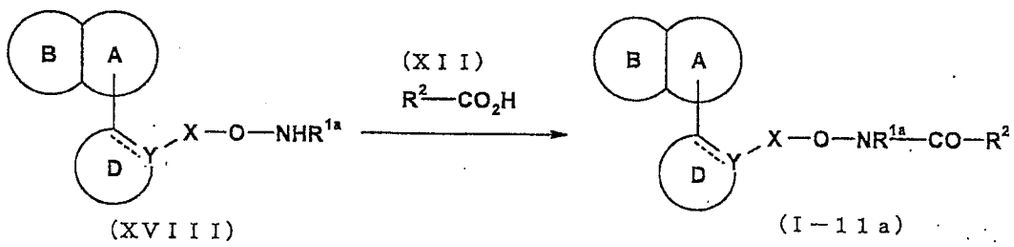
wherein each symbol is as defined above.

In this method, compound (I-10a), which is compound (I-10) wherein R^{1c} is a hydrogen atom, can be produced by reacting

compound (XVIII) with compound (VII-2). This reaction is carried out in the same manner as in the reaction described in the aforementioned Method D.

Compound (I-11a), which is compound (I) wherein W is -$ONR^{1a}CO_nR^2$ wherein n is 1 and the other symbols are as defined above, is produced, for example, according to the following Method P.

[Method P]



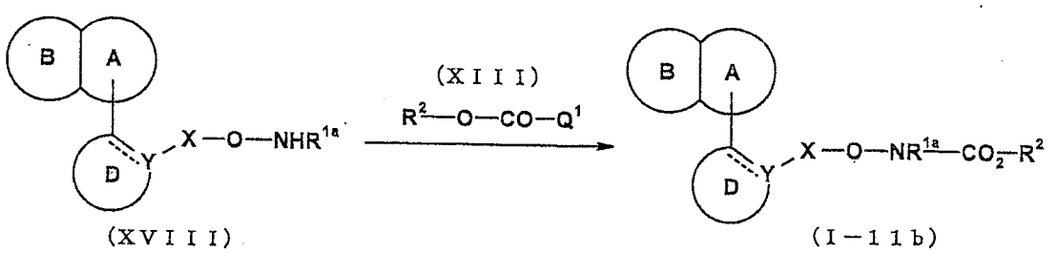
(XVIII) (I-11a)

wherein each symbol is as defined above.

In this method, compound (I-11a) can be produced by reacting compound (XVIII) with compound (XII). This reaction is carried out in the same manner as in the aforementioned Method A1.

Compound (I-11b), which is compound (I) wherein W is -$ONR^{1a}CO_nR^2$ wherein n is 2 and the other symbols are as defined above, is produced, for example, according to the following Method Q.

[Method Q]



(XVIII) (I-11b)

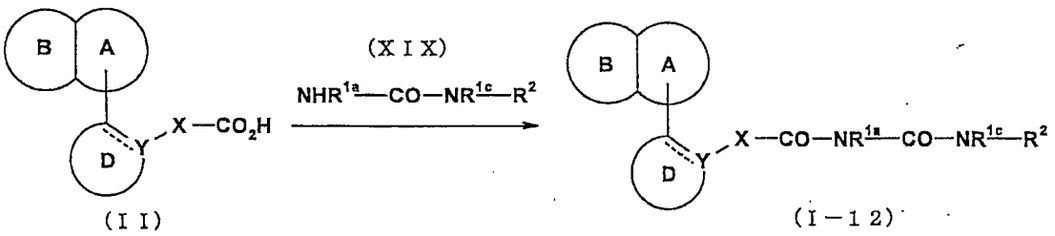
wherein each symbol is as defined above.

In this method, compound (I-11b) can be produced by reacting compound (XVIII) with compound (XIII). This reaction is carried out in the same manner as in the aforementioned Method A1.

Compound (I-12), which is compound (I) wherein W is -$CONR^{1a}CONR^{1c}R^2$ wherein each symbol is as defined above, is

produced, for example, according to the following Method R.

[Method R]



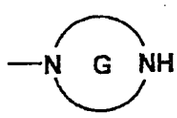
(II) (I-12)

wherein each symbol is as defined above.

In this method, compound (I-12) can be produced by reacting compound (II) with compound (XIX). This reaction is carried out in the same manner as in the aforementioned Method A1.

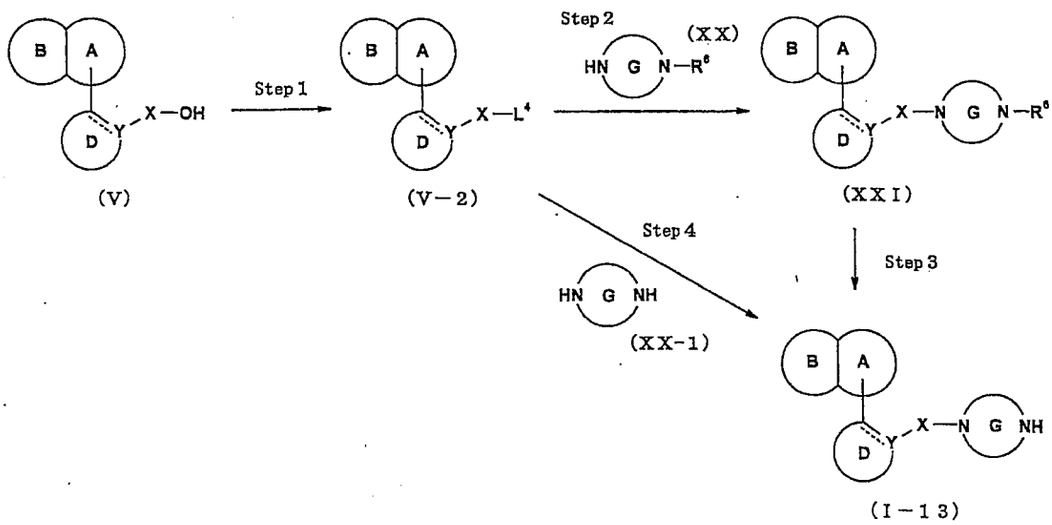
Compound (XIX) can be produced according to a method known per se.

Compound (I-13), which is compound (I) wherein W is a group represented by



wherein ring G is a 5- or 6-membered heterocycle containing NH and further containing, besides the NH, at least one nitrogen atom, which is optionally substituted, is produced, for example, according to the following Method S1.

[Method S1]



wherein L^4 is a leaving group, R^6 is a nitrogen atom-protecting group, and the other symbols are as defined above.

As the "5- or 6-membered heterocycle containing NH and further containing, besides the NH, at least one nitrogen atom" of the "5- or 6-membered heterocycle containing NH and further containing, besides the NH, at least one nitrogen atom, which is optionally substituted" for ring G, rings further containing, as a ring-constituting member besides "NH", at least one nitrogen atom (e.g., imidazolidine, 2-oxoimidazolidine, 2,4-dioxoimidazolidine, tetrahydropyrimidine, 2,6-dioxohexahydropyrimidine, 1,1-dioxido-3-oxothiadiazolidine, 2-oxopiperazine), from among rings corresponding to the "5- or 6-membered heterocyclic group containing NH" of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W, can be mentioned. As the substituents for the ring G, those similar to the substituents of the "5- or 6-membered heterocyclic group containing NH, which is optionally substituted" for W, can be mentioned.

As the "leaving group" for L^4, a halogen atom, $-OSO_2R^3$ wherein R^3 is as defined above, and the like can be mentioned.

As the "nitrogen atom-protecting group" for R^6, a C_{1-6} alkoxy-carbonyl (e.g., tert-butoxycarbonyl), a C_{7-13} aralkyloxy-carbonyl (e.g., benzyloxycarbonyl), tert-butyl, benzyl, a substituted benzyl (e.g., 4-methoxybenzyl, 2,4-dimethoxybenzyl) and the like can be mentioned.

[Step 1]

In this step, compound (V-2) can be produced by subjecting compound (V) to sulfonylation or halogenation.

The sulfonylation of compound (V) is carried out using a sulfonyl halide in the presence of a base, in a solvent that does not adversely influence the reaction.

The sulfonyl halide is preferably methanesulfonyl chloride, p-toluenesulfonyl chloride or the like.

As the base, for example, alkali metal salts such as

potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; acetonitrile and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the sulfonyl halide to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

The amount of the base to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V).

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 50 hr.

The halogenation of compound (V) is carried out in the same manner as in the reaction described in the aforementioned Step 5 of Method N.

[Step 2]

In this step, compound (XXI) can be produced by reacting compound (V-2) with compound (XX). This reaction is generally carried out in the presence of a base, in a solvent that does not adversely influence the reaction.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (XX) to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (V-2).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (V-2).

The reaction temperature is generally -30 to 180°C, preferably -10 to 120°C.

The reaction time is generally 0.5 to 100 hr.

Compound (XX) can be produced according to a method known per se.

[Step 3]

In this step, compound (I-13) can be produced by subjecting compound (XXI) to deprotection.

When R^6 is tert-butoxycarbonyl, tert-butyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, the reaction is carried out in the presence of an acid, in a solvent that does not adversely influence.

As the acid, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid and the like; solutions prepared by dissolving hydrogen chloride in methanol, ethyl acetate and the like, such as hydrogen chloride-methanol solution, hydrogen chloride-ethyl acetate solution and the like can be mentioned.

As the solvent that does not adversely influence the reaction, ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the acid to be used is generally 0.01 to 1000 mol, preferably 0.1 to 100 mol, per 1 mol of compound (XXI).

The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 30 hr.

When R^6 is benzyloxycarbonyl or benzyl, for example, the reaction can be carried out in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, palladium black, platinum-palladium, Raney-nickel, Raney-cobalt and the like and a hydrogen source, in a solvent that does not adversely influence.

The amount of the metal catalyst to be used is generally 0.001 to 1000 mol, preferably 0.01 to 100 mol, per 1 mol of compound (XXI).

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

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol,

tert-butyl alcohol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; ethyl acetate, acetic acid and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 120°C, preferably 10 to 80°C.

The reaction time is generally 0.5 to 100 hr.

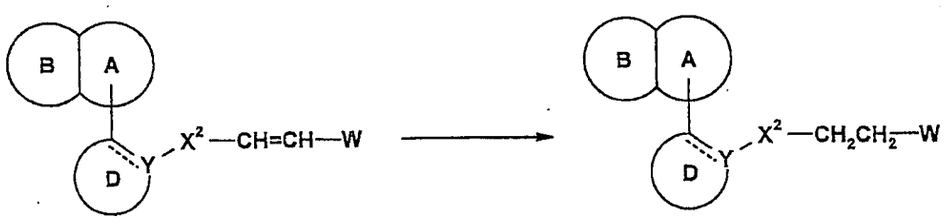
[Step 4]

In this step, compound (I-13) can be produced by reacting compound (V-2) with compound (XX-1). This reaction is carried out in the same manner as in the reaction described in the aforementioned Step 2 of this method.

Compound (XX-1) can be produced according to a method known per se.

Compound (I-14b), which is compound (I) wherein X is $-X^2-CH_2CH_2-$ wherein X^2 is a bond or a straight chain C_{1-2} alkylene, is produced, for example, according to the following Method S2.

[Method S2]



(I-14a) (I-14b)

wherein each symbol is as defined above.

In this method, compound (I-14b) can be produced by subjecting compound (I-14a) to a hydrogenation reaction. This

reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

Compound (I-14a) can be produced, for example, according to the aforementioned Method A1, Method B, Method J, Method K, Method L, Method R, the below-mentioned Method AA to Method AC, Method AF to Method AL or Method AU, or a method analogous thereto.

Compound (II) used in the aforementioned Method A1, Method B, Method H2 and Method R as a starting material compound is produced, for example, according to the following Method T1 - Method T5.

[Method T1]



(II-2) (II)

wherein each symbol is as defined above.

In this method, compound (II) can be produced by subjecting compound (II-2) to hydrolysis. This reaction is carried out in the presence of an acid or a base, in a water-containing solvent, according to a method known per se.

As the acid, for example, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like; solutions prepared by dissolving hydrogen chloride in methanol, ethyl acetate and the like, such as hydrogen chloride-methanol solution, hydrogen chloride-ethyl acetate solution and the like; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, acetic acid and the like, and the like can be mentioned.

As the base, for example, alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide and the like; alkali metal hydroxides such as potassium hydroxide, sodium

hydroxide, lithium hydroxide and the like, and the like can be mentioned.

The amount of the acid or base to be used is generally an excess amount, per 1 mol of compound (II-2). The amount of the acid to be used is preferably 2 to 100 mol, per 1 mol of compound (II-2). The amount of the base to be used is 1 to 10 mol, per 1 mol of compound (II-2).

As the water-containing solvent, for example, a mixed solvent 1 or more solvents selected from alcohols such as methanol, ethanol and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; dimethyl sulfoxide, acetone and the like, and water, and the like can be mentioned.

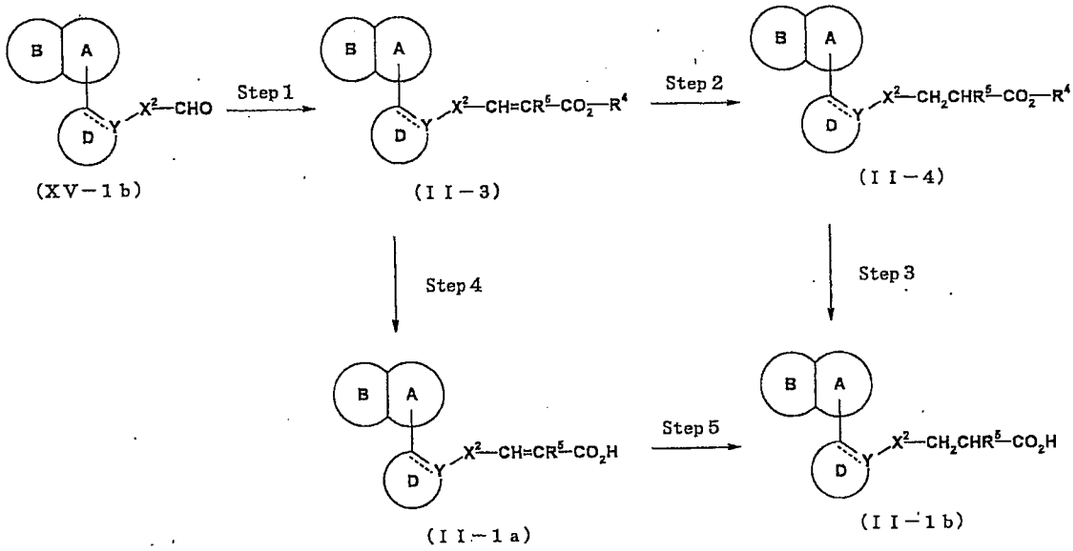
The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 50 hr.

Compound (II-2) can be produced, for example, according to Step 3 to Step 5 of the aforementioned Method N, Step 1 or Step 2 of the below-mentioned Method T2, Method AM, Method AN, Method AP or a method analogous thereto.

Compound (II-1a), which is compound (II) wherein X is -X^2-CH=CR^5- wherein R^5 is as defined below, and X^2 is as defined above, and compound (II-1b), which is compound (II) wherein X is -X^2-CH_2CHR^5- wherein R^5 is as defined below, and X^2 is as defined above, are produced, for example, according to the following Method T2.

[Method T2]



wherein R^5 is a C_{1-3} alkyl group, and the other symbols are as defined above.

[Step 1]

In this step, compound (II-3) can be produced by subjecting compound (XV-1b) to a carbon addition reaction. This reaction is generally carried out using an organic phosphorus reagent, in the presence of a base, in a solvent that does not adversely influence the reaction.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the organic phosphorus reagent, for example, ethyl (diethoxyphosphoryl)acetate, ethyl 2-(diethoxyphosphoryl)propanoate, tert-butyl (diethoxyphosphoryl)acetate and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene,

toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; alcohols such as methanol, ethanol and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (XV-1b).

The amount of the organic phosphorus reagent to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (XV-1b).

The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 30 hr.

Compound (XV-1b) can be produced, for example, according to the below-mentioned Step 2 of Method T4, Method Z1 to Method Z3, Method AO, Method AQ, Method AV or a method analogous thereto.

[Step 2]

In this step, compound (II-4) can be produced by subjecting compound (II-3) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

[Step 3]

In this step, compound (II-1b) can be produced by subjecting compound (II-4) to hydrolysis. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method T1.

[Step 4]

In this step, compound (II-1a) can be produced by

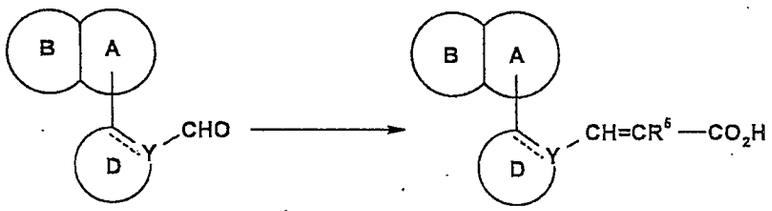
subjecting compound (II-3) to hydrolysis. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method T1.

[Step 5]

In this step, compound (II-1b) can be produced by subjecting compound (II-1a) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

Compound (II-1c), which is compound (II) wherein X is -$CH=CR^{5a}$- wherein R^{5a} is a hydrogen atom or a C_{1-3} alkyl group, is produced, for example, according to the following Method T3.

[Method T3]



(XV−1a) (II−1c)

wherein each symbol is as defined above.

In this method, compound (II-1c) can be produced by subjecting compound (XV-1a) to carbon addition reaction. This reaction is generally carried out using malonic acid or a substituted malonic acid, in the presence of a base, in a solvent that does not adversely influence the reaction.

As the substituted malonic acid, methyl malonate, ethyl malonate, propyl malonate and the like can be mentioned.

The amount of the malonic acid or substituted malonic acid to be used is generally 1 to 50 mol, preferably 1 to 20 mol, per 1 mol of compound (XV-1a).

As the base, for example, amines such as piperidine, pyrrolidine, morpholine, pyridine, diethylamine and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide and the like; alkali metal hydroxides such as potassium hydroxide, sodium hydroxide, lithium hydroxide and

the like, and the like can be mentioned.

The amount of the base to be used is generally 0.1 to 50 mol, preferably 1 to 20 mol, per 1 mol of compound (XV-1a).

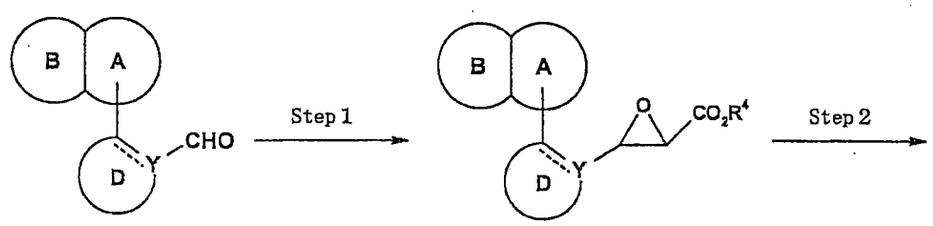
As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butyl alcohol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; acetic acid, pyridine and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 200°C, preferably 20 to 150°C.

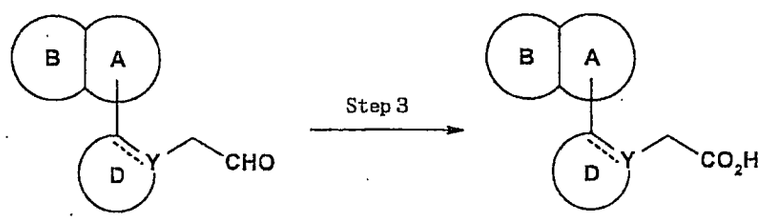
The reaction time is generally 0.5 to 100 hr.

Compound (II-1d), which is compound (II) wherein X is methylene, is produced, for example, according to the following Method T4.

[Method T4]



(XV-1a) (II-5)



(XV-1c) (II-1d)

wherein each symbol is as defined above.

[Step 1]

In this step, compound (II-5) can be produced by reacting compound (XV-1a) with a haloacetate. This reaction is generally carried out in the presence of a base, in a solvent that does not adversely influence.

As the haloacetate, ethyl bromoacetate, ethyl chloroacetate and the like can be mentioned.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the haloacetate to be used is generally 1 to 50 mol, preferably 1 to 10 mol, per 1 mol of compound (XV-1a).

The amount of the base to be used is generally 1 to 30 mol, preferably 1 to 10 mol, per 1 mol of compound (XV-1a).

The reaction temperature is generally -80 to 150°C,

preferably -20 to 100°C.

The reaction time is generally 0.5 to 20 hr.

[Step 2]

In this step, compound (XV-1c) can be produced by subjecting compound (II-5) to hydrolysis, and subjecting the obtained carboxylic acid to a decarboxylation reaction in the presence of an acid.

The hydrolysis of compound (II-5) is carried out in the same manner as in the reaction described in the aforementioned Method T1.

The decarboxylation reaction of the carboxylic acid obtained by the hydrolysis of compound (II-5) is carried out in the presence of an acid, in a solvent that does not adversely influence.

As the solvent that does not adversely influence the reaction, those similar to the water-containing solvent used for the hydrolysis of the aforementioned Method T1, can be mentioned.

As the acid, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as acetic acid and the like, and the like can be mentioned.

The amount of the acid to be used is generally 0.01 to 1000 mol, per 1 mol of compound (II-5).

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 30 hr.

[Step 3]

In this step, compound (II-1d) can be produced by subjecting compound (XV-1c) to an oxidization reaction. This reaction is carried out according to a method known per se, for example, using sodium dihydrogenphosphate, sodium chlorite and 2-methyl-2-butene, in a solvent that does not adversely influence the reaction.

As the solvent that does not adversely influence the reaction, for example, a mixed solvent of tert-butyl alcohol

and water; a mixed solvent of tert-butyl alcohol, tetrahydrofuran and water, and the like can be mentioned.

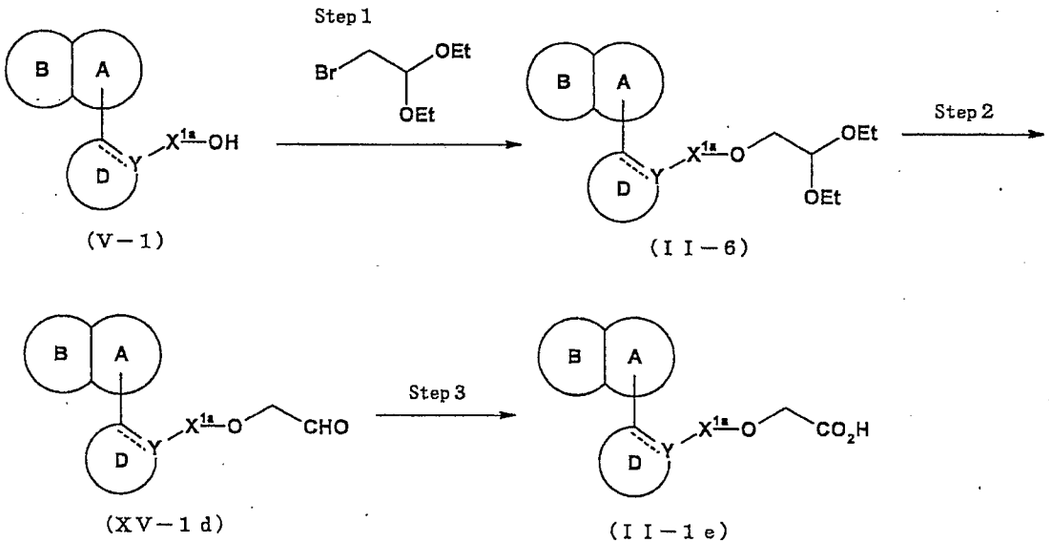
The amount of the sodium dihydrogenphosphate, sodium chlorite and 2-methyl-2-butene to be used is generally 1 to 50 mol, preferably 1 to 20 mol, per 1 mol of compound (XV-1c), respectively.

The reaction temperature is generally -30 to 150°C, preferably -10 to 80°C.

The reaction time is generally 0.5 to 30 hr.

Compound (II-1e), which is compound (II) wherein X is -X^{1a}-O-CH_2- wherein X^{1a} is as defined above, is produced, for example, according to the following Method T5.

[Method T5]



wherein each symbol is as defined above.

[Step 1]

In this step, compound (II-6) can be produced by reacting compound (V-1) with 2-bromo-1,1-diethoxyethane. This reaction is generally carried out in the presence of a base, in a solvent that does not adversely influence.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and

the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the 2-bromo-1,1-diethoxyethane to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (V-1).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (V-1).

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 100 hr.

Compound (V-1) can be produced, for example, according to the below-mentioned Method U1 or Method U2 or a method analogous thereto.

[Step 2]

In this step, compound (XV-1d) can be produced by subjecting compound (II-6) to a deacetalation reaction. This reaction is carried out in the presence of an acid, in a solvent that does not adversely influence, according to a method known per se.

As the acid, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid and the like; solutions prepared by dissolving hydrogen chloride in

methanol, ethyl acetate and the like, such as hydrogen chloride-methanol solution, hydrogen chloride-ethyl acetate solution and the like can be mentioned.

As the solvent that does not adversely influence the reaction, ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the acid to be used is generally 0.01 to 1000 mol, per 1 mol of compound (II-6).

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.1 to 20 hr.

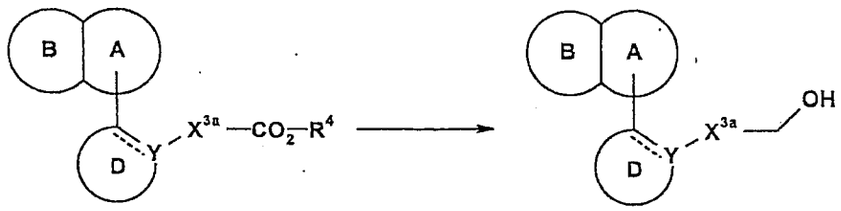
[Step 3]

In this step, compound (II-1e) can be produced by subjecting compound (XV-1d) to an oxidization reaction. This reaction is carried out in the same manner as in the reaction described in Step 3 of the aforementioned Method T4.

Compound (V) used as a starting material compound in the aforementioned Method C, Method D, Method E, Method F, Method I and Method S1, and the below-mentioned Method Y, compound (V-1) used as a starting material compound in the aforementioned Method T5, and compound (V-1a) used as a starting material compound in the below-mentioned Method Z3, are produced, for example, according to the following Method U1 or Method U2.

Compound (V-1a), which is compound (V) wherein X is $-X^{3a}-CH_2-$ wherein X^{3a} is as defined above, is produced, for example, according to the following Method U1 or Method U2.

[Method U1]



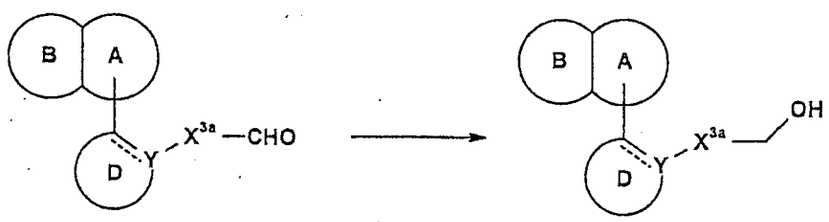
(II-7) (V-1a)

wherein each symbol is as defined above.

In this method, compound (V-1a) can be produced by subjecting compound (II-7) to a reduction reaction. This reaction is carried out in the same manner as in the reaction described in Step 4 of the aforementioned Method N.

Compound (II-7) can be produced, for example, according to Step 1 or Step 2 of the aforementioned Method T2, the below-mentioned Method AM, Method AN, Method AP or a method analogous thereto.

[Method U2]



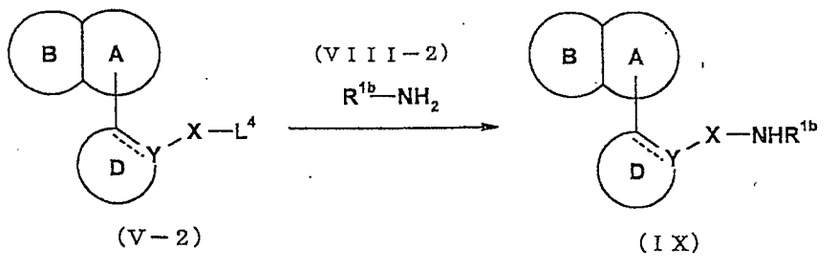
(XV) (V-1a)

wherein each symbol is as defined above.

In this method, compound (V-1a) can be produced by subjecting compound (XV) to a reduction reaction. This reaction is carried out in the same manner as in the reaction described in Step 4 of the aforementioned Method N.

Compound (IX) used as a starting material compound in the aforementioned Method G and Method H1 is produced, for example, according to the following Method V1 or Method V2.

[Method V1]



(V-2) (IX)

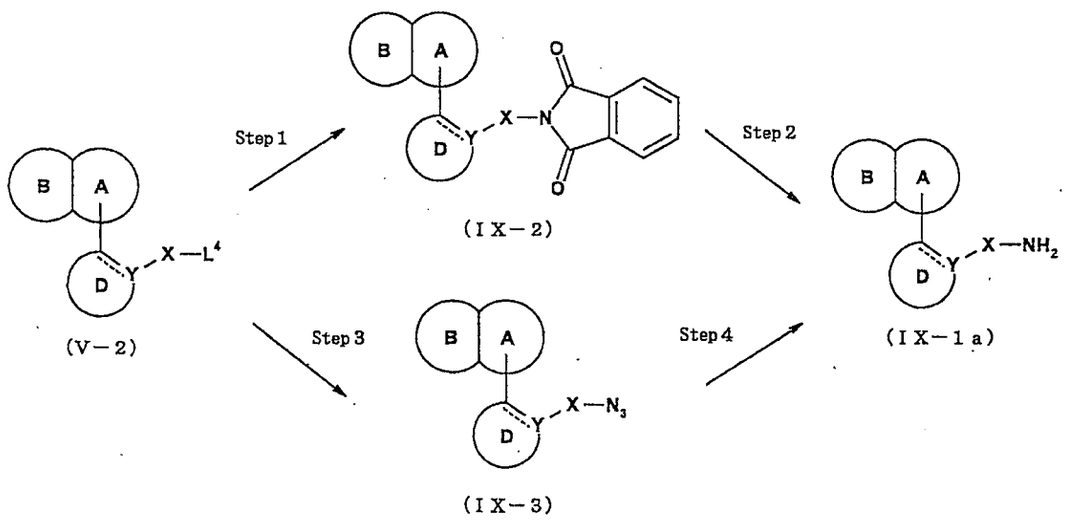
wherein each symbol is as defined above.

In this method, compound (IX) can be produced by reacting compound (V-2) with compound (VIII-2). This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method S1.

Compound (VIII-2) can be produced according to a method known per se.

Compound (IX-1a), which is compound (IX) wherein R^{1b} is a hydrogen atom, is produced, for example, according to the following Method V2.

[Method V2]



(V-2) (IX-2) (IX-1a) (IX-3)

wherein each symbol is as defined above.

[Step 1]

In this step, compound (IX-2) can be produced by reacting compound (V-2) with potassium phthalimide. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the solvent that does not adversely influence the

reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the potassium phthalimide to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V-2).

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 50 hr.

[Step 2]

In this step, compound (IX-1a) can be produced by subjecting compound (IX-2) to hydrolysis using an acid or a base. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the acid, for example, mineral acids such as sulfuric acid and the like can be mentioned. As the base, for example, hydrazine hydrate can be mentioned. Of these, hydrazine hydrate is preferable.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like; water and the like can be mentioned.

These solvents may be used in a mixture at an appropriate ratio.

The amount of the acid or base to be used is generally 1 to 100 mol, per 1 mol of compound (IX-2).

The reaction temperature is generally -10 to 150°C, preferably 10 to 100°C.

The reaction time is generally 0.5 to 50 hr.

[Step 3]

In this step, compound (IX-3) can be produced by reacting compound (V-2) with an azide compound. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the azide compound, sodium azide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the azide compound to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (V-2).

The reaction temperature is generally -10 to 150°C, preferably 0 to 100°C.

The reaction time is generally 0.1 to 30 hr.

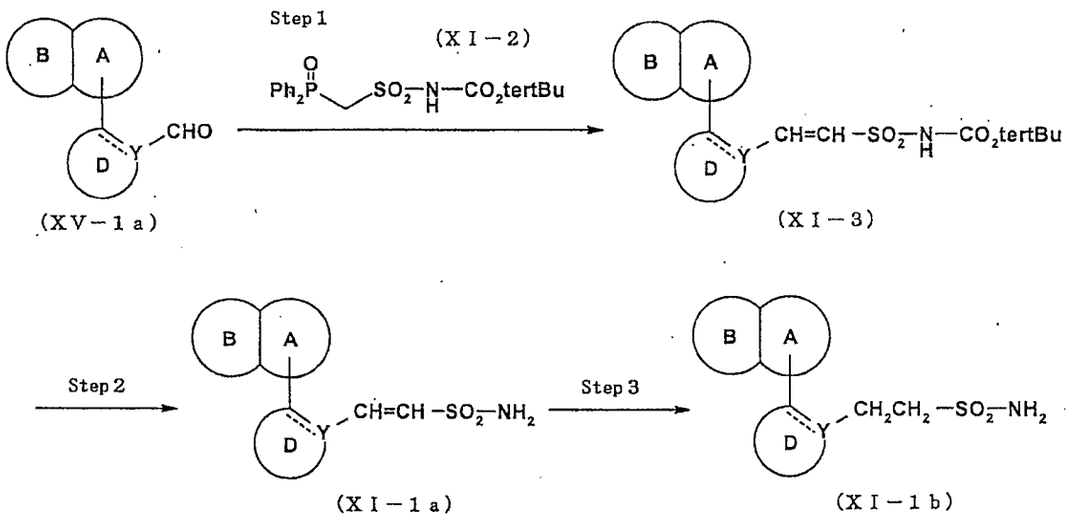
[Step 4]

In this step, compound (IX-1a) can be produced by subjecting compound (IX-3) to a reduction reaction. This

reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M or Step 4 of the aforementioned Method N.

Compound (XI-1a), which is compound (XI) (used as a starting material compound in the aforementioned Method J and Method K) wherein R^{1a} is a hydrogen atom, m is 2, and X is -CH=CH-, and compound (XI-1b), which is compound (XI) wherein R^{1a} is a hydrogen atom, m is 2, and X is $-CH_2CH_2-$, are produced, for example, according to the following Method W.

[Method W]



wherein each symbol is as defined above.

[Step 1]

In this step, compound (XI-3) can be produced by reacting compound (XV-1a) with compound (XI-2). This reaction is carried out according to a method known per se (e.g., the method described in Synthesis, page2321 (2003), Step 1 of the aforementioned Method T2 or a method analogous thereto etc.).

Compound (XI-2) can be produced according to a method known per se.

[Step 2]

In this step, compound (XI-1a) can be produced by subjecting compound (XI-3) to deprotection. This reaction is carried out in the presence of an acid, in a solvent that does not adversely influence, according to a method known per se.

As the acid, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid and the like; solutions prepared by dissolving hydrogen chloride in methanol, ethyl acetate and the like, such as hydrogen chloride-methanol solution, hydrogen chloride-ethyl acetate solution and the like can be mentioned.

As the solvent that does not adversely influence the reaction, ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like; ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the acid to be used is generally 0.01 to 1000 mol, per 1 mol of compound (XI-3).

The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

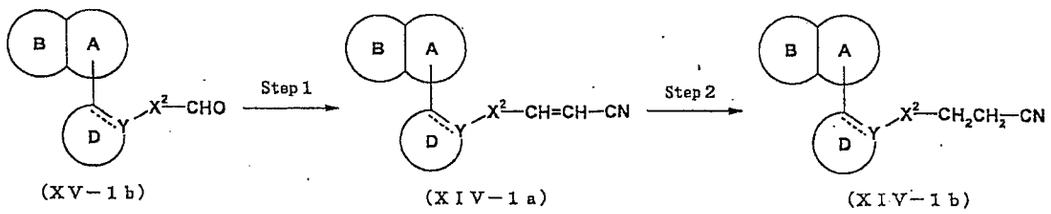
The reaction time is generally 0.1 to 30 hr.

[Step 3]

In this step, compound (XI-1b) can be produced by subjecting compound (XI-1a) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

Compound (XIV-1a), which is compound (XIV) (used as a starting material compound in the aforementioned Method L) wherein X is $-X^2-CH=CH-$ wherein X^2 is as defined above, and compound (XIV-1b), which is compound (XIV) wherein X is $-X^2-CH_2CH_2-$ wherein X^2 is as defined above, are produced, for example, according to the following Method X.

[Method X]



(XV-1b) (XIV-1a) (XIV-1b)

wherein each symbol is as defined above.

[Step 1]

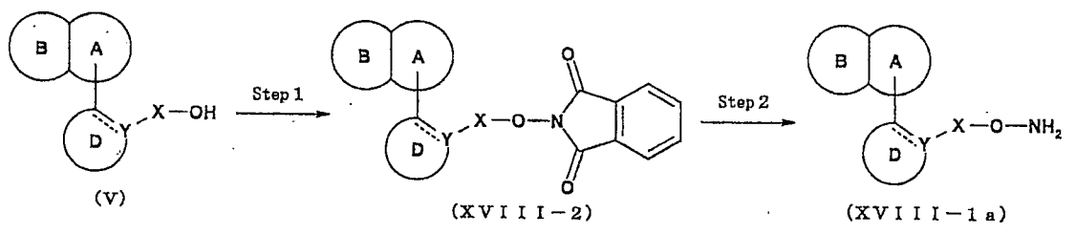
In this step, compound (XIV-1a) can be produced by reacting compound (XV-1b) with diethyl (cyanomethyl)phosphonate. This reaction is carried out in the same manner as in the reaction described in Step 1 of the aforementioned Method T2.

[Step 2]

In this step, compound (XIV-1b) can be produced by subjecting compound (XIV-1a) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

Compound (XVIII-1a), which is compound (XVIII) (used as a starting material compound in the aforementioned Method O1, Method O2, Method P and Method Q) wherein R^{1a} is a hydrogen atom, is produced, for example, according to the following Method Y.

[Method Y]



(V) (XVIII-2) (XVIII-1a)

wherein each symbol is as defined above.

[Step 1]

In this step, compound (XVIII-2) can be produced by reacting compound (V) with N-hydroxyphthalimide. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method I.

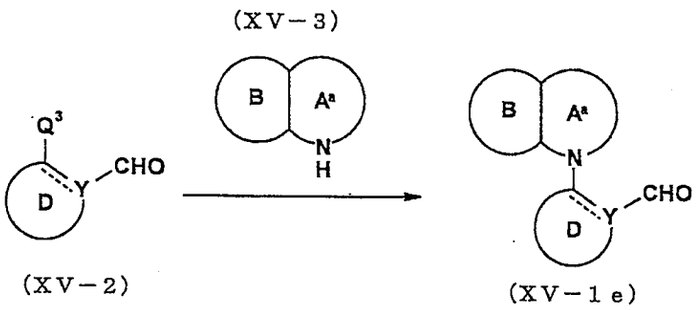
[Step 2]

In this step, compound (XVIII-1a) can be produced by subjecting compound (XVIII-2) to hydrolysis. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method V2.

Compound (XV-1a) used as a starting material compound in the aforementioned Method N, Method T3, Method T4 and Method W, compound (XV) used as a starting material compound in the aforementioned Method M and Method U2, compound (XV-1b) used as a starting material compound in the aforementioned Method T2 and Method X, compound (XV-1f) used as a starting material compound in the below-mentioned Method AL, compound (XV-1h) used as a starting material compound in the below-mentioned Method AO, compound (XV-1k) used as a starting material compound in the below-mentioned Method AQ, and compound (XV-1m) used as a starting material compound in the below-mentioned Method AV, are produced, for example, according to the following Method Z1 to Method Z3.

Compound (XV-1e), which is compound (XV-1a) wherein ring D is bonded to the nitrogen atom on ring A, is produced, for example, according to the following Method Z1.

[Method Z1]



(XV-2) (XV-1e)

wherein Q^3 is a halogen atom or trifluoromethylsulfonyloxy, ring A^a is a 5- to 7-membered monocycle containing NH, which is optionally substituted, and the other symbols are as defined above.

As the "5- to 7-membered monocycle containing NH, which is optionally substituted" for ring A^a, rings containing, as a ring-constituting member, at least one unsubstituted NH (-NH-)

(e.g., pyrrole, pyrazole, imidazole), from among the aforementioned "5- to 7-membered monocycle containing NH, which is optionally substituted" for ring A, can be mentioned.

In this method, compound (XV-1e) can be produced by reacting compound (XV-2) with compound (XV-3). This reaction is carried out in the presence of a base, in a solvent that does not adversely influence the reaction. This reaction may be carried out, in the presence of an organic metal catalyst and a phosphine ligand, as necessary.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

As the organic metal catalyst, palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), dichlorobis(triphenylphosphine)palladium(II) and the like can be mentioned.

As the phosphine ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), tris(2-methylphenyl)phosphine, 1,1'-

bis(diphenylphosphino)ferrocene and the like can be mentioned.

The amount of compound (XV-3) to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (XV-2).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (XV-2).

The amount of the organic metal catalyst to be used is generally 0.001 to 1 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (XV-2).

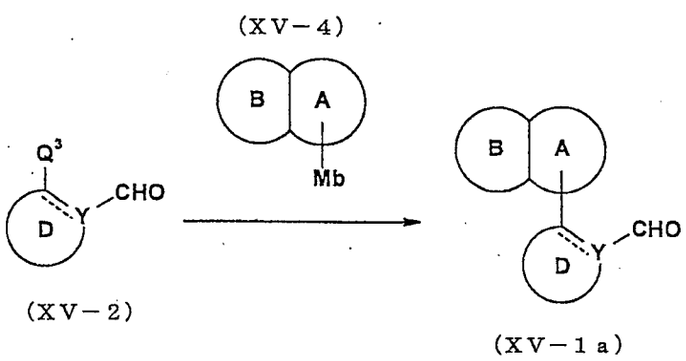
The amount of the phosphine ligand to be used is generally 0.001 to 1 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (XV-2).

The reaction temperature is generally -10 to 250°C, preferably 20 to 150°C.

The reaction time is generally 0.5 to 100 hr.

Compound (XV-2) can be produced, for example, according to the below-mentioned Method AR or a method analogous thereto. Compound (XV-3) can be produced according to a method known per se.

[Method Z2]



wherein Mb is a substituted boron atom when compound (XV-4) is an organic boronic acid or an organic boronate, or a substituted tin atom when compound (XV-4) is an organic tin reagent, and the other symbols are as defined above.

As the substituted boron atom for Mb, dihydroxyboryl group, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group and the like can be mentioned.

As the substituted tin atom for Mb, trimethylstannyl group, tributylstannyl group and the like can be mentioned.

In this method, compound (XV-1a) can be produced by subjecting compound (XV-2) and compound (XV-4) to a coupling reaction using an organic metal catalyst. This reaction is carried out in the presence of a base, in a solvent that does not adversely influence the reaction, as necessary. This reaction may be carried out, in the presence of a phosphine ligand, as necessary.

As the organic metal catalyst, palladium(II) acetate, tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0), dichlorobis(triphenylphosphine)palladium(II) and the like can be mentioned.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; metal hydrides such as potassium hydride, sodium hydride and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; alcohols such as methanol, ethanol, isopropanol, tert-butyl alcohol and the like; water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (XV-4) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (XV-2).

The amount of the organic metal catalyst to be used is generally 0.001 to 1 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (XV-2).

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (XV-2).

As the phosphine ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), tris(2-methylphenyl)phosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl and the like can be mentioned.

The amount of the phosphine ligand to be used is generally 0.001 to 1 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (XV-2).

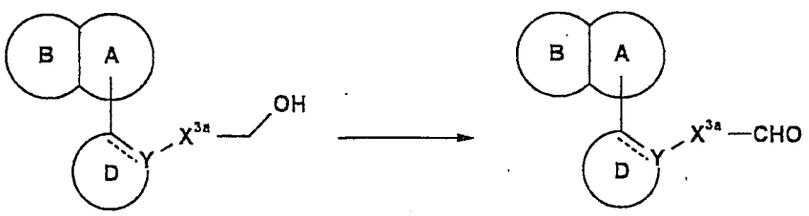
The reaction temperature is generally 0 to 200°C, preferably 50 to 150°C.

The reaction time is generally 0.5 to 50 hr.

Compound (XV-4) can be produced according to a method known per se.

Compound (XV) used as a starting material compound in the aforementioned Method M, and compound (XV-1b) used as a starting material compound in the aforementioned Method T2 and Method X, are produced, for example, according to the following Method Z3.

[Method Z3]



(V−1a) (XV)

wherein each symbol is as defined above.

In this reaction, compound (XV) can be produced by subjecting compound (V-1a) to an oxidization reaction. This reaction is generally carried out in the presence of an oxidant, in a solvent that does not adversely influence the reaction.

As the oxidant, for example, metal oxidants such as manganese dioxide, pyridinium chlorochromate, pyridinium dichromate, ruthenium oxide and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of the oxidant to be used is generally 1 to 50 mol, preferably 1 to 10 mol, per 1 mol of compound (V-1a).

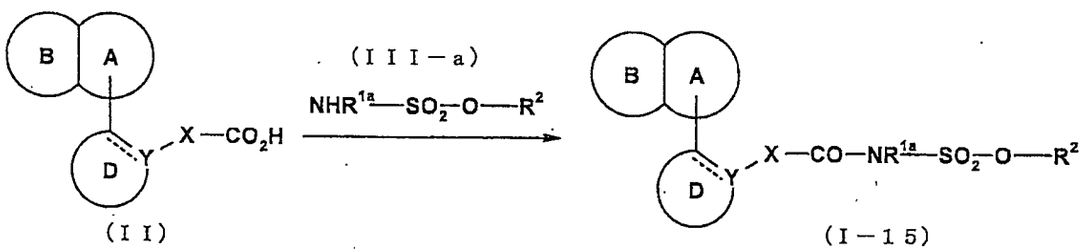
The reaction temperature is generally -50 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 50 hr.

Compound (V-1a) can be produced, for example, according to the aforementioned Method U1 or a method analogous thereto.

Compound (I-15), which is compound (I) wherein W is -$CONR^{1a}S(O)_mOR^2$ wherein m is 2 and the other symbols are as defined above, is produced, for example, according to the following Method AA.

[Method AA]



(II) (I-15)

wherein each symbol is as defined above.

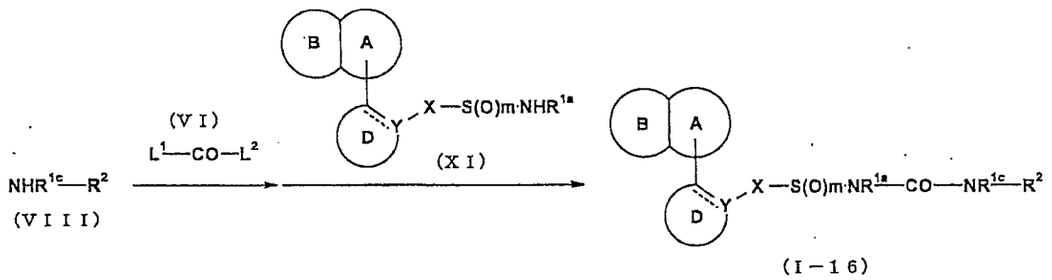
In this method, compound (I-15) can be produced by reacting compound (II) with compound (III-a). This reaction is carried out in the same manner as in the condensation reaction described in the aforementioned Method A1.

Compound (III-a) can be produced according to a method known per se.

Compound (I-16), which is compound (I) wherein W is -

$S(O)_mNR^{1a}CONR^{1c}R^2$ wherein each symbol is as defined above, is produced, for example, according to the following Method AB.

[Method AB]



wherein each symbol is as defined above.

In this method, compound (I-16) can be produced from compound (XI). This reaction is carried out according to a method known per se, for example, by reacting compound (VIII) with compound (VI) in a solvent that does not adversely influence the reaction, at -10°C to 120°C for 0.5 to 10 hr, and reacting the obtained compound with compound (XI) in a solvent that does not adversely influence the reaction, at -10°C to 120°C for 0.5 to 50 hr. This reaction may be carried out in the presence of 1 to 20 mol of a base, per 1 mol of compound (XI), where necessary.

As compound (VI), for example, N,N'-carbonyldiimidazole, diphosgene, triphosgene and the like can be mentioned.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned. These bases may be used in a mixture at an appropriate ratio.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like;

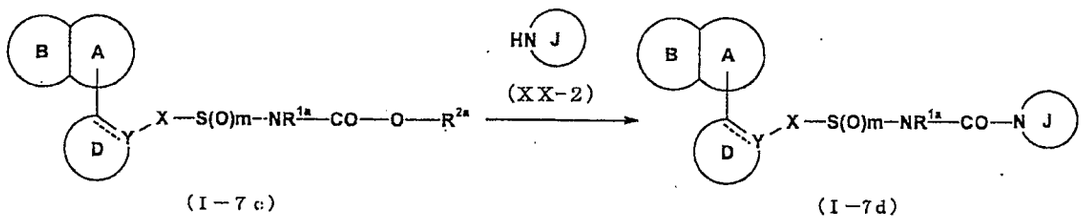
acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (VI) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (XI).

The amount of compound (VIII) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (XI).

Compound (I-7d), which is compound (I-7a) (compound (I) wherein W is $-S(O)_mNR^{1a}CO_nR^2$ wherein n is 1 and the other symbols are as defined above) wherein R^2 is a non-aromatic heterocyclic group containing NH, is produced, for example, according to the following Method AC.

[Method AC]



(I-7c) (I-7d)

wherein R^{2a} is a C_{1-6} alkyl group, ring J is a non-aromatic heterocycle containing NH, and the other symbols are as defined above.

The "C_{1-6} alkyl group" for R^{2a} is preferably ethyl, propyl or butyl.

As the "non-aromatic heterocycle containing NH" for ring J, pyrrolidine, morpholine, piperizine and the like can be mentioned.

In this method, compound (I-7d) can be produced by reacting compound (I-7c) with compound (XX-2). This reaction is carried out in a solvent that does not adversely influence the reaction.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers

such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

This reaction may be carried out in the presence of 1 to 5 mol of a base, per 1 mol of compound (I-7c), as necessary.

As the base that does not adversely influence the reaction, those exemplified in the aforementioned Method AB can be mentioned.

The amount of compound (XX-2) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (I-7c).

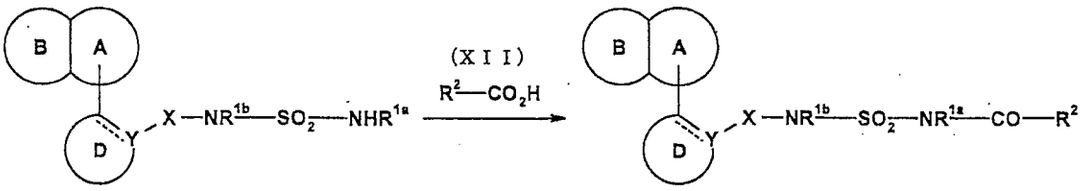
The reaction temperature is generally -30°C to 150°C.

The reaction time is generally 0.5 to 30 hr.

Compound (I-7c) can be produced, for example, according to the below-mentioned Method AU or a method analogous thereto. Compound (XX-2) can be produced according to a method known per se.

Compound (I-17a), which is compound (I) wherein W is -$NR^{1b}S(O)_mNR^{1a}CO_nR^2$ wherein m is 2, n is 1 and the other symbols are as defined above, is produced, for example, according to the following Method AD.

[Method AD]



(XXII) (I-17a)

wherein the each symbol is as defined above.

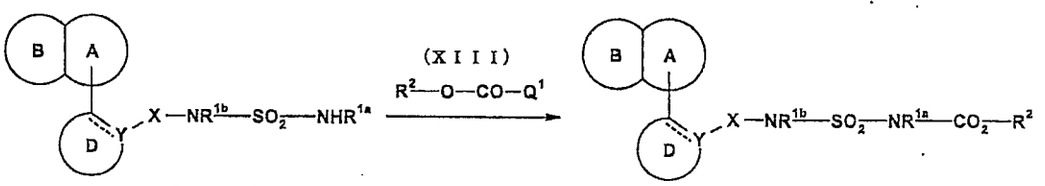
In this method, compound (I-17a) can be produced by reacting compound (XXII) with compound (XII). This reaction is carried out in the same manner as in the condensation reaction described in the aforementioned Method A1.

Compound (XXII) can be produced, for example, according to the below-mentioned Method AS or a method analogous

thereto.

Compound (I-17b), which is compound (I) wherein W is -$NR^{1b}S(O)_mNR^{1a}CO_nR^2$ wherein m is 2, n is 2 and the other symbols are as defined above, is produced, for example, according to the following Method AE.

[Method AE]

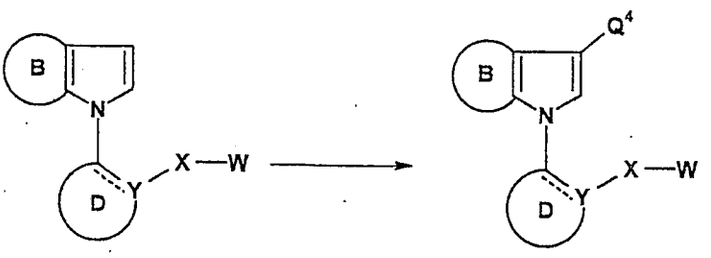


wherein the each symbol is as defined above.

In this method, compound (I-17b) can be produced by reacting compound (XXII) with compound (XIII). This reaction is carried out in the same manner as in the condensation reaction described in the aforementioned Method A1.

Compound (I-18b), which is compound (I) wherein ring A is pyrrole bonded to ring D at the 1-position and having a halogen atom at the 3-position, is produced, for example, according to the following Method AF.

[Method AF]



wherein Q^4 is a halogen atom, and the other symbols are as defined above.

The "halogen atom" for Q^4 is preferably a chlorine atom or a bromine atom.

In this method, compound (I-18b) can be produced by reacting compound (I-18a) with a halogenating agent. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the halogenating agent, N-chlorosuccinimide, N-bromosuccinimide and the like can be mentioned.

The amount of the halogenating agent to be used is generally 1 to 10 mol, per 1 mol of compound (I-18a).

The reaction temperature is generally -10°C to 150°C, preferably 0 to 80°C.

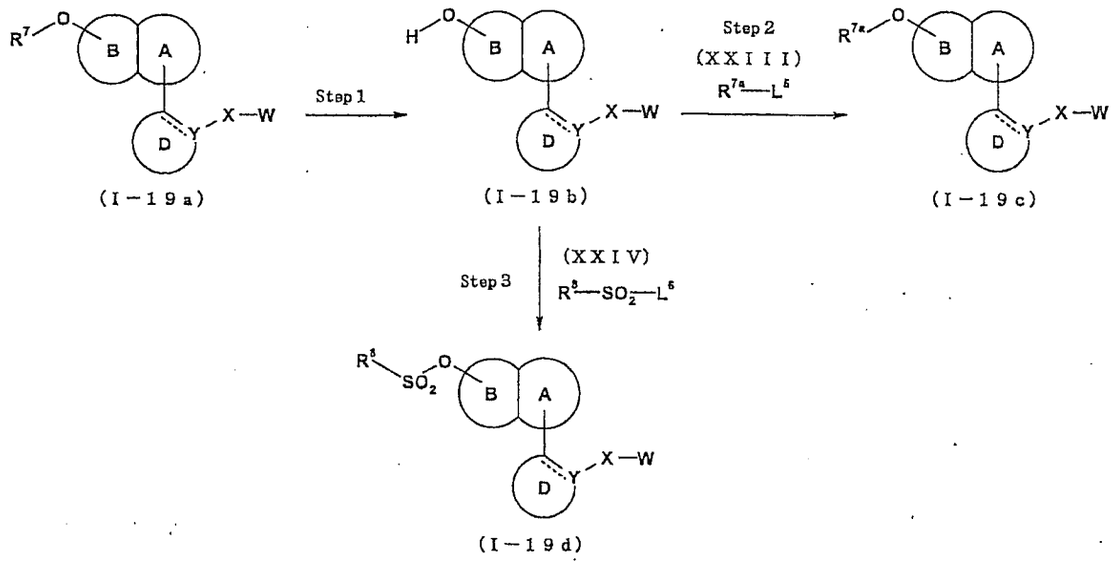
The reaction time is 0.5 to 50 hr.

As the solvent that does not adversely influence the reaction, for example, aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like; acetonitrile and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

Compound (I-18a) can be produced, for example, according to the aforementioned Method A1, Method B to Method G, Method H1, Method H2, Method I to Method N, Method O1, Method O2, Method P to Method R, Method S1, Method S2, Method AA to Method AE, the below-mentioned Method AG to Method AL, Method AU or a method analogous thereto .

Compound (I-19b), which is compound (I) having a hydroxyl group on ring B, compound (I-19c), which is compound (I) having an optionally substituted C_{1-6} alkoxy group on ring B, and compound (I-19d), which is compound (I) having an optionally substituted C_{1-6} alkylsulfonyloxy group on ring B, are produced, for example, according to the following Method AG.

[Method AG]



wherein R^7 is methyl or benzyl, R^{7a} is an optionally substituted C_{1-6} alkyl group, R^8 is a C_{1-6} alkyl group, L^5 and L^6 are the same or different and each is a leaving group, and the other symbols are as defined above.

As the "leaving group" for L^5 or L^6, those exemplified for the aforementioned L^1 or L^2 can be mentioned.

As the substituent of the "optionally substituted C_{1-6} alkyl group" for R^{7a}, 1 to 3 substituents selected from (a) a C_{6-14} aryl group, (b) a C_{1-6} alkoxy group, (c) a C_{3-10} cycloalkyl group and (d) a C_{1-6} alkyl-carbonyl group can be mentioned.

[Step 1]

In this step, compound (I-19b) can be produced from compound (I-19a).

When R^7 is methyl or benzyl, the reaction is carried out in the presence of boron tribromide, in a solvent that does not adversely influence the reaction.

As the solvent that does not adversely influence the reaction, halogenated hydrocarbons such as dichloromethane and the like, and the like can be mentioned.

The amount of the boron tribromide to be used is generally 1 to 20 mol, per 1 mol of compound (I-19a).

The reaction temperature is generally -100 to 150°C, preferably -80 to 100°C.

The reaction time is generally 0.1 to 30 hr.

When R^7 is benzyl, the reaction can be carried out in the presence of a metal catalyst such as palladium-carbon, palladium black, palladium chloride, platinum oxide, palladium black, platinum-palladium, Raney-nickel, Raney-cobalt and the like and a hydrogen source, or in the presence of an acid, in a solvent that does not adversely influence the reaction.

The amount of the metal catalyst to be used is generally 0.001 to 1000 mol, preferably 0.01 to 100 mol, per 1 mol of compound (I-19a).

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

As the acid, for example, organic acids such as trifluoroacetic acid and the like can be mentioned.

The amount of the acid to be used is generally 0.01 to 1000 mol, preferably 0.1 to 100 mol, per 1 mol of compound (I-19a).

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol, propanol, 2-propanol, 2-methoxyethanol, butanol, isobutanol, tert-butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; ethyl acetate; acetic acid and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 150°C, preferably 10 to 80°C.

The reaction time is generally 0.5 to 100 hr.

Compound (I-19a) can be produced, for example, according to the aforementioned Method A1, Method B, Method J, Method K, Method L, Method R, Method AA, Method AB or the below-mentioned Method AU, or a method analogous thereto.

[Step 2]

In this step, compound (I-19c) can be produced by reacting compound (I-19b) with compound (XXIII). This reaction is generally carried out in the presence of a base, in a solvent that does not adversely influence. The reaction efficiency can be improved by using sodium iodide, as necessary.

The amount of compound (XXIII) to be used is generally 1 to 20 mol, per 1 mol of compound (I-19b).

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

The amount of the base to be used is generally 1 to 20 mol, per 1 mol of compound (I-19b).

The amount of the sodium iodide to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (I-19b).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide,

N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like, acetone, acetnitrile and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -30 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 100 hr.

Compound (XXIII) can be produced according to a method known per se.

[Step 3]

In this step, compound (I-19d) can be produced by reacting compound (I-19b) with compound (XXIV). This reaction is generally carried out in the presence of a base, in a solvent that does not adversely influence.

The amount of compound (XXIV) to be used is generally 1 to 20 mol, preferably 1 to 10 mol, per 1 mol of compound (I-19b).

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

The amount of the base to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (I-19b).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like;

amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethyl sulfoxide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

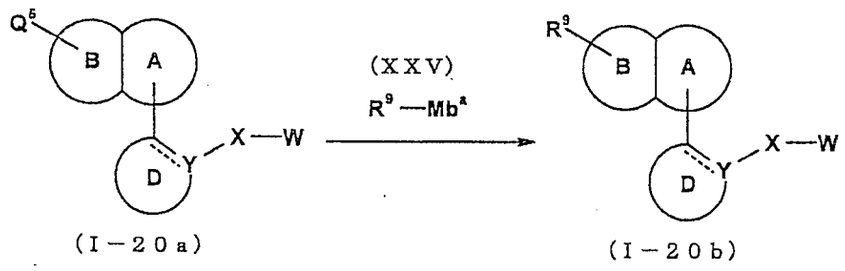
The reaction temperature is generally -80 to 150°C, preferably -10 to 100°C.

The reaction time is generally 0.5 to 100 hr.

Compound (XXIV) can be produced according to a method known per se.

Compound (I-20b), which is compound (I) having a C_{6-14} aryl group, an aromatic heterocyclic group or a C_{3-10} cycloalkyl group on ring B, is produced, for example, according to the following Method AH.

[Method AH]



wherein Q^5 is a halogen atom, Mb^a is a substituted boron atom when compound (XXV) is an organic boronic acid or an organic boronate, or a substituted tin atom when compound (XXV) is an organic tin reagent, R^9 is a C_{6-14} aryl group, an aromatic heterocyclic group or a C_{3-10} cycloalkyl group, and the other symbols are as defined above."

The "halogen atom" for Q^5 is preferably a bromine atom or an iodine atom.

As the "substituted boron atom" or "substituted tin atom" for Mb^a, those exemplified for the aforementioned Mb can be mentioned.

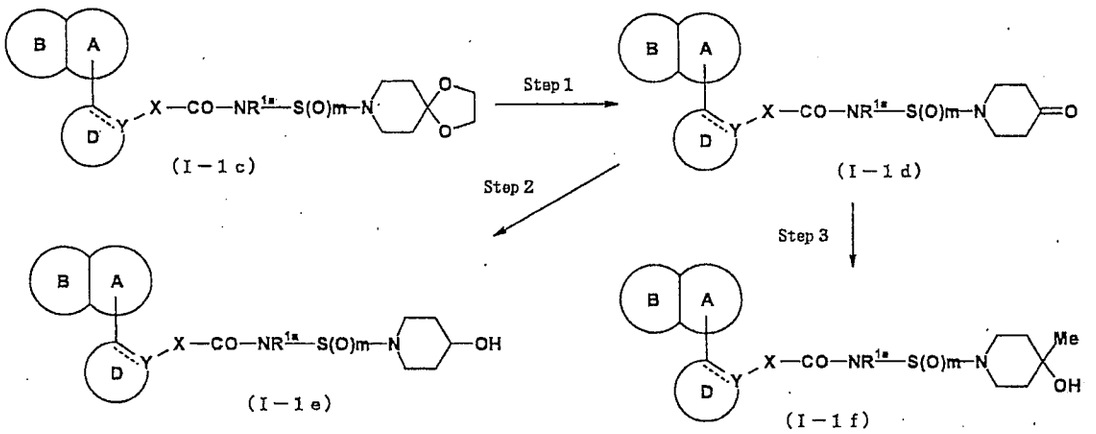
In this method, compound (I-20b) can be produced by subjecting compound (I-20a) and compound (XXV) to a coupling reaction using an organic metal catalyst. This reaction is carried out in the same manner as in the reaction described in

the aforementioned Method Z2.

Compound (I-20a) can be produced, for example, according to the aforementioned Method A1, Method B to Method G, Method H1, Method H2, Method I to Method N, Method O1, Method O2, Method P to Method R, Method S1, Method S2, Method AA to Method AG, Method AI to Method AL, Method AU or a method analogous thereto. Compound (XXV) can be produced according to a method known per se.

Compound (I-1d), which is compound (I-1) (compound (I) wherein W is $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above) wherein R^2 is 4-oxopiperidin-1-yl group), compound (I-1e), which is compound (I-1) wherein R^2 is 4-hydroxypiperidin-1-yl group, and compound (I-1f), which is compound (I-1) wherein R^2 is 4-hydroxy-4-methylpiperidin-1-yl group, are produced, for example, according to the following Method AI.

[Method AI]



wherein the each symbol is as defined above.

[Step 1]

In this step, compound (I-1d) can be produced by subjecting compound (I-1c) to a deketalation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method T5.

Compound (I-1c) can be produced, for example, according to the aforementioned Method A1 or a method analogous thereto.

[Step 2]

In this step, compound (I-1e) can be produced by

subjecting compound (I-1d) to a reduction reaction. This reaction is carried out in the same manner as in the reaction described in Step 4 of the aforementioned Method N.

[Step 3]

In this step, compound (I-1f) can be produced by reacting compound (I-1d) with a methylating agent. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the methylating agent, methylmagnesium chloride, methyl magnesium bromide, methyllithium and the like can be mentioned.

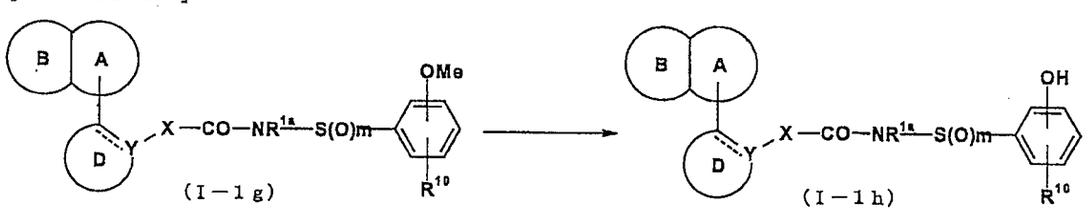
As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80 to 150°C, preferably -10 to 80°C.

The reaction time is generally 0.1 to 30 hr.

Compound (I-1h), which is compound (I-1) (compound (I) wherein W is $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above) wherein R^2 is an optionally substituted hydroxyphenyl group, is produced, for example, according to the following Method AJ.

[Method AJ]



wherein R^{10} is an optionally substituted C_{1-6} alkyl group, and the other symbols are as defined above.

As the substituents of the "optionally substituted C_{1-6} alkyl group" for R^{10}, 1 to 3 halogen atoms (preferably a fluorine atom) can be mentioned.

In this method, compound (I-1h) can be produced by reacting compound (I-1g) with boron tribromide. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the solvent that does not adversely influence the reaction, halogenated hydrocarbons such as dichloromethane and the like, and the like can be mentioned.

The amount of the boron tribromide to be used is generally 1 to 20 mol, per 1 mol of compound (I-1g).

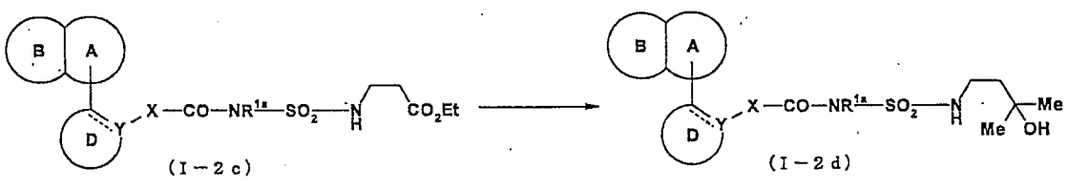
The reaction temperature is generally -100 to 150°C, preferably -80 to 100°C.

The reaction time is generally 0.1 to 50 hr.

Compound (I-1g) can be produced, for example, according to the aforementioned Method A1 or a method analogous thereto.

Compound (I-2d), which is compound (I-2a) (compound (I) wherein W is $-CONR^{1a}S(O)_mNR^{1c}R^2$ wherein m is 2 and the other symbols are as defined above) wherein $NR^{1c}R^2$ is (3-hydroxy-3-methylbutyl)amino group, is produced, for example, according to the following Method AK.

[Method AK]



wherein the each symbol is as defined above.

In this method, compound (I-2d) can be produced by subjecting compound (I-2c) to a dimethylation reaction. This reaction is carried out in a solvent that does not adversely influence the reaction.

As the methylating agent, methylmagnesium chloride, methylmagnesium bromide, methyllithium and the like can be mentioned.

The amount of the methylating agent to be used is generally 2 - 20 mol, preferably 2 to 10 mol, per 1 mol of compound (I-2c).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

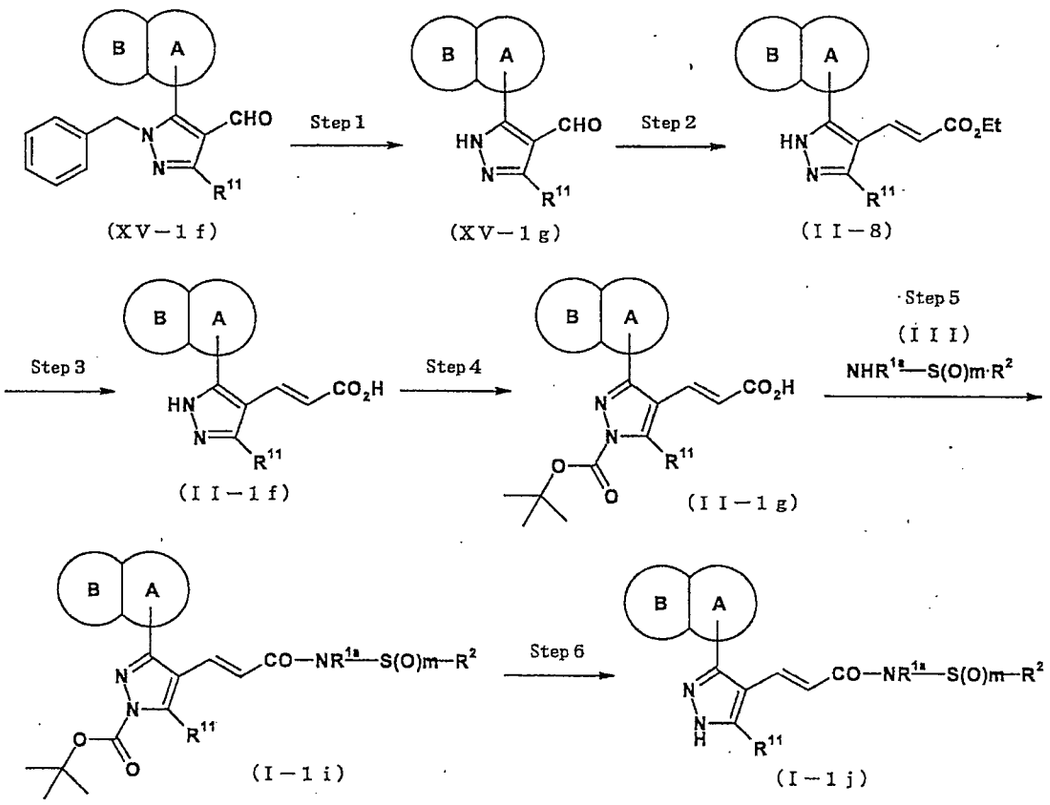
The reaction temperature is generally -80 to 100°C, preferably -10 to 60°C.

The reaction time is generally 0.1 to 30 hr.

Compound (I-2c) can be produced, for example, according to the aforementioned Method B or a method analogous thereto.

Compound (I-1i), which is compound (I-1) (compound (I) wherein W is $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined above) wherein X is -CH=CH- and ring D is pyrazole (bonded to ring A at the 3-position and bonded to X at the 4-position) having tert-butoxycarbonyl group at the 1-position, and compound (I-1j), which is compound (I-1) wherein X is -CH=CH- and ring D is pyrazole (bonded to ring A at the 3-position and bonded to X at the 4-position) having no substituents at the 1- and 2-positions, are produced, for example, according to the following Method AL.

[Method AL]



wherein R^{11} is an optionally substituted C_{1-6} alkyl group or a C_{1-6} cycloalkyl group, and the other symbols are as defined above."

As the substituents of the "optionally substituted C_{1-6} alkyl group" for R^{11}, 1 to 3 halogen atoms (preferably a fluorine atom) and a C_{1-6} alkoxy group can be mentioned.

[Step 1]

In this step, compound (XV-1g) can be produced by subjecting compound (XV-1f) to a debenzylation reaction. This reaction is carried out in trifluoroacetic acid at 0°C to 80°C for 1 to 200 hr.

The amount of the trifluoroacetic acid to be used is generally 5 to 1000 mol, per 1 mol of compound (XV-1f).

Compound (XV-1f) can be produced, for example, according to the aforementioned Method Z1, Method Z2, the below mentioned Method AO, Method AQ or a method analogous thereto.

[Step 2]

In this step, compound (II-8) can be produced by reacting

compound (XV-1g) with ethyl (triphenylphosphoranylidene)acetate. This reaction is carried out in a solvent that does not adversely influence the reaction.

The amount of the ethyl (triphenylphosphoranylidene)acetate to be used is generally 1 to 20 mol, preferably 1 to 5 mol, per 1 mol of compound (XV-1g).

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like, acetonitrile and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -10 to 150°C, preferably 10 to 120°C.

The reaction time is generally 0.5 to 50 hr.

[Step 3]

In this step, compound (II-1f) can be produced by subjecting compound (II-8) to hydrolysis. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method T1.

[Step 4]

In this step, compound (II-1g) can be produced by reacting compound (II-1f) with di-tert-butyl dicarbonate. This reaction is carried out in the presence of a base, in a solvent that does not adversely influence the reaction.

The amount of the di-tert-butyl dicarbonate to be used is generally 1 to 20 mol, per 1 mol of compound (II-1f).

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium carbonate and

the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like can be mentioned.

The amount of the base to be used is generally 1 to 10 mol, per 1 mol of compound (II-1f).

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; acetonitrile, ethyl acetate, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally 0 to 150°C, preferably 10 to 80°C.

The reaction time is generally 0.5 to 100 hr.

[Step 5]

In this step, compound (I-1i) can be produced by reacting compound (II-1g) with compound (III). This reaction is carried out in the same manner as in the reaction described in the aforementioned Method A1.

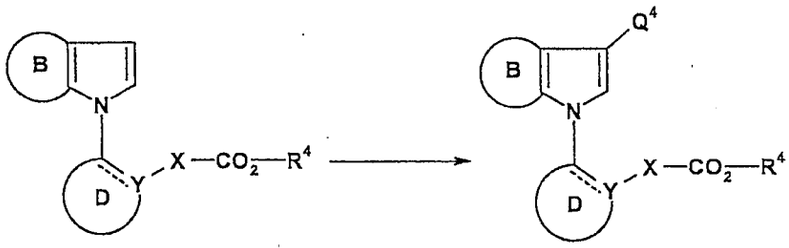
[Step 6]

In this step, compound (I-1j) can be produced by subjecting compound (I-1i) to deprotection. This reaction is carried out in the same manner as in the reaction described in Step 3 of the aforementioned Method S1.

Compound (II-9b), which is compound (II-2) wherein ring A is pyrrole bonded to ring D at the 1-position and having a

halogen atom at the 3-position, is produced, for example, according to the following Method AM.

[Method AM]



(II-9a) (II-9b)

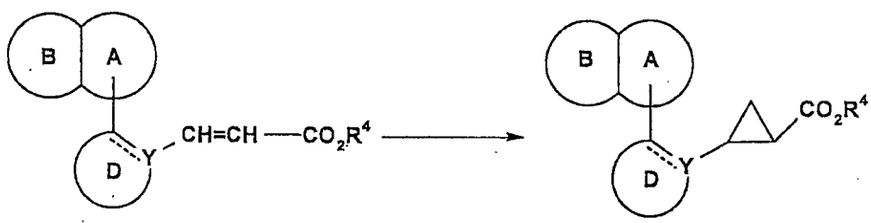
wherein the each symbol is as defined above.

In this method, compound (II-9b) can be produced by reacting compound (II-9a) with a halogenating agent. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method AF.

Compound (II-9a) can be produced, for example, according to Step 1 or Step 2 of the aforementioned Method T2, the below-mentioned Method AN, Method AP or a method analogous thereto.

Compound (II-10b), which is compound (II-2) wherein X is cyclopropane ring, is produced, for example, according to the following Method AN.

[Method AN]



(II-10a) (II-10b)

wherein the each symbol is as defined above.

In this method, compound (II-10b) can be produced by subjecting compound (II-10a) to a cyclopropanation reaction using a base or an organic metal catalyst.

The cyclopropanation reaction using a base is carried out using a cyclopropanating agent, in the presence of a base, in a solvent that does not adversely influence the reaction.

As the cyclopropanating agent, trimethylsulfoxonium iodide, methyltriphenylphosphonium bromide, nitromethane and the like can be mentioned.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium carbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, tributylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; organic metals such as methyllithium, butyllithium and the like; alkali metal fluorides such as cesium fluoride, potassium fluoride and the like, and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like; sulfoxides such as dimethylsulfoxide and the like; nitriles such as acetonitrile, propionitrile and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -70 to 150°C, preferably -20 to 80°C.

The reaction time is generally 1 to 100 hr, preferably 1 to 60 hr.

The amount of the cyclopropanating agent to be used is generally 1 to 50 mol, preferably 1 to 5 mol, per 1 mol of compound (II-10a).

The amount of the base to be used is generally 1 to 50 mol, preferably 1 to 5 mol, per 1 mol of compound (II-10a).

The cyclopropanation reaction using an organic metal catalyst is carried out using a diazoalkane in a solvent that does not adversely influence the reaction, in the presence of a ligand, as necessary.

As the organic metal catalyst, for example, palladium(II) acetate, coppertriflate(I), rhodium(II) acetate dimer and the like can be mentioned.

As the diazoalkane, diazomethane and the like can be mentioned.

As the ligand, 2,2'-diisopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] and the like can be mentioned.

As the solvent that does not adversely influence the reaction, for example, aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -70 to 150°C, preferably -20 to 80°C.

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

The amount of the organic metal catalyst to be used is generally 0.01 to 2 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (II-10a).

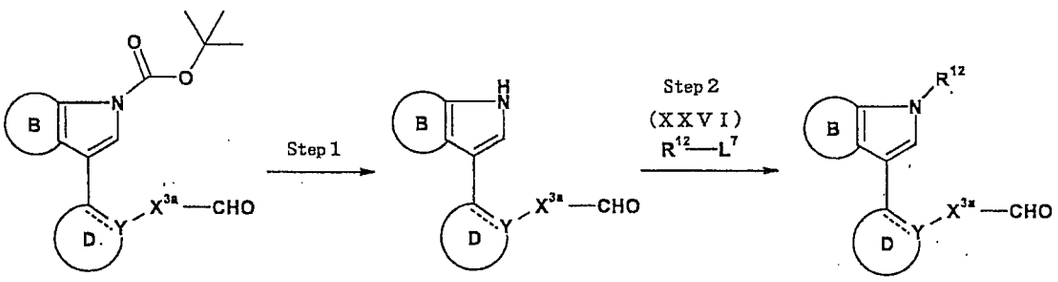
The amount of the diazoalkane to be used is generally 1 to 50 mol, preferably 1 to 5 mol, per 1 mol of compound (II-10a).

The amount of the ligand to be used is generally 0.01 to 2 mol, preferably 0.01 to 0.5 mol, per 1 mol of compound (II-10a).

Compound (II-10a) can be produced, for example, according to Step 1 of the aforementioned Method T2 or a method analogous thereto.

Compound (XV-1j), which is compound (XV) wherein ring A is a N-substituted pyrrole bonded to ring D at the 3-position, is produced for example, according to the following Method AO.

[Method AO]



(XV-1h) (XV-1i) (XV-1j)

wherein R^{12} is a C_{1-6} alkyl group, L^7 is a leaving group, and the other symbols are as defined above.

As the leaving group for L^7, those exemplified for the aforementioned L^1 or L^2 can be mentioned.

[Step 1]

In this step, compound (XV-1i) can be produced by subjecting compound (XV-1h) to deprotection. This reaction is carried out in the same manner as in the reaction described in Step 3 of the aforementioned Method S1.

Compound (XV-1h) can be produced, for example, according to the aforementioned Method Z2 or a method analogous thereto.

[Step 2]

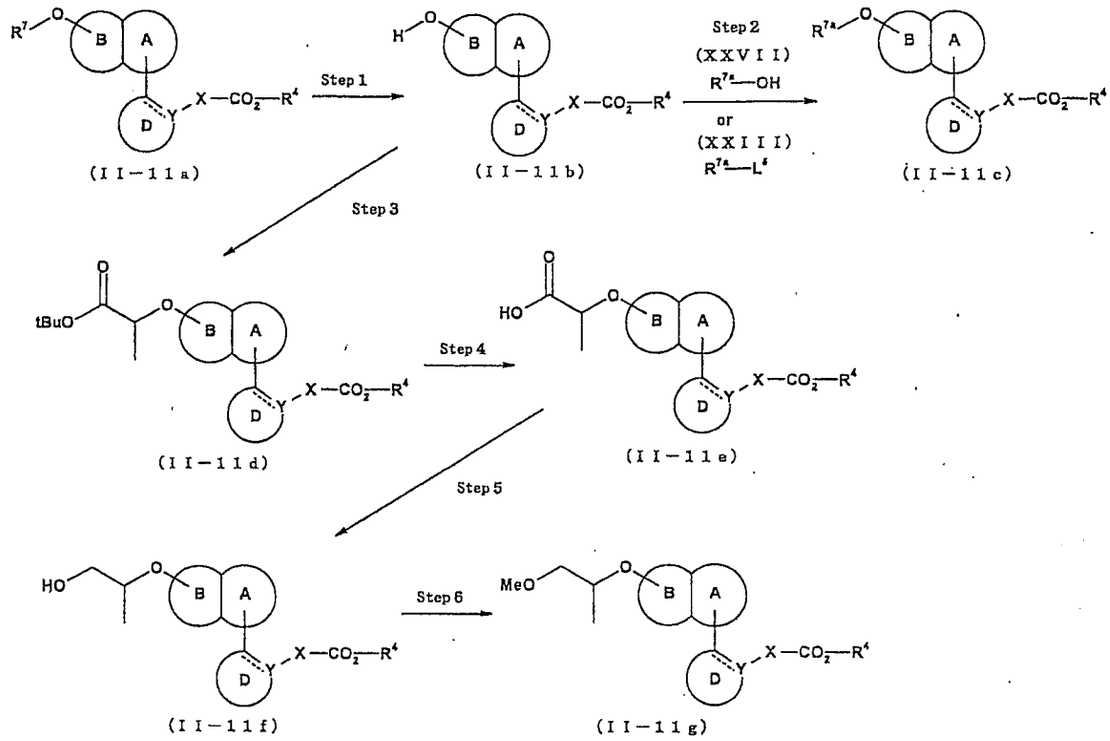
In this step, compound (XV-1j) can be produced by reacting compound (XV-1i) with compound (XXVI). This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method AG.

Compound (XXVI) can be produced according to a method known per se.

Compound (II-11c), which is compound (II-2) having an optionally substituted C_{1-6} alkoxy group on ring B, and compound (II-11g), which is compound (II-2) having 2-methoxy-1-

methylethoxy group on ring B, are produced, for example, according to the following Method AP.

[Method AP]



wherein the each symbol is as defined above.

[Step 1]

In this step, compound (II-11b) can be produced from compound (II-11a). This reaction is carried out in the same manner as in the reaction described in Step 1 of the aforementioned Method AG.

Compound (II-11a) can be produced, for example, according to Step 1 or Step 2 of the aforementioned Method T2, Method AM, Method AN or a method analogous thereto.

[Step 2]

In this step, compound (II-11c) can be produced by reacting compound (II-11b) with compound (XXVII) or compound (XXIII).

The reaction of compound (II-11b) with compound (XXVII) is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method I.

The reaction of compound (II-11b) with compound (XXIII)

is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method AG.

Compound (XXVII) can be produced according to a method known per se.

[Step 3]

In this step, compound (II-11d) can be produced by reacting compound (II-11b) with tert-butyl 2-bromopropionate. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method AG.

[Step 4]

In this step, compound (II-11e) can be produced by subjecting compound (II-11d) to hydrolysis. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method T1.

[Step 5]

In this step, compound (II-11f) can be produced from compound (II-11e). This reaction is carried out for example, by subjecting compound (II-11e) to halogenation at -10°C to 100°C for 0.5 to 30 hr, and subjecting the obtained compound to a reduction reaction at -10°C to 100°C for 0.1 to 50 hr.

The halogenation is carried out in the same manner as in the reaction described in the aforementioned Step 5 of Method N or the halogenation in the aforementioned Method A1.

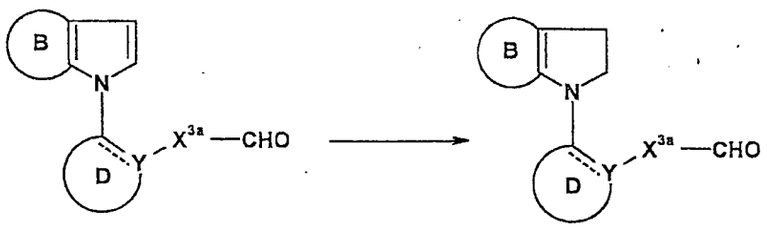
The reduction reaction of the compound obtained by the halogenation is carried out in the same manner as in the reaction described in Step 4 of the aforementioned Method N.

[Step 6]

In this step, compound (II-11g) can be produced by reacting compound (II-11f) with methyl iodide. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method AG.

Compound (XV-1L), which is compound (XV) wherein ring A is 2,3-dihydropyrrole bonded to ring D at the 1-position, is produced, for example, according to the following Method AQ.

[Method AQ]



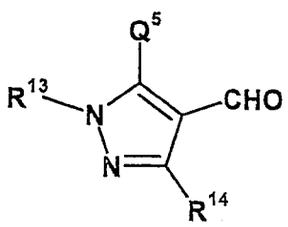
(XV−1k) (XV−1L)

wherein the each symbol is as defined above.

In this method, compound (XV-1L) can be produced by subjecting compound (XV-1k) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

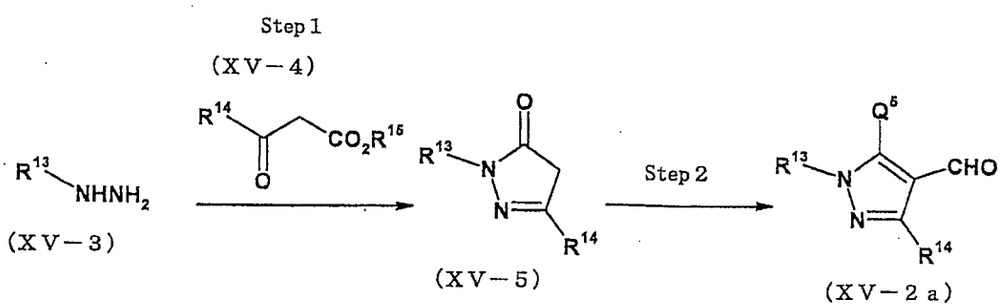
Compound (XV-1k) can be produced, for example, according to Step 2 of the aforementioned Method T4, the aforementioned Method Z1, Method Z3 or a method analogous thereto.

Of compound (XV-2), compound (XV-2a) represented by the formula:



wherein R^{13} is C_{1-6} alkyl group optionally substituted by C_{6-14} aryl group(s), R^{14} is a C_{1-6} alkyl group optionally substituted by 1 to 3 substituents selected from (a) a halogen atom and (b) a C_{1-6} alkoxy group, or a C_{3-10} cycloalkyl group, Q^5 is a chlorine atom, a bromine atom or an iodine atom, and the other symbols are as defined above, can be produced, for example, according to the following Method AR.

[Method AR]



(XV−3) (XV−4) (XV−5) (XV−2a)

wherein R^{15} is a C_{1-10} alkyl group, a benzyl group optionally substituted by C_{1-6} alkyl group(s), or a C_{6-14} aryl group optionally substituted by C_{1-6} alkyl group(s), and the other symbols are as defined above.

R^{15} is preferably methyl, ethyl, tert-butyl, benzyl, phenyl or the like.

[Step 1]

In this step, compound (XV-5) can be produced by reacting compound (XV-3) with compound (XV-4). This reaction is carried out in a solvent that does not adversely influence the reaction.

The amount of the compound (XV-3) to be used is generally 0.1 to 10 mol, preferably 0.5 to 5 mol, per 1 mol of compound (XV-4).

As the solvent that does not adversely influence the reaction, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethylsulfoxide and the like; ketones such as acetone, 2-butanone and the like; water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80 to 200°C, preferably 0 to 150°C.

The reaction time is generally 0.5 to 100 hr.

Compound (XV-3) and compound (XV-4) can be produced according to a method known per se.

[Step 2]

In this step, compound (XV-2a) can be produced by reacting compound (XV-5) with N,N-dimethylformamide and a phosphorus oxyhalide compound. This reaction is carried out without a solvent or in a solvent that does not adversely influence the reaction.

The amount of the N,N-dimethylformamide to be used is generally 1 to 20 mol, per 1 mol of compound (XV-5).

As the phosphorus oxyhalide compound, for example, phosphorus oxychloride, phosphorus oxybromide and the like can be mentioned.

The amount of the phosphorus oxyhalide compound to be used is generally 1 to 20 mol, per 1 mol of compound (XV-5).

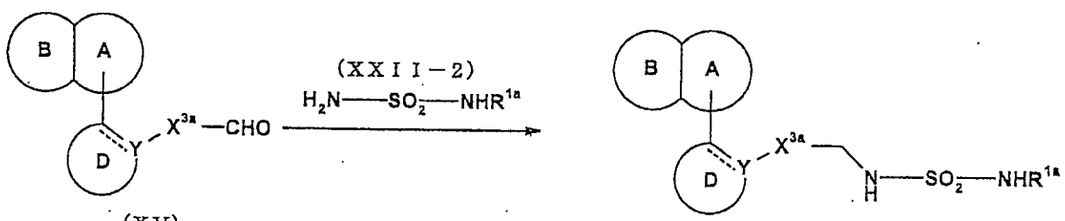
As the solvent that does not adversely influence the reaction, for example, halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as nitrobenzene and the like; amides such as N,N-dimethylformamide and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The reaction temperature is generally -80 to 200°C, preferably 0 to 150°C.

The reaction time is generally 0.5 to 30 hr.

Compound (XXII-1), which is compound (XXII) wherein X is $-X^{3a}-CH_2-$ wherein X^{3a} is as defined above, and R^{1b} is a hydrogen atom, is produced, for example, according to the following Method AS.

[Method AS]



wherein the each symbol is as defined above.

In this method, compound (XXII-1) can be produced by subjecting compound (XV) to a reductive amination reaction with compound (XXII-2). This reaction is carried out by subjecting compound (XV) to an imination reaction with compound (XXII-2) in a solvent that does not adversely influence the reaction, at -100°C to 100°C for 0.1 to 30 hr, and subjecting the obtained compound to a reduction reaction

at -100°C to 100°C for 0.1 to 50 hr.

The imination reaction may be carried out in the presence of an acid or a base.

The amount of compound (XXII-2) to be used is generally 1 to 10 mol, per 1 mol of compound (XV).

As the acid, for example, mineral acids such as hydrochloric acid, sulfuric acid and the like; Lewis acids such as boron trichloride, boron tribromide and the like; organic acids such as acetic acid, trifluoroacetic acid, p-toluenesulfonic acid and the like, and the like can be mentioned.

As the base, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate, potassium carbonate and the like; amines such as pyridine, triethylamine, N,N-diisopropylethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, piperidine and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal C_{1-6} alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like, and the like can be mentioned.

The amount of the acid or base to be used is generally 0.1 to 50 mol, preferably 0.5 to 20 mol, per 1 mol of compound (XV), respectively.

As the solvent that does not adversely influence the reaction, for example, alcohols such as methanol, ethanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; aliphatic hydrocarbons such as hexane, heptane and the like; ethers such as diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane, dimethoxyethane and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like, and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

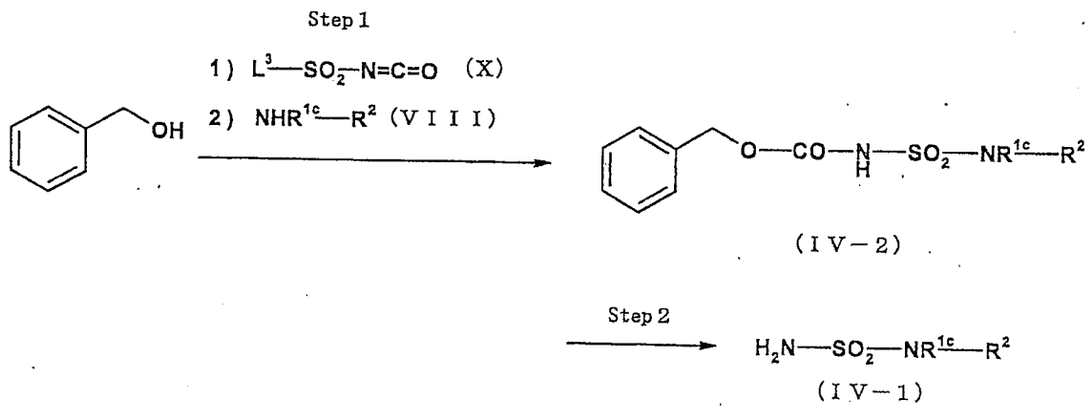
The reduction reaction of the compound obtained by the imination reaction is carried out in the same manner as in the

reaction described in Step 4 of the aforementioned Method N.

Compound (XXII-2) can be produced according to a method known per se.

Compound (IV-1), which is compound (IV) wherein R^{1a} is a hydrogen atom, is produced, for example, according to the following Method AT.

[Method AT]



wherein the each symbol is as defined above.

[Step 1]

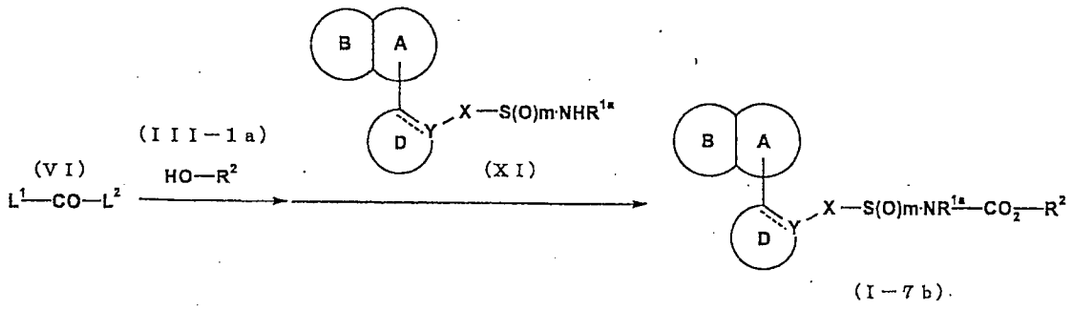
In this step, compound (IV-2) can be produced by reacting benzyl alcohol with compound (X) and compound (VIII) successively. This reaction is carried out in the same manner as in the reaction described in Step 1 of the aforementioned Method I.

[Step 2]

In this step, compound (IV-1) can be produced by subjecting compound (IV-2) to a hydrogenation reaction. This reaction is carried out in the same manner as in the reaction described in Step 2 of the aforementioned Method M.

Compound (I-7b), which is compound (I) wherein W is $-S(O)_mNR^{1a}CO_nR^2$ wherein n is 2 and the other symbols are as defined above, is produced, for example, according to the following Method AU.

[Method AU]



(I-7b)

wherein the each symbol is as defined above.

In this method, compound (I-7b) can be produced from compound (XI). This reaction is carried out according to a method known per se, for example, by reacting compound (VI) with compound (III-1a) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 10 hr, and reacting the obtained compound with compound (XI) in a solvent that does not adversely influence the reaction, at -10°C to 100°C for 0.5 to 50 hr. This reaction may be carried out in the presence of 1 to 20 mol of a base, per 1 mol of compound (XI), where necessary.

As the base, for example, amines such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydrogencarbonate, sodium carbonate, potassium carbonate and the like, and the like can be mentioned. These bases may be used in a mixture at an appropriate ratio.

As the solvent that does not adversely influence the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; acetonitrile, ethyl acetate, pyridine, water and the like can be mentioned. These solvents may be used in a mixture at an appropriate ratio.

The amount of compound (VI) to be used is generally 1 to

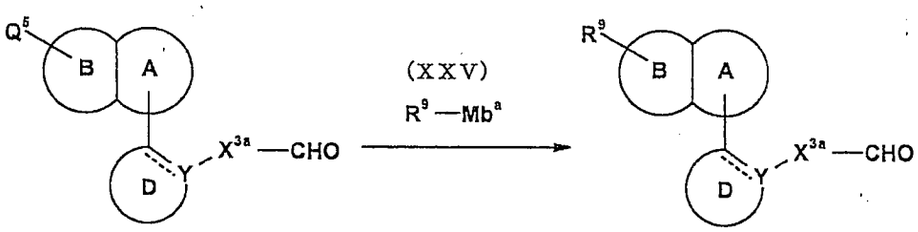
10 mol, preferably 1 to 5 mol, per 1 mol of compound (XI).

The amount of compound (III-1a) to be used is generally 1 to 10 mol, preferably 1 to 5 mol, per 1 mol of compound (XI).

Compound (III-1a) can be produced according to a method known per se.

Compound (XV-1n), which is compound (XV) having a C_{6-14} aryl group, an aromatic heterocyclic group or a C_{3-10} cycloalkyl group on ring B, is produced, for example, according to the following Method AV.

[Method AV]



(XV−1m) (XV−1n)

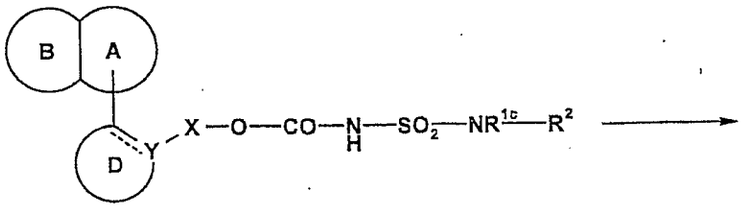
wherein the each symbol is as defined above.

In this method, compound (XV-1n) can be produced by subjecting compound (XV-1m) and compound (XXV) to a coupling reaction using an organic metal catalyst. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method Z2.

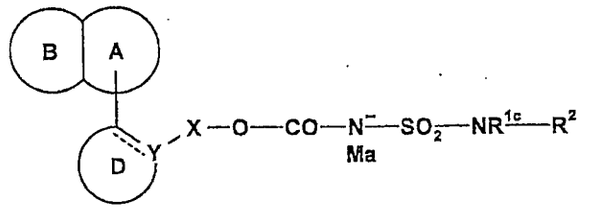
Compound (XV-1m) can be produced, for example, according to the aforementioned Method Z1 to Method Z3 or a method analogous thereto.

The alkali metal salt (I-6c) of compound (I-6a), which is compound (I) wherein W is $-OCONR^{1a}S(O)_mNR^{1c}R^2$ wherein R^{1a} is a hydrogen atom, m is 2 and the other symbols are as defined above, is produced, for example, according to the following Method AW.

[Method AW]



(I-6a)



(I-6c)

wherein the each symbol is as defined above.

As the alkali metal for Ma, sodium, potassium and the like can be mentioned.

In this method, compound (I-6c) can be produced by reacting compound (I-6a) with a base. This reaction is carried out in the same manner as in the reaction described in the aforementioned Method A2.

Compound (I-6a) can be produced, for example, according to the above-mentioned Method I or a method analogous thereto.

In each of the aforementioned reactions, when the starting material compound has an amino group, a carboxyl group, a hydroxy group or a carbonyl group as a substituent, a protecting group generally used in the peptide chemistry and the like may be introduced into these groups, and the object compound can be obtained by eliminating the protecting group as necessary after the reaction.

Examples of the amino-protecting group include a formyl group; a C_{1-6} alkyl-carbonyl group, a C_{1-6} alkoxy-carbonyl group, a benzoyl group, a C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl), a C_{7-13} aralkyloxy-carbonyl group (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl), a trityl group, a phthaloyl group, an N,N-dimethylaminomethylene group, a tri-substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl,

tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group, a nitro group and the like.

Examples of the carboxyl-protecting group include a C_{1-6} alkyl group, a C_{7-20} aralkyl group (e.g., benzyl), a phenyl group, a trityl, a tri-substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkoxy group, a nitro group and the like.

Examples of the hydroxy-protecting group include a C_{1-6} alkyl group, a phenyl group, a trityl group, a C_{7-13} aralkyl group (e.g., benzyl), a formyl group, a C_{1-6} alkyl-carbonyl group, a benzoyl group, a C_{7-13} aralkyl-carbonyl group (e.g., benzylcarbonyl), a 2-tetrahydropyranyl group, a 2-tetrahydrofuranyl group, a tri-substituted silyl group (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl), a C_{2-6} alkenyl group (e.g., 1-allyl) and the like. These groups are optionally substituted by 1 to 3 substituents selected from a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a nitro group and the like.

Examples of the carbonyl-protecting group include a cyclic acetal (e.g., 1,3-dioxane), a non-cyclic acetal (e.g., a di-C_{1-6} alkylacetal) and the like.

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

and the like, reduction and the like.

The compound of the present invention obtained by each production method mentioned above can be isolated and purified by a known means such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like. Each starting material compound used in each of the above-mentioned production methods can be isolated and purified by a known means similar to those mentioned above. It is also possible to use such starting material compound as it is in a reaction mixture without isolation, as a starting material for the next step.

When compound (I) contains an optical isomer, a stereoisomer, a positional isomer or a rotational isomer, they are also encompassed in compound (I) and can be obtained as single products by synthesis techniques and separation techniques known *per se*. For example, when compound (I) contains an optical isomer, an optical isomer separated from the compound is also encompassed in compound (I).

The present invention is explained in detail in the following by referring to Experimental Example, Reference Examples, Examples and Formulation Examples, which are not to be construed as limitative.

Examples

In the following Reference Examples and Examples, "%" means wt% unless otherwise specified, and "room temperature" means a temperature of 1°C to 30°C unless otherwise specified.

Reference Example 1 5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a solution of 1H-indole (719 mg) in N,N-dimethylformamide (10 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 275 mg) with stirring, and the mixture was stirred at 0°C for 30 min. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (900 mg) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at

60°C for 5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 80:20, v/v) to give the title compound (1.10 g, yield 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.81 (d, J = 3.0 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 7.19 (d, J = 3.4 Hz, 1 H), 7.20 - 7.31 (m, 2 H), 7.70 - 7.73 (m, 1 H), 9.52 (s, 1 H).

Reference Example 2 (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

To a solution of 5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 1 (1.09 g) in acetic acid (10 mL) were added malonic acid (573 mg) and pyrrolidine (495 mg), and the mixture was stirred with heating at 100°C for 5 hr. Malonic acid (239 mg) and pyrrolidine (648 mg) were added again to the reaction mixture, and the mixture was stirred with heating at 100°C for 15 hr. After the reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid (1 mL) and water (20 mL) were added, and the mixture was stirred at room temperature for 30 min. The resulting crystals were collected by filtration, and dissolved in ethyl acetate. The obtained solution was dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (1.11 g, yield 87%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.47 (s, 3 H), 5.40 (d, J = 16.2 Hz, 1 H), 6.86 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 7.11 (m, 2 H), 7.15 - 7.27 (m, 2 H), 7.57 (d, J = 3.3 Hz, 1 H), 7.71 - 7.77 (m, 1 H), 12.13 (s, 1 H).

By a method similar to that in Reference Example 1, 5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde of Reference Example 3, which is less polar compound, and 5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde of

Reference Example 4, which is more polar compound were obtained from 1H-indazole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

Reference Example 3 5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.58 (s, 3 H), 3.70 (s, 3 H), 7.28 - 7.38 (m, 2 H), 7.47 - 7.55 (m, 1 H), 7.84 - 7.87 (m, 1 H), 8.35 (d, J = 0.9 Hz, 1 H), 9.58 (s, 1 H).

Reference Example 4 5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.86 (s, 3 H), 7.17 - 7.22 (m, 1 H), 7.39 - 7.44 (m, 1 H), 7.73 - 7.79 (m, 2 H), 8.35 (d, J = 0.9 Hz, 1 H), 9.74 (s, 1 H).

Reference Example 5 (2E)-3-[5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 3 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.40 (s, 3 H), 3.51 (s, 3 H), 5.46 (d, J = 16.2 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.27 - 7.37 (m, 2 H), 7.49 - 7.55 (m, 1 H), 7.96 - 7.99 (m, 1 H), 8.60 (d, J = 1.1 Hz, 1 H), 12.16 (s, 1 H).

Reference Example 6 (2E)-3-[5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 4 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 3.60 (s, 3 H), 5.67 (d, J = 16.2 Hz, 1 H), 7.16 (d, J = 16.2 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.37 - 7.44 (m, 1 H), 7.77 (dd, J = 8.9, 0.9 Hz, 1 H), 7.84 - 7.86 (m, 1 H), 8.85 (d, J = 0.9 Hz, 1 H), 12.26 (s, 1 H).

Reference Example 7 5-(1H-benzimidazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-benzimidazole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.58 (s, 3 H), 3.64 (s, 3 H), 7.19 - 7.21 (m, 1 H), 7.33 - 7.45 (m, 2 H), 7.92 - 7.96 (m, 1 H), 8.03 (s, 1 H), 9.60 (s, 1 H).

Reference Example 8 (2E)-3-[5-(1H-benzimidazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(1H-benzimidazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 7 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.40 (s, 3 H), 3.54 (s, 3 H), 5.49 (d, J = 16.3 Hz, 1 H), 7.04 (d, J = 16.3 Hz, 1 H), 7.22 - 7.28 (m, 1 H), 7.32 - 7.45 (m, 2 H), 7.84 - 7.88 (m, 1 H), 8.55 (s, 1 H), 12.20 (s, 1 H).

Reference Example 9 5-(1-benzothien-3-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a mixture of 1-benzothien-3-ylboronic acid (1.61 g), 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (1.20 g), a 2.0M aqueous sodium carbonate solution (8.0 mL) and 1,2-dimethoxyethane (25 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.44 g), and the reaction mixture was heated under reflux for 6 hr under nitrogen atmosphere. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30 - 50:50, v/v) to give the title compound (0.83 g, yield 42%) as a brown oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.58 (s, 3 H), 3.68 (s, 3 H), 7.38 - 7.51 (m, 3 H), 7.62 (s, 1 H), 7.97 (dd, J = 6.4, 3.0 Hz, 1 H), 9.57 (s, 1 H).

Reference Example 10 (2E)-3-[5-(1-benzothien-3-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(1-benzothien-3-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 9 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 3.58 (s, 3 H), 5.75 (d, J = 16.3 Hz, 1 H), 7.17 (d, J = 16.3 Hz, 1 H), 7.36 - 7.51 (m, 3 H), 8.11 (s, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 12.00 (s, 1 H).

Reference Example 11 1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

To a solution of 1H-pyrrolo[2,3-b]pyridine (5.60 g) in N,N-dimethylformamide (100 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 2.00 g) with stirring, and the mixture was stirred at 0°C for 1 hr. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (5.00 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 60°C for 7 hr. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v) to give the title compound (4.02 g, yield 53%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.68 (s, 3 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.9, 4.7 Hz, 1 H), 7.32 (d, J = 3.6 Hz, 1 H), 8.03 (dd, J = 7.9, 1.6 Hz, 1 H), 8.36 (dd, J = 4.7, 1.6 Hz, 1 H), 9.58 (s, 1 H).

Reference Example 12 ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (diethoxyphosphoryl)acetate (845 mg) in tetrahydrofuran (15 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 163 mg) with stirring, and the mixture was stirred at 0°C for 15 min. A

solution of 1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 11 (780 mg) in tetrahydrofuran (8 mL) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 0°C for 4 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 65:35, v/v) to give the title compound (929 mg, yield 92%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.1 Hz, 3 H), 2.45 (s, 3 H), 3.58 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.70 (d, J = 16.3 Hz, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.30 (d, J = 16.3 Hz, 1 H), 8.03 (dd, J = 7.9, 1.5 Hz, 1 H), 8.35 (dd, J = 4.9, 1.5 Hz, 1 H).

Reference Example 13 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

To a solution of ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 12 (925 mg) in a mixed solvent of tetrahydrofuran (6 mL) and ethanol (6 mL) was added a 1N aqueous sodium hydroxide solution (6 mL), and the mixture was stirred with heating at 60°C for 3 hr. The reaction mixture was allowed to cool to room temperature, neutralized with an aqueous solution (30 mL) of potassium hydrogensulfate (820 mg), and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (763 mg, yield 90%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 3.49 (s, 3 H), 5.48 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.2 Hz, 1 H), 7.27 (dd, J = 8.0, 4.9 Hz, 1 H), 7.70 (d, J = 3.6 Hz, 1 H), 8.16 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 (dd, J = 4.9, 1.5 Hz,

1 H), 12.15 (s, 1 H).

Reference Example 14 1,3-dimethyl-5-(1-naphthyl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 9, the title compound was obtained from 1-naphthylboronic acid and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.61 (s, 3 H), 3.55 (s, 3 H), 7.42 - 7.63 (m, 5 H), 7.97 (d, J = 7.2 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H), 9.43 (s, 1 H).

Reference Example 15 (2E)-3-[1,3-dimethyl-5-(1-naphthyl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 1,3-dimethyl-5-(1-naphthyl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 14 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.41 (s, 3 H), 3.45 (s, 3 H), 5.61 (d, J = 16.2 Hz, 1 H), 7.07 (d, J = 16.2 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.53 - 7.73 (m, 4 H), 8.07 - 8.10 (m, 1 H), 8.17 (d, J = 8.3 Hz, 1 H), 11.95 (s, 1 H).

Reference Example 16 1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 4-methyl-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 2.61 (s, 3 H), 3.58 (s, 3 H), 6.83 (dd, J = 3.4, 0.9 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.16 - 7.19 (m, 2 H), 9.51 (s, 1 H).

Reference Example 17 (2E)-3-[1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 16 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 2.55 (s, 3 H), 3.46 (s, 3 H), 5.45 (d, J = 16.2 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H),

6.89 (dd, J = 3.4, 0.9 Hz, 1 H), 6.98 - 7.01 (m, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.11 - 7.14 (m, 1 H), 7.54 (d, J = 3.4 Hz, 1 H), 12.13 (s, 1 H).

Reference Example 18 5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 4-chloro-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.94 (dd, J = 3.4, 0.9 Hz, 1 H), 6.97 - 7.04 (m, 1 H), 7.15 - 7.30 (m, 3 H), 9.53 (s, 1 H).

Reference Example 19 (2E)-3-[5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 18 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.48 (s, 3 H), 5.39 (d, J = 15.9 Hz, 1 H), 6.89 (d, J = 3.2 Hz, 1 H), 6.99 - 7.09 (m, 2 H), 7.20 - 7.25 (m, 1 H), 7.27 - 7.31 (m, 1 H), 7.72 (d, J = 3.2 Hz, 1 H), 12.15 (s, 1 H).

Reference Example 20 5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-fluoro-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.58 (s, 3 H), 6.77 (d, J = 3.3 Hz, 1 H), 7.00 - 7.03 (m, 2 H), 7.22 (d, J = 3.3 Hz, 1 H), 7.33 - 7.37 (m, 1 H), 9.51 (s, 1 H).

Reference Example 21 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 20 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.48 (s, 3 H), 5.38 (d, J = 16.2 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.99 - 7.10 (m, 3 H), 7.49 - 7.53 (m, 1 H), 7.66 (d, J = 3.4 Hz, 1 H), 12.15 (s, 1 H).

Reference Example 22 5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-methoxy-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.58 (s, 3 H), 3.87 (s, 3 H), 6.73 (dd, J = 3.3, 0.9 Hz, 1 H), 6.90 (dd, J = 8.5, 2.4 Hz, 1 H), 6.99 (dd, J = 8.5, 1.5 Hz, 1 H), 7.14 - 7.15 (m, 2 H), 9.51 (s, 1 H).

Reference Example 23 (2E)-3-[5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 22 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 5.40 (d, J = 16.2 Hz, 1 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 6.81 - 6.85 (m, 1 H), 6.89 - 6.93 (m, 1 H), 7.07 (d, J = 16.2 Hz, 1 H), 7.22 (d, J = 2.1 Hz, 1 H), 7.51 (d, J = 3.4 Hz, 1 H), 12.13 (s, 1 H).

Reference Example 24 5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 6-chloro-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.79 (dd, J = 3.4, 0.8 Hz, 1 H), 7.08 - 7.10 (m, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.5, 1.9 Hz, 1 H), 7.62 (d, J = 8.5 Hz, 1 H), 9.53 (s, 1 H).

Reference Example 25 (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 24 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.48 (s, 3 H), 5.35 (d, J = 16.3 Hz, 1 H), 6.89 (d, J = 3.4 Hz, 1 H), 7.06 (d, J = 16.3 Hz, 1 H), 7.08 - 7.09 (m, 1 H), 7.23 (dd, J = 8.3, 1.9 Hz, 1 H), 7.62 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 12.15 (s, 1 H).

Reference Example 26 5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 6-(benzyloxy)-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.49 (s, 3 H), 4.99 - 5.08 (m, 2 H), 6.59 (d, J = 2.1 Hz, 1 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.98 (dd, J = 8.7, 2.1 Hz, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.29 - 7.48 (m, 5 H), 7.58 (d, J = 8.7 Hz, 1 H), 9.52 (s, 1 H).

Reference Example 27 ethyl (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 26 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.43 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.00 (s, 2 H), 5.64 (d, J = 16.4 Hz, 1 H), 6.50 (d, J = 2.1 Hz, 1 H), 6.72 (dd, J = 3.2, 0.8 Hz, 1 H), 6.93 - 6.99 (m, 2 H), 7.27 - 7.45 (m, 6 H), 7.58 (d, J = 8.7 Hz, 1 H).

Reference Example 28 (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 27.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.44 (s, 3 H), 4.99 (d, J = 11.7 Hz, 1 H), 5.07 (d, J = 11.7 Hz, 1 H), 5.43 (d, J = 16.1 Hz, 1 H), 6.60 (d, J = 1.9 Hz, 1 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.92 (dd, J = 8.5, 1.9 Hz, 1 H), 7.08 (d, J = 16.1 Hz, 1 H), 7.27 - 7.44 (m, 6 H), 7.60 (d, J = 8.5 Hz, 1 H), 12.13 (s, 1 H).

Reference Example 29 1,3-dimethyl-5-(2-naphthyl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 9, the title compound was obtained from 2-naphthylboronic acid and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 3.78 (s, 3 H), 7.47 (dd, J = 8.5, 1.7 Hz, 1 H), 7.58 - 7.64 (m, 2 H), 7.88 - 7.96 (m, 3 H), 8.00 (d, J = 8.5 Hz, 1 H), 9.67 (s, 1 H).

Reference Example 30 (2E)-3-[1,3-dimethyl-5-(2-naphthyl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 1,3-dimethyl-5-(2-naphthyl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 29 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.68 (s, 3 H), 5.89 (d, J = 16.2 Hz, 1 H), 7.29 (d, J = 16.2 Hz, 1 H), 7.53 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 - 7.70 (m, 2 H), 8.00 - 8.06 (m, 3 H), 8.12 (d, J = 8.5 Hz, 1 H), 12.04 (s, 1 H).

Reference Example 31 1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 9, the title compound was obtained from (quinolin-8-yl)boronic acid and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.60 (s, 3 H), 3.60 (s, 3 H), 7.46 - 7.76 (m, 3 H), 8.04 (dd, J = 8.0, 1.9 Hz, 1 H), 8.28 (dd, J = 8.3, 1.9 Hz, 1 H), 8.96 (dd, J = 4.2, 1.5 Hz, 1 H), 9.51 (s, 1 H).

Reference Example 32 ethyl (2E)-3-[1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the

title compound was obtained from 1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 31 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.51 (s, 3 H), 3.55 (s, 3 H), 4.11 (q, J = 7.2 Hz, 2 H), 5.91 (d, J = 16.4 Hz, 1 H), 7.37 (d, J = 16.4 Hz, 1 H), 7.48 (dd, J = 8.3, 4.3 Hz, 1 H), 7.62 - 7.74 (m, 2 H), 7.96 - 8.05 (m, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 8.94 (d, J = 4.1 Hz, 1 H).

Reference Example 33 (2E)-3-[1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 32.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 3.43 (s, 3 H), 5.69 (d, J = 16.3 Hz, 1 H), 7.10 (d, J = 16.3 Hz, 1 H), 7.64 (dd, J = 8.3, 4.2 Hz, 1 H), 7.73 - 7.88 (m, 2 H), 8.23 (dd, J = 6.8, 2.7 Hz, 1 H), 8.53 (dd, J = 8.3, 1.7 Hz, 1 H), 8.91 (dd, J = 4.2, 1.7 Hz, 1 H), 11.90 (s, 1 H).

Reference Example 34 5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5,6-difluoro-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.76 (d, J = 2.3 Hz, 1 H), 6.88 (dd, J = 9.8, 6.8 Hz, 1 H), 7.20 (d, J = 3.4 Hz, 1 H), 7.46 (dd, J = 10.2, 7.6 Hz, 1 H), 9.54 (s, 1 H).

Reference Example 35 ethyl (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 34 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.50 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.59 (d, J = 16.3 Hz,

1 H), 6.72 - 6.83 (m, 2 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.27 (d, J = 16.3 Hz, 1 H), 7.45 (dd, J = 10.2, 7.6 Hz, 1 H).

Reference Example 36 (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 35.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.49 (s, 3 H), 5.34 (d, J = 16.2 Hz, 1 H), 6.87 (dd, J = 3.4, 0.8 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.19 (dd, J = 10.7, 6.8 Hz, 1 H), 7.65 (d, J = 3.4 Hz, 1 H), 7.76 (dd, J = 10.9, 7.9 Hz, 1 H), 12.18 (s, 1 H).

Reference Example 37 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a solution of 5-chloro-1H-indole (2.00 g) in N,N-dimethylformamide (10 mL) was added 60% sodium hydride (in oil, 550 mg) with stirring, and the mixture was stirred at room temperature for 1 hr. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (2.00 g) was added to this reaction mixture at room temperature, and the mixture was stirred with heating at 70°C for 2 hr. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 85:15 - 65:35, v/v), and crystallized from hexane-diisopropyl ether to give the title compound (1.67 g, yield 49%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.19 - 7.27 (m, 2 H), 7.69 (d, J = 1.5 Hz, 1 H), 9.53 (s, 1 H).

Reference Example 38 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

To a solution of 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-

1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (1.91 g) in pyridine (10 mL) were added malonic acid (2.90 g) and piperidine (1.7 mL), and the mixture was stirred with heating at 110°C for 2.5 hr. After the reaction mixture was allowed to cool to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous ammonium chloride solution and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 65:35 - 25:75, v/v) to give the title compound (1.74 g, yield 79%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.45 (s, 3 H), 3.51 (s, 3 H), 5.54 (d, J = 15.9 Hz, 1 H), 6.74 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 2.3 Hz, 1 H), 7.32 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Reference Example 39 5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

A mixture of 3-chloro-1H-indazole (1.53 g), 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (1.00 g) and potassium carbonate (1.38 g) in N,N-dimethylformamide (30 mL) was stirred with heating at 120°C for 12 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 95:5 - 75:25, v/v) to give the title compound (1.65 g, yield 60%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.56 (s, 3 H), 3.73 (s, 3 H), 7.28 (dd, J = 7.5, 0.9 Hz, 1 H), 7.30 - 7.41 (m, 1 H), 7.54 - 7.58 (m, 1 H), 7.81 (dd, J = 7.5, 0.9 Hz, 1 H), 9.60 (s, 1 H).

Reference Example 40 (2E)-3-[5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

A solution of 5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 39 (1.65 g) and ethyl (diethoxyphosphoryl)acetate (1.41 g) in tetrahydrofuran (30 mL) was cooled at 0°C in an ice bath, 60% sodium hydride (in oil, 252 mg) was added with stirring, and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was dissolved in a mixed solvent of tetrahydrofuran (30 mL) and methanol (30 mL). A 4N aqueous sodium hydroxide solution (4 mL) was added, and the mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid (20 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated to give the title compound (1.59 g, yield 84%) as colorless crystals.
^{1}H-NMR (300 MHz, DMSO-d_6) δ:2.40 (s, 3 H), 3.56 (s, 3 H), 5.50 (d, J = 16.2 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.61 - 7.66 (m, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 12.21 (br s, 1 H).

Reference Example 41 1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 6-(trifluoromethyl)-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.59 (s, 3 H), 3.59 (s, 3 H), 6.71 - 6.99 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.43 - 7.58 (m, 1 H), 7.82 (d, J = 8.3 Hz, 1 H), 9.55 (s, 1 H).

Reference Example 42 (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 40, the title compound was obtained from 1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazole-4-carbaldehyde

obtained in Reference Example 41.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.40 (s, 3 H), 3.50 (s, 3 H), 5.35 (d, J = 16.3 Hz, 1 H), 6.87 - 7.19 (m, 2 H), 7.21 - 7.40 (m, 1 H), 7.44 - 7.65 (m, 1 H), 7.85 (d, J = 3.4 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 11.99 (s, 1 H).

Reference Example 43 ethyl 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoate

Ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 12 (7.49 g) was dissolved in ethanol (200 mL), 10% palladium carbon (800 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50 - 0:100, v/v) to give the title compound (6.64 g, yield 88%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.15 (t, J = 7.2 Hz, 3 H), 2.25 - 2.35 (m, 5 H), 2.55 - 2.64 (m, 2 H), 3.51 (s, 3 H), 4.00 (q, J = 7.2 Hz, 2 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.17 (dd, J = 7.8, 4.8 Hz, 1 H), 7.21 (d, J = 3.6 Hz, 1 H), 8.00 (dd, J = 7.8, 1.6 Hz, 1 H), 8.34 (dd, J = 4.8, 1.6 Hz, 1 H).

Reference Example 44 ethyl 3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoate

By a method similar to that in Reference Example 43, the title compound (more polar compound, 0.48 g, yield 6%) was obtained as a colorless oil, together with the compound of Reference Example 43, from ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 12.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.20 (t, J = 7.1 Hz, 3 H), 2.21 (s, 3 H), 2.36 - 2.45 (m, 2 H), 2.55 - 2.65 (m, 2 H), 3.17 - 3.27 (m, 2 H), 3.63 (s, 3 H), 3.85 (t, J = 8.6 Hz, 2 H), 4.05 (q, J = 7.1 Hz, 2 H), 6.59 (dd, J = 7.0, 5.3 Hz, 1 H), 7.34 (dd, J = 7.0, 1.0 Hz, 1 H), 7.88 (dd, J = 5.3, 1.0 Hz, 1 H).

Reference Example 45 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-

b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoate obtained in Reference Example 43.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.08 - 2.17 (m, 2 H), 2.19 (s, 3 H), 2.31 - 2.45 (m, 2 H), 3.40 (s, 3 H), 6.79 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.65 (d, J = 3.6 Hz, 1 H), 8.11 (dd, J = 7.8, 1.6 Hz, 1 H), 8.25 (dd, J = 4.7, 1.6 Hz, 1 H), 12.02 (s, 1 H).

Reference Example 46 3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl 3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoate obtained in Reference Example 44.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.08 (s, 3 H), 2.21 - 2.29 (m, 2 H), 2.37 - 2.44 (m, 2 H), 3.15 - 3.22 (m, 2 H), 3.49 (s, 3 H), 3.70 - 3.88 (m, 2 H), 6.61 (dd, J = 7.1, 5.2 Hz, 1 H), 7.43 (dd, J = 7.1, 1.5 Hz, 1 H), 7.73 (dd, J = 5.2, 1.5 Hz, 1 H), 12.02 (s, 1 H).

Reference Example 47 ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-2-methylacrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 11 and ethyl 2-(diethoxyphosphoryl)propanoate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 2.29 (s, 3 H), 3.66 (s, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 6.65 (d, J = 3.4 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.0, 4.7 Hz, 1 H), 7.32 (s, 1 H), 7.97 (dd, J = 8.0, 1.5 Hz, 1 H), 8.34 - 8.40 (m, 1 H).

Reference Example 48 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-2-methylacrylic acid

By a method similar to that in Reference Example 13, the

title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-2-methylacrylate obtained in Reference Example 47.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.06 (d, J = 1.3 Hz, 3 H), 2.20 (s, 3 H), 3.54 (s, 3 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 1.3 Hz, 1 H), 7.25 (dd, J = 7.9, 4.7 Hz, 1 H), 7.56 (d, J = 3.8 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H), 12.32 (s, 1 H).

Reference Example 49 5-chloro-N-methoxy-N,1-dimethyl-1H-pyrazole-4-carboxamide

To a mixture of N,O-dimethylhydroxyamine hydrochloride (6.78 g) and N,N-dimethylformamide (50 mL) was added triethylamine (9.68 mL), and the mixture was stirred at room temperature for 10 min. 5-Chloro-1-methyl-1H-pyrazole-4-carboxylic acid (9.70 g), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (13.32 g) and 1-hydroxybenzotriazole monohydrate (10.64 g) were added to this reaction mixture, and the mixture was stirred at room temperature for 15 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with aqueous potassium carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 67:33 - 25:75, v/v) to give the title compound (9.92 g, yield 81%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.33 (s, 3 H), 3.66 (s, 3 H), 3.88 (s, 3 H), 7.92 (s, 1 H).

Reference Example 50 5-chloro-1-methyl-1H-pyrazole-4-carbaldehyde

To a solution of 5-chloro-N-methoxy-N,1-dimethyl-1H-pyrazole-4-carboxamide obtained in Reference Example 49 (9.47 g) in tetrahydrofuran (60 mL) was added dropwise diisobutylaluminum hydride (1.5M toluene solution, 37.2 mL) with stirring at 0°C, and the reaction mixture was stirred at 0°C for 1 hr. Magnesium

sulfate 10 hydrate (19.0 g) was gradually added, and the mixture was stirred at room temperature for 5 hr. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 75:25 - 33:67, v/v), and crystallized from hexane-diethyl ether to give the title compound (2.88 g, yield 43%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.90 (s, 3 H), 7.96 (s, 1 H), 9.83 (s, 1 H).

Reference Example 51 1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-chloro-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 50 and 1H-pyrrolo[2,3-b]pyridine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.78 (s, 3 H), 6.79 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 7.9, 4.7 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.03 (dd, J = 7.9, 1.6 Hz, 1 H), 8.10 (s, 1 H), 8.36 (dd, J = 4.7, 1.6 Hz, 1 H), 9.62 (s, 1 H).

Reference Example 52 ethyl (2E)-2-methyl-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 51 and ethyl 2-(diethoxyphosphoryl)propanoate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (t, J = 7.1 Hz, 3 H), 2.10 (d, J = 1.1 Hz, 3 H), 3.70 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 6.74 (d, J = 3.6 Hz, 1 H), 7.08 (d, J = 1.1 Hz, 1 H), 7.17 - 7.24 (m, 2 H), 7.91 (s, 1 H), 8.02 (dd, J = 7.8, 1.6 Hz, 1 H), 8.36 (dd, J = 4.8, 1.6 Hz, 1 H).

Reference Example 53 (2E)-2-methyl-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-2-methyl-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-

yl]acrylate obtained in Reference Example 52.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.00 (s, 3 H), 3.59 (s, 3 H), 6.84 (s, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.28 (dd, J = 8.0, 4.5 Hz, 1 H), 7.73 (d, J = 3.6 Hz, 1 H), 8.02 (s, 1 H), 8.16 (dd, J = 8.0, 1.6 Hz, 1 H), 8.28 (dd, J = 4.5, 1.6 Hz, 1 H), 12.19 (s, 1 H).

Reference Example 54 5-(6-hydroxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

5-[6-(Benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 26 (1.59 g) was dissolved in methanol (120 mL), 10% palladium carbon (330 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 24 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v) to give the title compound (574 mg, yield 48%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.45 (s, 3 H), 3.14 - 3.22 (m, 2 H), 3.67 (s, 3 H), 3.83 - 3.95 (m, 1 H), 3.98 - 4.07 (m, 1 H), 5.54 (br s, 1 H), 5.80 (d, J = 2.1 Hz, 1 H), 6.28 (dd, J = 8.0, 2.1 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 1 H), 9.77 (s, 1 H).

Reference Example 55 5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

A mixture of 5-(6-hydroxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 54 (267 mg), methyl iodide (2.61 g) and potassium carbonate (430 mg) in acetone (8 mL) was heated under reflux for 24 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 75:25, v/v) to give the title compound (250 mg, yield 89%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:2.48 (s, 3 H), 3.14 - 3.26 (m, 2 H),

3.68 (s, 3 H), 3.69 (s, 3 H), 3.83 - 3.93 (m, 1 H), 3.97 - 4.07 (m, 1 H), 5.88 (d, J = 2.3 Hz, 1 H), 6.34 (dd, J = 8.0, 2.3 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 1 H), 9.77 (s, 1 H).

Reference Example 56 ethyl (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 55 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.26 (t, J = 7.2 Hz, 3 H), 2.38 (s, 3 H), 3.14 - 3.25 (m, 2 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 3.75 - 3.95 (m, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.76 (d, J = 2.3 Hz, 1 H), 5.94 (d, J = 16.1 Hz, 1 H), 6.31 (dd, J = 8.0, 2.3 Hz, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 16.1 Hz, 1 H).

Reference Example 57 (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 56.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.28 (s, 3 H), 3.10 - 3.18 (m, 2 H), 3.59 (s, 3 H), 3.60 (s, 3 H), 3.65 - 3.77 (m, 1 H), 3.87 - 3.97 (m, 1 H), 5.65 (d, J = 2.3 Hz, 1 H), 5.77 (d, J = 16.2 Hz, 1 H), 6.29 (dd, J = 8.1, 2.3 Hz, 1 H), 7.08 (d, J = 8.1 Hz, 1 H), 7.25 (d, J = 16.2 Hz, 1 H), 12.06 (s, 1 H).

Reference Example 58 5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 6-methoxy-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 3.59 (s, 3 H), 3.78 (s, 3 H), 6.53 (d, J = 2.3 Hz, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.6, 2.3 Hz, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.6 Hz, 1 H), 9.54 (s, 1 H).

Reference Example 59 ethyl (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-

1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 58 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 3.76 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.65 (d, J = 16.3 Hz, 1 H), 6.42 (d, J = 2.1 Hz, 1 H), 6.72 (d, J = 3.2 Hz, 1 H), 6.88 (dd, J = 8.7, 2.1 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.32 (d, J = 16.3 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Reference Example 60 (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 59.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.49 (s, 3 H), 3.69 (s, 3 H), 5.43 (d, J = 16.2 Hz, 1 H), 6.48 (d, J = 2.1 Hz, 1 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 6.84 (dd, J = 8.7, 2.1 Hz, 1 H), 7.10 (d, J = 16.2 Hz, 1 H), 7.38 (d, J = 3.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 12.14 (s, 1 H).

Reference Example 61 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol

5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (4.08 g) was dissolved in a mixed solvent of tetrahydrofuran (24 mL) and methanol (6 mL), sodium borohydride (845 mg) was added, and the mixture was stirred at 0°C for 3 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (3.99 g, yield 97%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.28 (t, J = 5.2 Hz, 1 H), 2.38 (s, 3 H),

3.50 (s, 3 H), 4.22 - 4.39 (m, 2 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.15 - 7.22 (m, 2 H), 7.66 (d, J = 1.5 Hz, 1 H).

Reference Example 62 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetaldehyde

5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (5.26 g) was dissolved in a mixed solvent of tetrahydrofuran (30 mL) and tert-butyl alcohol (30 mL), potassium tert-butoxide (2.59 g) and ethyl bromoacetate (3.53 g) were added, and the mixture was stirred at room temperature for 5 hr. This reaction mixture was filtrated through celite®, and the filtrate was concentrated. The residue was dissolved in a mixed solvent of tetrahydrofuran (10 mL) and ethanol (10 mL), a 8N aqueous sodium hydroxide solution (5 ml) was added, and the mixture was stirred at room temperature for 3 hr. Acetic acid (30 ml) was added, and the mixture was stirred at 60°C for 3 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (2.89 g, yield 52%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.24 (s, 3 H), 3.20 - 3.40 (m, 2 H), 3.50 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.65 (d, J = 1.5 Hz, 1 H), 9.51 (t, J =1.5 Hz, 1 H).

Reference Example 63 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanol

By a method similar to that in Reference Example 61, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetaldehyde obtained in Reference Example 62.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.31 (s, 3 H), 2.37 - 2.57 (m, 2 H), 3.44 - 3.55 (m, 5 H), 6.66 (dd, J = 3.2, 0.8 Hz, 1 H), 6.94 (d,

J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Reference Example 64 ethyl (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.49 (s, 3 H), 4.12 (q, J = 6.9 Hz, 2 H), 5.60 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.28 (d, J = 16.3 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H)

Reference Example 65 ethyl 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoate

Ethyl (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 64 (5.09 g) was dissolved in a mixed solvent of tetrahydrofuran (25 mL) and ethanol (25 mL), platinum oxide (500 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 16 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 75:25, v/v) to give the title compound (4.91 g, yield 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.12 - 1.19 (m, 3 H), 2.18 - 2.25 (m, 2 H), 2.30 (s, 3 H), 2.47 - 2.66 (m, 2 H), 3.41 - 3.45 (m, 3 H), 3.94 - 4.03 (m, 2 H), 6.66 - 6.70 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Reference Example 66 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol

To a solution of ethyl 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoate obtained in Reference Example 65 (4.11 g) in tetrahydrofuran (24 mL), which was cooled

at 0°C in an ice bath, was added diisobutylaluminum hydride (1.5M toluene solution, 20mL) by small portions with stirring. The reaction mixture was stirred at room temperature for 1 hr, and was cooled again at 0°C in an ice bath. Methanol and water were added to the reaction mixture with stirring, the mixture was filtrated through celite®, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (3.47 g, yield 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.44 - 1.56 (m, 2 H), 2.20 - 2.40 (m, 5 H), 3.39 - 3.47 (m, 5 H), 6.66 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 2.1 Hz, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Reference Example 67 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetic acid

[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetaldehyde obtained in Reference Example 62 (501 mg) was dissolved in a mixed solvent of tert-butyl alcohol (5.8 mL) and water (1.2 mL). Sodium dihydrogenphosphate (627 mg), sodium chlorite (236 mg) and 2-methyl-2-butene (611 mg) were added, and the mixture was stirred at room temperature for 14 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (ethyl acetate), and crystallized from hexane-ethyl acetate to give the title compound (412 mg, yield 78%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.17 (s, 3 H), 3.01 - 3.16 (m, 2 H), 3.40 (s, 3 H), 6.75 (d, J = 3.0 Hz, 1 H), 7.04 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.5, 2.1 Hz, 1 H), 7.51 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 12.25 (br s, 1 H).

Reference Example 68 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoic acid

By a method similar to that in Reference Example 65, the

title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.09 (t, J = 7.8 Hz, 2 H), 2.20 (s, 3 H), 2.49 - 2.53 (m, 2 H), 3.37 (s, 3 H), 6.76 (d, J = 2.7 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.56 (d, J = 3.0 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 12.07 (br s, 1 H).

Reference Example 69 ethyl (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]but-2-enoate

By a method similar to that in Reference Example 12, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetaldehyde obtained in Reference Example 62 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.18 - 1.29 (m, 3 H), 2.25 (s, 3 H), 2.96 - 3.17 (m, 2 H), 3.49 (s, 3 H), 4.07 - 4.17 (m, 2 H), 5.49 - 5.60 (m, 1 H), 6.65 (dd, J = 3.3, 0.8 Hz, 1 H), 6.71 - 6.82 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (d, J = 1.7 Hz, 1 H).

Reference Example 70 (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]but-2-enoic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]but-2-enoate obtained in Reference Example 69.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.30 (s, 3 H), 3.37 - 3.52 (m, 5 H), 5.32 - 5.49 (m, 1 H), 5.88 - 5.98 (m, 1 H), 6.72 - 6.83 (m, 1 H), 6.96 - 7.07 (m, 1 H), 7.14 - 7.23 (m, 1 H), 7.51 - 7.65 (m, 1 H), 7.70 - 7.80 (m, 1 H), 12.11 (br s, 1 H).

Reference Example 71 4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]butanoic acid

By a method similar to that in Reference Example 65, the title compound was obtained from (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]but-2-enoic acid obtained in Reference Example 70.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 1.34 - 1.47 (m, 2 H), 1.95 - 2.32 (m, 7 H), 3.37 (s, 3 H), 6.75 (d, J = 2.7 Hz, 1 H), 7.01 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.55 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H).

Reference Example 72 2-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}-1H-isoindole-1,3(2H)-dione

To a solution of [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 (3.52 g) in tetrahydrofuran (25 mL) were added methanesulfonyl chloride (2.05 g) and triethylamine (1.94 g) with stirring at 0°C, and the mixture was stirred at room temperature for 16 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was dissolved in N,N-dimethylformamide (15 mL). Potassium phthalimide (2.07 g) was added, and the mixture was stirred at 50°C for 16 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (3.23 g, yield 62%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.37 (s, 3 H), 3.41 (s, 3 H), 4.38 (d, J = 15.3 Hz, 1 H), 4.73 (d, J = 15.3 Hz, 1 H), 6.59 (dd, J = 3.4, 0.8 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 1 H), 6.89 (dd, J = 8.7, 1.9 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 1.7 Hz, 1 H), 7.55 - 7.65 (m, 4 H).

Reference Example 73 2-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-1H-isoindole-1,3(2H)-dione

By a method similar to that in Reference Example 72, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanol obtained in Reference Example 63.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.23 (s, 3 H), 2.50 - 2.84 (m, 2 H),

3.42 (s, 3 H), 3.50 - 3.75 (m, 2 H), 6.65 (dd, J = 3.3, 0.8 Hz, 1 H), 6.80 - 6.96 (m, 2 H), 7.19 (d, J = 3.2 Hz, 1 H), 7.57 (d, J = 1.7 Hz, 1 H), 7.68 (s, 4 H).

Reference Example 74 2-{3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl}-1H-isoindole-1,3(2H)-dione

By a method similar to that in Reference Example 72, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.55 - 1.73 (m, 2 H), 2.15 - 2.54 (m, 5 H), 3.42 - 3.56 (m, 5 H), 6.58 (d, J = 3.4 Hz, 1 H), 6.88 - 6.97 (m, 1 H), 7.06 - 7.14 (m, 2 H), 7.52 (d, J = 1.7 Hz, 1 H), 7.65 - 7.97 (m, 4 H).

Reference Example 75 1-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanamine

To a solution of 2-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}-1H-isoindole-1,3(2H)-dione obtained in Reference Example 72 (543 mg) in tetrahydrofuran (13 mL) was added a 35% aqueous hydrazine solution (1.23 g) with stirring, and the mixture was heated under reflux for 16 hr. After the reaction mixture was allowed to cool to room temperature, and concentrated, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (305 mg, yield 83%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.25 (br s, 2 H), 2.35 (s, 3 H), 3.40 - 3.55 (m, 5 H), 6.68 (d, J = 2.3 Hz, 1 H), 6.97 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Reference Example 76 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanamine

By a method similar to that in Reference Example 75, the

title compound was obtained from 2-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-1H-isoindole-1,3(2H)-dione obtained in Reference Example 73.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.12 - 1.32 (m, 2 H), 2.24 - 2.44 (m, 5 H), 2.60 (br s, 2 H), 3.46 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Reference Example 77 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-amine

By a method similar to that in Reference Example 75, the title compound was obtained from 2-{3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl}-1H-isoindole-1,3(2H)-dione obtained in Reference Example 74.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.07 - 1.23 (m, 2 H), 1.34 - 1.46 (m, 2 H), 2.15 - 2.36 (m, 5 H), 2.50 (br s, 2 H), 3.45 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.15 - 7.21 (m, 1 H), 7.65 (d, J = 1.9 Hz, 1 H).

Reference Example 78 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanal

To a mixture of celite® (4.00 g) in dichloromethane (35 mL) was added pyridinium dichromate (4.00 g) with stirring, and the mixture was stirred at room temperature for 10 min. 3-[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66 (2.70 g) was added to this reaction mixture, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was filtrated through celite®, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (1.49 g, yield 56%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.31 (s, 3 H), 2.35 (dd, J = 5.7, 1.9 Hz, 2 H), 2.52 - 2.61 (m, 2 H), 3.44 (s, 3 H), 6.69 (d, J = 3.4 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.66 (d, J = 1.9 Hz, 1 H), 9.53 (s, 1 H).

Reference Example 79 1-(4-formyl-1,3-dimethyl-1H-pyrazol-5-yl)-1H-indole-5-carbonitrile

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-indole-5-carbonitrile and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.58 (s, 3 H), 6.90 (d, J = 3.3 Hz, 1 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.31 (d, J = 3.3 Hz, 1 H), 7.53 (dd, J = 8.7, 1.6 Hz, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 9.54 (s, 1 H).

Reference Example 80 ethyl (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1-(4-formyl-1,3-dimethyl-1H-pyrazol-5-yl)-1H-indole-5-carbonitrile obtained in Reference Example 79 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.19 - 1.25 (m, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 4.08 - 4.17 (m, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.90 (dd, J = 3.4, 0.8 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.21 - 7.28 (m, 2 H), 7.50 (dd, J = 8.5, 1.5 Hz, 1 H), 8.09 (d, J = 0.9 Hz, 1 H).

Reference Example 81 (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 80.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.37 (s, 3 H), 3.48 (s, 3 H), 5.38 (d, J = 16.2 Hz, 1 H), 6.92 - 7.02 (m, 2 H), 7.21 (d, J = 8.5 Hz, 1 H), 7.58 (dd, J = 8.7, 1.3 Hz, 1 H), 7.81 (d, J = 3.2 Hz, 1 H), 8.29 (s, 1 H).

Reference Example 82 5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 6-fluoro-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.59 (s, 3 H), 6.76 - 6.82 (m, 2 H), 6.97 - 7.05 (m, 1 H), 7.17 (d, J = 3.4 Hz, 1 H), 7.63 (dd, J = 8.7, 5.3 Hz, 1 H), 9.54 (s, 1 H).

Reference Example 83 (2E)-3-[5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 2, the title compound was obtained from 5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 82 and malonic acid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.38 (s, 3 H), 3.49 (s, 3 H), 5.33 - 5.42 (m, 1 H), 6.84 - 6.91 (m, 2 H), 7.01 - 7.11 (m, 2 H), 7.57 (d, J = 3.4 Hz, 1 H), 7.73 (dd, J = 8.5, 5.5 Hz, 1 H), 12.17 (br s, 1 H).

Reference Example 84 5-(methoxymethyl)-2-methyl-2,4-dihydro-3H-pyrazol-3-one

To a solution of methyl 4-methoxyacetacetate (3.48 g) in toluene (110 mL) was added dropwise a solution of methylhydrazine (1.10 g) in toluene (35 mL) over 20 min at 0°C, and the mixture was stirred at 100°C for 1.5 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was crystallized from diisopropyl ether-hexane to give the title compound (3.20 g, yield 95%) as brown crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.29 (s, 2 H), 3.31 (s, 3 H), 3.39 (s, 3 H), 4.17 (s, 2 H).

Reference Example 85 5-chloro-3-(methoxymethyl)-1-methyl-1H-pyrazole-4-carbaldehyde

Phosphoryl chloride (201 g) was added dropwise over 30 min to N,N-dimethylformamide (31.9 g) cooled at 0°C. 5-(Methoxymethyl)-2-methyl-2,4-dihydro-3H-pyrazol-3-one obtained in Reference Example 84 (31.0 g) was added to this reaction mixture, and the mixture was stirred with heating at 80°C for 3 hr. The reaction mixture was allowed to cool to room temperature, and poured into ice water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine,

dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10 - 50:50, v/v) to give the title compound (23.5 g, yield 57%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.48 (s, 3 H), 3.88 (s, 3 H), 4.69 (s, 2 H), 9.90 (s, 1 H).

Reference Example 86 5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-fluoro-1H-indole and 5-chloro-3-(methoxymethyl)-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 85.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.55 (s, 3 H), 3.64 (s, 3 H), 4.78 (s, 2 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.97 - 7.05 (m, 2 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.33 - 7.40 (m, 1 H), 9.59 (s, 1 H).

Reference Example 87 ethyl (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 86 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.18 - 1.26 (m, 3 H), 3.50 (s, 3 H), 3.55 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.54 - 4.64 (m, 2 H), 5.76 (d, J = 16.2 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.88 - 7.04 (m, 2 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.31 (d, J = 16.2 Hz, 1 H), 7.36 (dd, J = 9.1, 2.4 Hz, 1 H).

Reference Example 88 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 87.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 3.34 (s, 3 H), 3.55 (s, 3 H), 4.47 - 4.59 (m, 2 H), 5.47 (d, J = 16.2 Hz, 1 H), 6.87 (d, J = 3.4 Hz,

1 H), 6.98 - 7.15 (m, 3 H), 7.52 (dd, J = 9.5, 2.2 Hz, 1 H), 7.69 (d, J = 3.2 Hz, 1 H), 12.22 (br s, 1 H).

Reference Example 89 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylonitrile

To a solution of diethyl (cyanomethyl)phosphonate (1.07 g) in tetrahydrofuran (22 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 263 mg) with stirring, and the mixture was stirred at 0°C for 30 min. A solution of 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (1.50 g) in tetrahydrofuran (8 mL) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at room temperature for 4 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (1.49 g, yield 92%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.41 (s, 3 H), 3.54 (s, 3 H), 4.83 (d, J = 17.0 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.8, 2.0 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Reference Example 90 (1Z,2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N'-hydroxyprop-2-enimidamide

To a solution of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylonitrile obtained in Reference Example 89 (321 mg) in dimethylsulfoxide (11 mL) were added hydroxylammonium chloride (377 mg) and triethylamine (549 mg) with stirring, and the mixture was stirred at 75°C for 3 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to

silica gel column chromatography (hexane-ethyl acetate 35:65, v/v) to give the title compound (159 mg, yield 44%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.44 (s, 3 H), 3.49 (s, 3 H), 4.42 (br s, 2 H), 5.73 (d, J = 17.0 Hz, 1 H), 6.34 (d, J = 17.0 Hz, 1 H), 6.73 (d, J = 2.7 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 2.7 Hz, 1 H), 7.20 (d, J = 9.1 Hz, 1 H), 7.67 (s, 1 H).

Reference Example 91 5-chloro-1-{4-[(2,2-diethoxyethoxy)methyl]-1,3-dimethyl-1H-pyrazol-5-yl}-1H-indole

To a solution of [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 (1.12 g) in N,N-dimethylformamide (8 mL) was added 60% sodium hydride (in oil, 195 mg) with stirring, and the mixture was stirred at 0°C for 30 min. 2-Bromo-1,1-diethoxyethane (1.20 g) was added to this reaction mixture, and the mixture was stirred at 80°C for 72 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 75:25, v/v) to give the title compound (1.05 g, yield 66%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.14 (t, J = 7.0 Hz, 6 H), 2.35 (s, 3 H), 3.31 (d, J = 4.9 Hz, 2 H), 3.36 - 3.65 (m, 7 H), 4.08 - 4.26 (m, 2 H), 4.46 (t, J = 5.3 Hz, 1 H), 6.66 (d, J = 3.0 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.14 - 7.21 (m, 2 H), 7.65 (d, J = 1.9 Hz, 1 H).

Reference Example 92 {[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methoxy}acetaldehyde

To a solution of 5-chloro-1-{4-[(2,2-diethoxyethoxy)methyl]-1,3-dimethyl-1H-pyrazol-5-yl}-1H-indole obtained in Reference Example 91 (1.03 g) in tetrahydrofuran (5.3 mL) was added 1N hydrochloric acid (5.3 mL), and the mixture was stirred at 50°C for 2.5 hr. After the reaction

mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v) to give the title compound (643 mg, yield 77%) as a pale-yellow amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.46 - 3.53 (m, 5 H), 3.89 (dd, J = 1.8, 0.8 Hz, 2 H), 6.69 (dd, J = 3.3, 0.8 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.16 - 7.22 (m, 2 H), 7.66 (d, J = 1.5 Hz, 1 H), 9.53 (t, J = 0.9 Hz, 1 H).

Reference Example 93 {[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methoxy}acetic acid

By a method similar to that in Reference Example 67, the title compound was obtained from {[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methoxy}acetaldehyde obtained in Reference Example 92.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.26 (s, 3 H), 3.39 - 3.45 (m, 5 H), 3.81 (s, 2 H), 6.76 (dd, J = 3.2, 0.8 Hz, 1 H), 7.07 - 7.13 (m, 1 H), 7.16 - 7.22 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.74 (d, J = 1.7 Hz, 1 H).

Reference Example 94 (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxobut-3-enoic acid

5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (1.03 g) was dissolved in a mixed solvent of methanol (18 mL) and water (18 mL), pyruvic acid (1.32 g) and sodium carbonate (1.59 g) were added, and the mixture was heated under reflux for 8 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (750 mg, yield 58%) as

pale-yellow crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.43 (s, 3 H), 3.52 (s, 3 H), 6.22 (d, J = 16.7 Hz, 1 H), 6.88 (d, J = 3.0 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.15 - 7.26 (m, 2 H), 7.70 (d, J = 3.4 Hz, 1 H), 7.81 (d, J = 1.9 Hz, 1 H), 13.92 (br s, 1 H).

Reference Example 95 ethyl (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxobut-3-enoate

To a solution of (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxobut-3-enoic acid obtained in Reference Example 94 (545 mg) in ethanol (10 mL) was added hydrochloric acid (0.5 mL), and the mixture was heated under reflux for 18 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (403 mg, yield 68%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 - 1.29 (m, 3 H), 2.50 (s, 3 H), 3.56 (s, 3 H), 4.18 - 4.28 (m, 2 H), 6.43 (d, J = 16.4 Hz, 1 H), 6.79 (dd, J = 3.3, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.41 - 7.50 (m, 1 H), 7.70 (d, J = 1.7 Hz, 1 H).

Reference Example 96 ethyl 4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-hydroxybutanoate

Ethyl (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxobut-3-enoate obtained in Reference Example 95 (403 mg) was dissolved in a mixed solvent of tetrahydrofuran (15 mL) and ethanol (15 mL), 10% palladium carbon (42 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 16 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in a mixed solvent of tetrahydrofuran (15 mL) and ethanol (15 mL), sodium borohydride (41 mg) was added, and the mixture was stirred at 0°C for 3 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine,

dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (251 mg, yield 62%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.08 - 1.18 (m, 3 H), 1.48 - 1.78 (m, 2 H), 2.19 - 2.51 (m, 5 H), 2.65 (dd, J = 10.6, 5.2 Hz, 1 H), 3.41 - 3.47 (m, 3 H), 3.95 - 4.16 (m, 2 H), 6.65 - 6.69 (m, 1 H), 6.94 (dd, J = 8.8, 2.5 Hz, 1 H), 7.12 (dd, J = 5.0, 3.3 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Reference Example 97 ethyl 2-chloro-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]butanoate

To a solution of ethyl 4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-hydroxybutanoate obtained in Reference Example 96 (241 mg) in tetrahydrofuran (7 mL) was added thionyl chloride (229 mg), and the mixture was heated under reflux for 22 hr. The reaction mixture was allowed to cool to room temperature, and concentrated. The residue was purified by preparative HPLC (tool: Gilson, Inc., high through-put purification system, column: YMC Combiprep ODS-A, S-5 μm, 50 x 20 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), 1.00 min (SOLUTION A/SOLUTION B = 90/10), 4.20 min (SOLUTION A/SOLUTION B = 10/90), 5.40 min (SOLUTION A/SOLUTION B = 10/90), 5.50 min (SOLUTION A/SOLUTION B = 90/10), 5.60 min (SOLUTION A/SOLUTION B = 90/10), flow rate: 25 mL/min, detection method: UV 220 nm) to give the title compound (93.7 mg, yield 37%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 - 1.23 (m, 3 H), 1.81 - 1.94 (m, 2 H), 2.30 (s, 3 H), 2.33 - 2.52 (m, 2 H), 3.46 (s, 3 H), 4.00 - 4.17 (m, 3 H), 6.68 (d, J = 3.4 Hz, 1 H), 6.92 (dd, J = 8.7, 1.9 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Reference Example 98 sodium cyclopropylmethanesulfonate

(Bromomethyl)cyclopropane (3.00 g) was added to an saturated aqueous sodium sulfite solution (27 mL), and the mixture was heated under reflux for 24 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. Ethanol was added to the residue, and the mixture was stirred at 50°C for 30 min. The mixture was filtrated, and the filtrate was concentrated. Toluene was added to the residue, and the mixture was concentrated again under reduced pressure. The residue was dried to give the title compound (2.54 g, yield 72%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.12 - 0.19 (m, 2 H), 0.36 - 0.45 (m, 2 H), 0.86 - 0.99 (m, 1 H), 2.32 (d, J = 6.8 Hz, 2 H).

Reference Example 99 sodium 4-methylpentane-1-sulfonate

By a method similar to that in Reference Example 98, the title compound was obtained from 1-bromo-4-methylpentane.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.85 (d, J = 6.6 Hz, 6 H), 1.11 - 1.26 (m, 2 H), 1.43 - 1.62 (m, 3 H), 2.31 - 2.41 (m, 2 H).

Reference Example 100 1-cyclopropylmethanesulfonamide

Sodium cyclopropylmethanesulfonate obtained in Reference Example 98 (961 mg) was dissolved in a mixed solvent of N,N-dimethylformamide (0.5 mL) and tetrahydrofuran (12 mL), thionyl chloride (1.45 g) was added, and the mixture was heated under reflux for 3 hr. The reaction mixture was allowed to cool to room temperature, and filtrated, and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (12 mL), and the solution was added to 35% aqueous ammonia (6 mL) at 0°C. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated to give the title compound (579 mg, yield 70%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.28 - 0.37 (m, 2 H), 0.51 - 0.64 (m, 2 H), 0.92 - 1.08 (m, 1 H), 3.14 - 3.29 (m, 2 H).

Reference Example 101 4-methylpentane-1-sulfonamide

By a method similar to that in Reference Example 100, the

title compound was obtained from sodium 4-methylpentane-1-sulfonate obtained in Reference Example 99.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.87 (d, J = 6.8 Hz, 6 H), 1.13 - 1.31 (m, 2 H), 1.46 - 1.75 (m, 3 H), 2.87 - 3.00 (m, 2 H).

Reference Example 102 benzyl (morpholin-4-ylsulfonyl)carbamate

To a solution of benzyl alcohol (3.00 g) in acetonitrile (200 mL) was added chlorosulfonyl isocyanate (4.70 g) with stirring at 0°C, and the mixture was stirred at 0°C for 30 min. Pyridine (6.58 g) was added to this reaction mixture, and the mixture was stirred at 0°C for 1 hr. Morpholine (9.67 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 5 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (9.23 g, yield 99%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:3.15 - 3.21 (m, 4 H), 3.57 - 3.63 (m, 4 H), 5.15 (s, 2 H), 7.31 - 7.45 (m, 5 H), 11.50 (br s, 1 H).

Reference Example 103 benzyl {[methyl(pentyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and N-methylpentan-1-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 6.8 Hz, 3 H), 1.16 - 1.38 (m, 4 H), 1.48 - 1.61 (m, 2 H), 2.90 (s, 3 H), 3.17 - 3.26 (m, 2 H), 5.17 (s, 2 H), 7.32 - 7.39 (m, 5 H).

Reference Example 104 benzyl [(butylamino)sulfonyl]carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and butan-1-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.4 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.42 - 1.57 (m, 2 H), 2.98 - 3.09 (m, 2 H), 5.12 - 5.17 (m, 1 H), 5.18 (s, 2 H), 7.29 - 7.43 (m, 5 H), 7.50 (br s,

1 H).

Reference Example 105 benzyl {[(1-propylbutyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and heptan-4-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.2 Hz, 6 H), 1.19 - 1.51 (m, 8 H), 3.27 - 3.42 (m, 1 H), 4.73 - 4.91 (m, 1 H), 5.19 (s, 2 H), 7.33 - 7.46 (m, 5 H).

Reference Example 106 benzyl {[(1-ethylpropyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and pentan-3-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.4 Hz, 6 H), 1.35 - 1.59 (m, 4 H), 3.16 - 3.36 (m, 1 H), 4.87 (d, J = 7.3 Hz, 1 H), 5.19 (s, 2 H), 7.30 (br s, 1 H), 7.32 - 7.43 (m, 5 H).

Reference Example 107 benzyl [(cyclohexylamino)sulfonyl]carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and cyclohexylamine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.95 - 1.37 (m, 6 H), 1.48 - 1.74 (m, 2 H), 1.77 - 1.94 (m, 2 H), 2.97 - 3.33 (m, 1 H), 4.97 (d, J = 6.8 Hz, 1 H), 5.20 (s, 2 H), 7.29 (br s, 1 H), 7.37 (s, 5 H).

Reference Example 108 benzyl {[(cyclopropylmethyl)amino]sulfonyl}carbamate

To a solution of benzyl alcohol (12.08 g) in acetonitrile (250 mL) was added chlorosulfonyl isocyanate (9.75 mL) with stirring at 0°C, and the mixture was stirred at 0°C for 30 min. Pyridine (17.9 mL) was added to this reaction mixture, and the mixture was stirred at 0°C for 1 hr. Cyclopropylmethylamine (11.92 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 5 hr. 1N Hydrochloric acid was added to this reaction mixture, and the mixture was extracted

with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (21.22 g, yield 67%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.18 (m, 2 H), 0.45 - 0.54 (m, 2 H), 0.82 - 1.04 (m, 1 H), 2.90 (dd, J = 7.2, 5.8 Hz, 2 H), 5.19 (s, 2 H), 5.22 (br s, 1 H), 7.30 (br s, 1 H), 7.33 - 7.44 (m, 5 H).

Reference Example 109 morpholine-4-sulfonamide

Benzyl (morpholin-4-ylsulfonyl)carbamate obtained in Reference Example 102 (9.23 g) was dissolved in a mixed solvent of tetrahydrofuran (100 mL) and ethanol (100 mL), 10% palladium carbon (923 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 4 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was crystallized from hexane-ethanol to give the title compound (4.93 g, yield 97%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.13 - 3.20 (m, 4 H), 3.77 - 3.82 (m, 4 H), 4.43 (br s, 2 H).

Reference Example 110 N-methyl-N-pentylsulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[methyl(pentyl)amino]sulfonyl}carbamate obtained in Reference Example 103.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.94 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.53 - 1.65 (m, 2 H), 2.80 (s, 3 H), 3.06 - 3.14 (m, 2 H), 4.59 (br s, 2 H).

Reference Example 111 N-butylsulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl [(butylamino)sulfonyl]carbamate obtained in Reference Example 104.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.3 Hz, 3 H), 1.31 - 1.47 (m, 2 H), 1.50 - 1.63 (m, 2 H), 3.07 - 3.19 (m, 2 H), 4.41 (br s, 1 H), 4.63 (br s, 2 H).

Reference Example 112 N-(1-propylbutyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(1-propylbutyl)amino]sulfonyl}carbamate obtained in Reference Example 105.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (t, J = 7.2 Hz, 6 H), 1.27 - 1.66 (m, 8 H), 3.29 - 3.50 (m, 1 H), 4.15 (br s, 1 H), 4.50 (br s, 2 H).

Reference Example 113 N-(1-ethylpropyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(1-ethylpropyl)amino]sulfonyl}carbamate obtained in Reference Example 106.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.95 (t, J = 7.4 Hz, 6 H), 1.26 - 1.78 (m, 4 H), 3.05 - 3.46 (m, 1 H), 4.23 (d, J = 8.1 Hz, 1 H), 4.55 (br s, 2 H).

Reference Example 114 N-cyclohexylsulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl [(cyclohexylamino)sulfonyl]carbamate obtained in Reference Example 107.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.06 - 1.49 (m, 6 H), 1.49 - 1.83 (m, 2 H), 1.93 - 2.14 (m, 2 H), 3.09 - 3.42 (m, 1 H), 4.51 (br s, 1 H), 4.74 (br s, 2 H).

Reference Example 115 N-(cyclopropylmethyl)sulfamide

Benzyl {[(cyclopropylmethyl)amino]sulfonyl}carbamate obtained in Reference Example 108 (20.30 g) was dissolved in a mixed solvent of tetrahydrofuran (150 mL) and ethanol (150 mL), 10% palladium carbon (30.39 g) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 6 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was crystallized from

hexane-ethyl acetate to give the title compound (9.37 g, yield 87%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.17 - 0.31 (m, 2 H), 0.49 - 0.64 (m, 2 H), 0.94 - 1.18 (m, 1 H), 3.00 (dd, J = 7.2, 6.0 Hz, 2 H), 4.40 (br s, 1 H), 4.51 (br s, 2 H).

Reference Example 116 ethyl N-({[(benzyloxy)carbonyl]amino}sulfonyl)glycinate

To a solution of benzyl alcohol (2.01 g) in acetonitrile (40 ml) was added chlorosulfonyl isocyanate (1.70 mL) with stirring at 0°C, and the mixture was stirred for 30 min. Pyridine (3.0 mL) was added to this reaction mixture, and the mixture was stirred at 0°C for 1 hr. Glycine ethyl ester hydrochloride (3.90 g) and N,N-diisopropylethylamine (6.4 mL) were added, and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (5.70 g, yield 96%) as tetartohydrate colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.28 (t, J = 7.2 Hz, 3 H), 3.96 (d, J = 5.7 Hz, 2 H), 4.21 (q, J = 6.9 Hz, 2 H), 5.21 (s, 2 H), 5.61 (t, J = 5.7 Hz, 1 H), 7.31 - 7.49 (m, 5 H).

Reference Example 117 ethyl N-(aminosulfonyl)glycinate

By a method similar to that in Reference Example 109, the title compound was obtained from ethyl N-({[(benzyloxy)carbonyl]amino}sulfonyl)glycinate obtained in Reference Example 116.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.31 (t, J = 7.2 Hz, 3 H), 3.94 (d, J = 5.7 Hz, 2 H), 4.25 (q, J = 7.1 Hz, 2 H), 4.80 (br s, 2 H), 5.09 (br s, 1 H).

Reference Example 118 benzyl (1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)carbamate

By a method similar to that in Reference Example 102, the

title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and 1,4-dioxa-8-azaspiro[4.5]decane.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.66 - 1.86 (m, 4 H), 3.50 (t, J = 5.8 Hz, 4 H), 3.97 (s, 4 H), 5.18 (s, 2 H), 7.17 (br s, 1 H), 7.30 - 7.44 (m, 5 H).

Reference Example 119 benzyl {[(3-isopropoxypropyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and 3-isopropoxypropan-1-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.15 (d, J = 6.0 Hz, 6 H), 1.70 - 1.91 (m, 2 H), 3.04 - 3.34 (m, 2 H), 3.48 (t, J = 5.6 Hz, 2 H), 3.52 - 3.59 (m, 1 H), 5.20 (s, 2 H), 5.85 (t, J = 5.6 Hz, 1 H), 7.31 (br s, 1 H), 7.34 - 7.42 (m, 5 H).

Reference Example 120 1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl (1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)carbamate obtained in Reference Example 118.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.83 (t, J = 5.9 Hz, 4 H), 3.32 (t, J = 5.8 Hz, 4 H), 3.98 (s, 4 H), 4.38 (br s, 2 H).

Reference Example 121 N-(3-isopropoxypropyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(3-isopropoxypropyl)amino]sulfonyl}carbamate obtained in Reference Example 119.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.16 (d, J = 6.0 Hz, 6 H), 1.57 - 1.98 (m, 2 H), 3.27 (t, J = 6.1 Hz, 2 H), 3.33 - 3.69 (m, 3 H), 4.54 (br s, 2 H), 5.15 (br s, 1 H).

Reference Example 122 benzyl {[(cyclohexylmethyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and 1-cyclohexylmethanamine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.78 - 0.98 (m, 2 H), 1.04 - 1.32 (m, 3 H), 1.32 - 1.53 (m, 1 H), 1.62 - 1.82 (m, 5 H), 2.70 - 2.94 (m, 2 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.20 (s, 2 H), 7.23 (br s, 1 H), 7.31 - 7.43 (m, 5 H).

Reference Example 123 N-(cyclohexylmethyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(cyclohexylmethyl)amino]sulfonyl}carbamate obtained in Reference Example 122.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 1.05 (m, 2 H), 1.11 - 1.35 (m, 3 H), 1.42 - 1.55 (m, 1 H), 1.62 - 1.84 (m, 5 H), 2.90 - 3.03 (m, 2 H), 4.30 (br s, 1 H), 4.48 (br s, 2 H).

Reference Example 124 benzyl {[(3-methylbutyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and 3-methylbutan-1-amine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (d, J = 6.6 Hz, 6 H), 1.30 - 1.47 (m, 2 H), 1.50 - 1.73 (m, 1 H), 2.95 - 3.13 (m, 2 H), 5.11 (br s, 1 H), 5.19 (s, 2 H), 7.38 - 7.56 (m, 6 H).

Reference Example 125 N-(3-methylbutyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(3-methylbutyl)amino]sulfonyl}carbamate obtained in Reference Example 124.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (d, J = 6.6 Hz, 6 H), 1.36 - 1.54 (m, 2 H), 1.59 - 1.75 (m, 1 H), 3.05 - 3.18 (m, 2 H), 4.32 (br s, 3 H).

Reference Example 126 benzyl [(propylamino)sulfonyl]carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and propan-1-amine.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.3 Hz, 3 H), 1.12 - 1.56 (m, 2 H), 2.75 - 2.86 (m, 2 H), 5.14 (s, 2 H), 7.14 - 7.41 (m, 5 H), 7.76 (t, J = 5.9 Hz, 1 H), 11.20 (s, 1 H).

Reference Example 127 N-propylsulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl [(propylamino)sulfonyl]carbamate obtained in Reference Example 126.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.97 (t, J = 7.4 Hz, 3 H), 1.55 - 1.67 (m, 2 H), 3.09 (t, J = 7.2 Hz, 2 H), 4.47 (br s, 3 H).

Reference Example 128 ethyl (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 1 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.05 - 1.33 (m, 3 H), 2.47 (s, 3 H), 3.50 (s, 3 H), 3.98 - 4.22 (m, 2 H), 5.54 - 5.73 (m, 1 H), 6.80 (d, J = 2.7 Hz, 1 H), 6.95 - 7.04 (m, 1 H), 7.05 - 7.15 (m, 1 H), 7.16 - 7.30 (m, 3 H), 7.65 - 7.78 (m, 1 H).

Reference Example 129 ethyl (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 128 (5.00 g) in acetonitrile (75 mL) was added N-chlorosuccinimide (2.16 g) at room temperature, and the mixture was stirred at room temperature for 2 hr, and then at 50°C for 2 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40 - 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (4.50 g, yield 81%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.1 Hz, 3 H), 2.47 (s, 3 H), 3.50 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.71 (d, J = 16.2 Hz, 1 H), 6.96 - 7.01 (m, 1 H), 7.10 (s, 1 H), 7.27 (d, J = 16.2 Hz, 1 H), 7.29 - 7.33 (m, 2 H), 7.65 - 7.77 (m, 1 H).

Reference Example 130 (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 129.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.50 (s, 3 H), 5.44 (d, J = 16.2 Hz, 1 H), 7.04 (d, J = 16.2 Hz, 1 H), 7.08 - 7.13 (m, 1 H), 7.29 - 7.39 (m, 2 H), 7.61 - 7.77 (m, 1 H), 7.91 (s, 1 H), 12.20 (br s, 1 H).

Reference Example 131 5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 3-chloro-1H-pyrrolo[2,3-b]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.69 (s, 3 H), 7.28 - 7.34 (m, 2 H), 8.06 (dd, J = 8.0, 1.6 Hz, 1 H), 8.41 (dd, J = 4.9, 1.5 Hz, 1 H), 9.62 (s, 1 H).

Reference Example 132 ethyl (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 131 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.14 (t, J = 7.1 Hz, 3 H), 2.39 (s, 3 H), 3.52 (s, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.41 (dd, J = 7.9, 4.7 Hz, 1 H), 8.09 (s, 1 H), 8.18 (dd, J = 8.0, 1.6 Hz, 1 H), 8.39 (dd, J = 4.7, 1.5 Hz, 1 H).

Reference Example 133 (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 132.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.52 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 7.04 (d, J = 16.2 Hz, 1 H), 7.41 (dd, J = 8.1,

4.7 Hz, 1 H), 8.08 (s, 1 H), 8.17 (dd, J = 7.9, 1.5 Hz, 1 H), 8.39 (dd, J = 4.7, 1.5 Hz, 1 H), 12.22 (br s, 1 H).

Reference Example 134 1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 3-methyl-1H-pyrrolo[2,3-b]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.
^{1}H-NMR (300 MHz, CDCl3)δ:2.39 (d, J = 1.1 Hz, 3 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.98 - 7.11 (m, 1 H), 7.21 (dd, J = 7.9, 4.7 Hz, 1 H), 7.97 (dd, J = 7.8, 1.6 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 9.58 (s, 1 H).

Reference Example 135 ethyl (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 134 and ethyl (diethoxyphosphoryl)acetate.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (t, J = 7.2 Hz, 3 H), 2.39 (d, J = 1.1 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.76 (d, J = 16.4 Hz, 1 H), 6.96 (d, J = 1.1 Hz, 1 H), 7.19 (dd, J = 7.8, 4.8 Hz, 1 H), 7.30 (d, J = 16.2 Hz, 1 H), 7.96 (dd, J = 7.8, 1.6 Hz, 1 H), 8.33 (dd, J = 4.7, 1.5 Hz, 1 H).

Reference Example 136 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 135.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 6 H), 3.47 (s, 3 H), 5.54 (d, J = 16.2 Hz, 1 H), 7.01 (d, J = 16.4 Hz, 1 H), 7.26 (dd, J = 7.9, 4.7 Hz, 1 H), 7.46 (s, 1 H), 8.13 (dd, J = 7.9, 1.5 Hz, 1 H), 8.26 (dd, J = 4.7, 1.5 Hz, 1 H), 12.19 (br s, 1 H).

Reference Example 137 5-(1H-indol-3-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a mixture of [1-(tert-butoxycarbonyl)-1H-indol-3-

yl]boronic acid (2.01 g), 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (2.44 g), a 2.0M aqueous sodium carbonate solution (8.0 mL) and 1,2-dimethoxyethane (16 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.45 g), and the reaction mixture was heated under reflux under nitrogen atmosphere for 12 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 95:5 - 80:20, v/v) to give a mixture (2.86 g), as a brown solid, of tert-butyl 3-(4-formyl-1,3-dimethyl-1H-pyrazol-5-yl)-1H-indole-1-carboxylate and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde, and the title compound (0.44 g, yield 24%) as a pale-brown solid.

The obtained mixture (2.86 g) of tert-butyl 3-(4-formyl-1,3-dimethyl-1H-pyrazol-5-yl)-1H-indole-1-carboxylate and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde was dissolved in a 4M hydrogen chloride-ethyl acetate solution (45 mL), and the mixture was stirred at room temperature for 3.5 hr. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50 - 0:100, v/v) to give the title compound (1.01 g, yield 54%) as a pale-brown solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 3.76 (s, 3 H), 7.03 - 7.73 (m, 5 H), 8.65 (br s, 1 H), 9.66 (s, 1 H).

Reference Example 138 1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazole-4-carbaldehyde

To a solution of 5-(1H-indol-3-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 137 (1.42 g) in N,N-dimethylformamide (30 mL) was added 60% sodium hydride (in oil, 285 mg) with stirring, and the mixture was stirred at

0°C for 30 min. Methyl iodide (0.58 mL) was added to this reaction mixture, and the mixture was stirred at room temperature for 5 hr. The reaction mixture was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10 - 65:35, v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.15 g, yield 77%) as pale-brown crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 3.76 (s, 3 H), 3.92 (s, 3 H), 7.07 - 7.57 (m, 5 H), 9.65 (s, 1 H).

Reference Example 139 ethyl (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 138 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.25 (t, J = 7.2 Hz, 3 H), 2.49 (s, 3 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 6.04 (d, J = 16.2 Hz, 1 H), 7.07 - 7.66 (m, 6 H).

Reference Example 140 (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 139.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 3.63 (s, 3 H), 3.92 (s, 3 H), 5.88 (d, J = 16.2 Hz, 1 H), 7.05 - 7.16 (m, 1 H), 7.20 - 7.36 (m, 3 H), 7.59 (d, J = 8.9 Hz, 1 H), 7.67 (s, 1 H), 11.91 (br s, 1 H).

Reference Example 141 1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 39, the title compound was obtained from 3-methyl-1H-indazole and 5-

chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.56 (s, 3 H), 2.67 (s, 3 H), 3.71 (s, 3 H), 6.87 - 7.88 (m, 4 H), 9.58 (s, 1 H).

Reference Example 142 ethyl (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 141 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 2.67 (s, 3 H), 3.57 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.72 (d, J = 16.4 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 1 H), 7.21 - 7.35 (m, 2 H), 7.37 - 7.48 (m, 1 H), 7.77 (d, J = 7.9 Hz, 1 H).

Reference Example 143 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 142.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 2.62 (s, 3 H), 3.51 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 1 H), 7.27 - 7.37 (m, 1 H), 7.44 - 7.57 (m, 1 H), 7.93 (d, J = 8.1 Hz, 1 H), 12.17 (br s, 1 H).

Reference Example 144 ethyl (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

To a solution of 1H-pyrrolo[2,3-b]pyridin-6-ol (5.27 g) in acetone (300 mL) were added dimethylsulfuric acid (4.10 mL) and potassium carbonate (5.50 g), and the mixture was stirred at room temperature for 13 hr. The reaction mixture was filtrated through celite®, and the filtrate was concentrated. The obtained residue was dissolved in N,N-dimethylformamide (80 mL), 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (7.47 g) and 60% sodium hydride (in oil, 2.36 g) were added with stirring, and the mixture was stirred at 80°C for 15 hr. After the reaction mixture was allowed to cool to room temperature, water was added,

and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10 - 75:25, v/v) to give a brown solid (7.53 g).

To a solution of the obtained brown solid (7.53 g) in ethanol (60 mL) were added ethyl (diethoxyphosphoryl)acetate (9.37 g) and sodium ethoxide (3.79 g), and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10 - 65:35, v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.36 g, yield 14%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.64 (s, 3 H), 3.83 (s, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 5.77 (d, J = 16.2 Hz, 1 H), 6.54 - 6.76 (m, 2 H), 6.98 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 16.2 Hz, 1 H), 7.86 (d, J = 8.5 Hz, 1 H).

Reference Example 145 (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 144.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.56 (s, 3 H), 3.74 (s, 3 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.50 - 6.84 (m, 2 H), 7.12 (d, J = 16.2 Hz, 1 H), 7.43 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 12.15 (br s, 1 H).

Reference Example 146 tert-butyl (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 and tert-butyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.42 (s, 9 H), 2.45 (s, 3 H), 3.49 (s, 3 H), 5.61 (d, J = 16.4 Hz, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.17 (d, J = 16.2 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Reference Example 147 tert-butyl trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxylate

To a solution of trimethylsulfoxonium iodide (4.71 g) in dimethylsulfoxide (20 mL) was added 60% sodium hydride (in oil, 856 mg) with stirring at room temperature, and the mixture was stirred at room temperature for 1.5 hr. A solution of tert-butyl (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 146 (3.97 g) in dimethylsulfoxide (60 mL) was added to this reaction mixture with stirring, and the mixture was stirred at room temperature for 48 hr. A saturated aqueous ammonium chloride solution and water were added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated, and the filtrate was concentrated. The obtained residue was subjected to silica gel column chromatography (hexane-ethyl acetate 100:0 - 60:40, v/v) to give the title compound (2.21 g, yield 54%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.36 - 0.65 (m, 1 H), 0.99 - 1.22 (m, 2 H), 1.26 (s, 5 H), 1.33 (s, 4 H), 1.86 - 2.00 (m, 1 H), 2.32 (s, 3 H), 3.47 (s, 1.5 H), 3.49 (s, 1.5 H), 6.53 - 6.72 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.07 (dd, J = 11.0, 3.4 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Reference Example 148 trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxylic acid

tert-Butyl trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxylate obtained in Reference Example 147 (2.15 g) was dissolved in a 4M hydrogen

chloride-ethyl acetate solution (10 mL), and the mixture was stirred at room temperature for 3 hr, and then at 50°C for 12 hr. The reaction mixture was allowed to cool to room temperature, and diluted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated, and the filtrate was concentrated. The obtained residue was crystallized from hexane-ethyl acetate to give the title compound (0.52 g, yield 43%) as colorless crystals (a solvate with 0.05 mol ethyl acetate/mol).

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.40 - 0.60 (m, 1 H), 0.71 - 0.87 (m, 0.5 H), 0.88 - 1.03 (m, 0.5 H), 1.11 - 1.24 (m, 0.5 H), 1.25 - 1.38 (m, 0.5 H), 1.80 - 1.97 (m, 1 H), 2.22 (s, 3 H), 3.38 (s, 1.5 H), 3.38 (s, 1.5 H), 6.76 (dd, J = 2.3, 1.1 Hz, 1 H), 7.04 (t, J = 9.3 Hz, 1 H), 7.13 - 7.25 (m, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.74 (t, J = 1.9 Hz, 1 H), 12.09 (br s, 1 H).

Reference Example 149 5-cyclopropyl-2-methyl-2,4-dihydro-3H-pyrazol-3-one

To a solution of methyl 3-cyclopropyl-3-oxopropionoate (39.8 g) in toluene (150 mL) was added methylhydrazine (13.0 g), and the mixture was heated under reflux for 4 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was crystallized from diethyl ether to give the title compound (37.9 g, yield 98%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.74 - 0.82 (m, 2 H), 0.92 - 1.01 (m, 2 H), 1.71 - 1.83 (m, 1 H), 3.05 (s, 2 H), 3.26 (s, 3 H).

Reference Example 150 5-chloro-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde

Phosphoryl chloride (165 g) was added dropwise over 25 min to N,N-dimethylformamide (19.0 g) cooled at 0°C. 5-Cyclopropyl-2-methyl-2,4-dihydro-3H-pyrazol-3-one obtained in Reference Example 149 (29.7 g) was added to this reaction mixture, and the mixture was stirred with heating at 100°C for 2 hr. The reaction mixture was allowed to cool to room temperature, and poured into ice water, and the mixture was extracted with ethyl acetate. The

organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 85:15, v/v) to give the title compound (39.1 g, yield 98%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 1.03 (m, 4 H), 2.39 - 2.51 (m, 1 H), 3.77 (s, 3 H), 9.91 (s, 1 H).

Reference Example 151 benzyl [(ethylamino)sulfonyl]carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and ethanamine.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 - 1.20 (m, 3 H), 3.05 - 3.16 (m, 2 H), 5.17 - 5.21 (m, 2 H), 7.33 - 7.39 (m, 5 H), 7.64 (br s, 1 H).

Reference Example 152 N-ethylsulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl [(ethylamino)sulfonyl]carbamate obtained in Reference Example 151.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.03 - 1.10 (m, 3 H), 2.84 - 2.95 (m, 2 H), 6.37 - 6.49 (m, 3 H).

Reference Example 153 3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-fluoro-1H-indole and 5-chloro-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 150.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.99 - 1.11 (m, 4 H), 2.50 - 2.61 (m, 1 H), 3.53 (s, 3 H), 6.77 (d, J = 3.4 Hz, 1 H), 7.00 - 7.04 (m, 2 H), 7.22 (d, J = 3.2 Hz, 1 H), 7.33 - 7.38 (m, 1 H), 9.57 (s, 1 H).

Reference Example 154 ethyl (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazole-4-carbaldehyde obtained in

Reference Example 153 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 - 1.07 (m, 4 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.94 - 2.06 (m, 1 H), 3.47 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.79 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.88 - 7.03 (m, 2 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.33 - 7.43 (m, 2 H).

Reference Example 155 (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 154.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 - 1.02 (m, 4 H), 1.99 - 2.12 (m, 1 H), 3.46 (s, 3 H), 5.49 (d, J = 16.3 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.99 - 7.11 (m, 2 H), 7.15 - 7.22 (m, 1 H), 7.52 (dd, J = 9.5, 1.9 Hz, 1 H), 7.67 (d, J = 3.0 Hz, 1 H), 12.15 (br s, 1 H).

Reference Example 156 ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 27 (31.9 g) in dichloromethane (150 mL) was added dropwise boron tribromide (1M dichloromethane solution, 154 mL) with stirring at -78°C, and the mixture was stirred at -78°C for 3 hr. The reaction mixture was quenched with ethanol (100 mL), and concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (18.9 g, yield 76%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.41 (s, 3 H), 3.48 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.64 (d, J = 16.2 Hz,

1 H), 6.32 (d, J = 2.1 Hz, 1 H), 6.69 - 6.73 (m, 1 H), 6.83 (dd, J = 8.6, 2.2 Hz, 1 H), 6.94 (d, J = 3.2 Hz, 1 H), 7.19 (s, 1 H), 7.30 (d, J = 16.4 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H).

Reference Example 157 ethyl (2E)-3-{1,3-dimethyl-5-[6-(2-oxopropoxy)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylate

To a solution of ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 (2.02 g) in acetone (10 mL) were added chloroacetone (689 mg), potassium carbonate (1.28 g) and sodium iodide (1.28 g), and the mixture was stirred at 50°C for 16 hr. The reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (2.26 g, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.18 - 1.25 (m, 3 H), 2.27 (s, 3 H), 2.47 (s, 3 H), 3.48 - 3.52 (m, 3 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.49 (s, 2 H), 5.55 - 5.68 (m, 1 H), 6.42 (d, J = 1.7 Hz, 1 H), 6.73 (d, J = 3.2 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 7.00 (d, J = 3.4 Hz, 1 H), 7.25 - 7.34 (m, 1 H), 7.58 - 7.64 (m, 1 H).

Reference Example 158 ethyl (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

To a solution of ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 (1.08 g) in N,N-dimethylformamide (5 mL) were added bromoethyl methyl ether (553 mg), potassium carbonate (688 mg) and sodium iodide (995 mg), and the mixture was stirred at 80°C for 16 hr. The reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50,

v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.26 g, yield 99%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.16 - 1.25 (m, 3 H), 2.46 (s, 3 H), 3.43 (s, 3 H), 3.48 - 3.52 (m, 3 H), 3.70 - 3.77 (m, 2 H), 4.03 - 4.17 (m, 4 H), 5.55 - 5.68 (m, 1 H), 6.41 - 6.48 (m, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.89 - 6.98 (m, 2 H), 7.28 - 7.35 (m, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Reference Example 159 (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 158.
^{1}H-NMR (300 MHz DMSO-d_6)δ:2.38 (s, 3 H), 3.27 (s, 3 H), 3.49 (s, 3 H), 3.61 (t, J = 4.5 Hz, 2 H), 3.92 - 4.11 (m, 2 H), 5.38 - 5.48 (m, 1 H), 6.50 (d, J = 1.7 Hz, 1 H), 6.76 (d, J = 3.2 Hz, 1 H), 6.84 (dd, J = 8.7, 2.1 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.39 (d, J = 3.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 12.15 (br s, 1 H).

Reference Example 160 ethyl (2E)-3-{5-[6-(cyclopropylmethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

By a method similar to that in Reference Example 157, the title compound was obtained from ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 and bromomethylcyclopropane.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.29 - 0.36 (m, 2 H), 0.58 - 0.66 (m, 2 H), 1.17 - 1.29 (m, 4 H), 2.47 (s, 3 H), 3.49 (s, 3 H), 3.73 (d, J = 6.8 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.41 (d, J = 2.1 Hz, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.31 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H).

Reference Example 161 (2E)-3-{5-[6-(cyclopropylmethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-{5-[6-

(cyclopropylmethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 160.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.24 - 0.32 (m, 2 H), 0.47 - 0.56 (m, 2 H), 1.12 - 1.21 (m, 1 H), 2.38 (s, 3 H), 3.48 (s, 3 H), 3.66 - 3.80 (m, 2 H), 5.42 (d, J = 16.2 Hz, 1 H), 6.45 (d, J = 1.7 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.84 (dd, J = 8.7, 2.3 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.37 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 12.13 (br s, 1 H).

Reference Example 162 ethyl (2E)-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 (1.54 g) in tetrahydrofuran (20 mL) were added isopropanol (426 mg) and tributylphosphine (1.91 g), 1,1'-azodicarbonyldipiperidine (2.38 g) was added with stirring, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, diisopropyl ether was added to the residue, and the insoluble material was filtered off. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (1.66 g, yield 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.19 - 1.24 (m, 3 H), 1.29 (dd, J = 6.0, 3.6 Hz, 6 H), 2.46 (s, 3 H), 3.51 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.42 - 4.52 (m, 1 H), 5.66 (d, J = 16.2 Hz, 1 H), 6.46 (d, J = 2.1 Hz, 1 H), 6.68 - 6.71 (m, 1 H), 6.86 (dd, J = 8.6, 2.2 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.32 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H).

Reference Example 163 (2E)-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 162.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.20 (dd, J = 9.5, 5.9 Hz, 6 H), 2.38

(s, 3 H), 3.49 (s, 3 H), 4.46 - 4.56 (m, 1 H), 5.41 - 5.49 (m, 1 H), 6.47 (d, J = 1.7 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.81 (dd, J = 8.7, 2.1 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.40 (d, J = 3.2 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 12.19 (br s, 1 H).

Reference Example 164 benzyl {[(allyloxy)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and O-allylhydroxylamine hydrochloride.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:4.47 (d, J = 6.4 Hz, 2 H), 5.22 (s, 2 H), 5.27 - 5.39 (m, 2 H), 5.85 - 6.00 (m, 1 H), 7.31 - 7.42 (m, 5 H), 7.50 (br s, 1 H), 7.83 (s, 1 H).

Reference Example 165 N-propoxysulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(allyloxy)amino]sulfonyl}carbamate obtained in Reference Example 164.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.4 Hz, 3 H), 1.60 - 1.74 (m, 2 H), 3.96 (t, J = 6.8 Hz, 2 H), 5.17 (br s, 2 H).

Reference Example 166 ethyl (2E)-3-[5-(6-ethoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 162, the title compound was obtained from ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 and ethanol.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.1 Hz, 3 H), 1.39 (t, J = 7.0 Hz, 3 H), 2.46 (s, 3 H), 3.50 (s, 3 H), 3.97 (q, J = 7.0 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 16.4 Hz, 1 H), 6.43 (d, J = 1.7 Hz, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.87 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.32 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H).

Reference Example 167 (2E)-3-[5-(6-ethoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(6-ethoxy-1H-

indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 166.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.28 (t, J = 7.0 Hz, 3 H), 2.38 (s, 3 H), 3.49 (s, 3 H), 3.84 - 4.02 (m, 2 H), 5.38 - 5.47 (m, 1 H), 6.46 (s, 1 H), 6.75 (d, J = 3.2 Hz, 1 H), 6.82 (dd, J = 8.7, 2.1 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.38 (d, J = 3.2 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 12.14 (br s, 1 H).

Reference Example 168 ethyl (2E)-3-{5-[6-(2-tert-butoxy-1-methyl-2-oxoethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

By a method similar to that in Reference Example 158, the title compound was obtained from ethyl (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 156 and tert-butyl 2-bromopropionoate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 6.6 Hz, 3 H), 1.35 (d, J = 3.8 Hz, 9 H), 1.53 - 1.60 (m, 3 H), 2.45 (d, J = 3.4 Hz, 3 H), 3.44 - 3.50 (m, 3 H), 4.07 - 4.17 (m, 2 H), 4.49 - 4.59 (m, 1 H), 5.61 (dd, J = 16.3, 8.0 Hz, 1 H), 6.40 (dd, J = 8.5, 2.1 Hz, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.84 - 6.92 (m, 1 H), 6.97 (d, J = 3.4 Hz, 1 H), 7.24 - 7.35 (m, 1 H), 7.57 (d, J = 8.3 Hz, 1 H).

Reference Example 169 2-[(1-{4-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-1,3-dimethyl-1H-pyrazol-5-yl}-1H-indol-6-yl)oxy]propanoic acid

A solution of ethyl (2E)-3-{5-[6-(2-tert-butoxy-1-methyl-2-oxoethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 168 (2.51 g) in trifluoroacetic acid (20 mL) was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (1.81 g, yield 83%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.13 (t, J = 7.1 Hz, 3 H), 1.44 (dd, J

= 6.8, 1.5 Hz, 3 H), 2.39 (s, 3 H), 3.46 (d, J = 7.9 Hz, 3 H), 3.99 - 4.09 (m, 2 H), 4.71 - 4.86 (m, 1 H), 5.49 (dd, J = 20.5, 16.2 Hz, 1 H), 6.45 (dd, J = 8.9, 1.8 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.83 (dd, J = 8.6, 2.2 Hz, 1 H), 7.15 (dd, J = 16.3, 6.7 Hz, 1 H), 7.40 (d, J = 3.4 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 12.95 (br s, 1 H).

Reference Example 170 ethyl (2E)-3-{5-[6-(2-hydroxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

To a solution of 2-[(1-{4-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]-1,3-dimethyl-1H-pyrazol-5-yl}-1H-indol-6-yl)oxy]propanoic acid obtained in Reference Example 169 (201 mg) and N,N-dimethylformamide (0.1 mL) in tetrahydrofuran (5 mL) was added dropwise oxalyl chloride (96.3 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and tetrahydrofuran (5 mL) and water (0.5 mL) were added to the residue. Sodium borohydride (28.7 mg) was added, and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 35:65, v/v) to give the title compound (97.3 mg, yield 50%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.18 - 1.26 (m, 6 H), 2.47 (s, 3 H), 3.52 (s, 3 H), 3.63 - 3.76 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.38 - 4.47 (m, 1 H), 5.66 (dd, J = 16.3, 1.5 Hz, 1 H), 6.52 (d, J = 1.9 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 6.99 (d, J = 3.4 Hz, 1 H), 7.31 (dd, J = 16.3, 2.7 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H).

Reference Example 171 ethyl (2E)-3-{5-[6-(2-methoxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate

To a solution of ethyl (2E)-3-{5-[6-(2-hydroxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 170 (656 mg) in N,N-dimethylformamide (2 mL) was added 60% sodium hydride (in oil, 102 mg) with stirring, and the mixture was stirred at 0°C for 30 min. Methyl iodide (0.16 mL) was added to this reaction mixture, and the mixture was stirred at room temperature for 48 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 65:35, v/v) to give the title compound (496 mg, yield 73%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 - 1.30 (m, 6 H), 2.46 (s, 3 H), 3.38 (d, J = 1.5 Hz, 3 H), 3.42 - 3.59 (m, 5 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.41 - 4.52 (m, 1 H), 5.57 - 5.69 (m, 1 H), 6.50 - 6.54 (m, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.95 - 6.99 (m, 1 H), 7.28 - 7.36 (m, 1 H), 7.53 - 7.60 (m, 1 H).

Reference Example 172 (2E)-3-{5-[6-(2-methoxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-{5-[6-(2-methoxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylate obtained in Reference Example 171.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.15 (dd, J = 11.1, 6.2 Hz, 3 H), 2.38 (s, 3 H), 3.24 (d, J = 7.0 Hz, 3 H), 3.37 - 3.46 (m, 2 H), 3.49 (s, 3 H), 4.47 - 4.57 (m, 1 H), 5.44 (dd, J = 16.2, 4.3 Hz, 1 H), 6.53 (s, 1 H), 6.75 (d, J = 3.2 Hz, 1 H), 6.83 (dd, J = 8.7, 2.1 Hz, 1 H), 7.05 - 7.13 (m, 1 H), 7.41 (dd, J = 3.4, 2.1 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 12.17 (br s, 1 H).

Reference Example 173 1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-methyl-1H-indole and 5-

chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.47 (s, 3 H), 2.55 (s, 3 H), 3.57 (s, 3 H), 6.72 (d, J = 3.4 Hz, 1 H), 6.98 - 7.02 (m, 1 H), 7.08 - 7.13 (m, 1 H), 7.15 (d, J = 3.0 Hz, 1 H), 7.49 (s, 1 H), 9.51 (s, 1 H).

Reference Example 174 ethyl (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 173 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.44 - 2.49 (m, 6 H), 3.49 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.89 (d, J = 8.3 Hz, 1 H), 7.03 - 7.09 (m, 2 H), 7.30 (d, J = 16.4 Hz, 1 H), 7.50 (s, 1 H).

Reference Example 175 (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 174.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.35 - 2.42 (m, 6 H), 3.47 (s, 3 H), 5.41 (d, J = 16.4 Hz, 1 H), 6.76 (d, J = 3.2 Hz, 1 H), 6.90 (1 H, d, J = 8.3 Hz), 7.01 - 7.10 (m, 2 H), 7.47 - 7.52 (m, 2 H), 12.15 (br s, 1 H).

Reference Example 176 benzyl (piperidin-1-ylsulfonyl)carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and piperidine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.46 - 1.69 (m, 6 H), 3.27 - 3.35 (m, 4 H), 5.17 (s, 2 H), 7.37 (s, 5 H).

Reference Example 177 piperidine-1-sulfonamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl (piperidin-1-

ylsulfonyl)carbamate obtained in Reference Example 176.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.47 - 1.58 (m, 2 H), 1.63 - 1.73 (m, 4 H), 3.11 - 3.16 (m, 4 H), 4.79 (br s, 2 H).

Reference Example 178 (E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

To a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (3.46 g) in N,N-dimethylformamide (73 mL) was added 60% sodium hydride (in oil, 876 mg) with stirring at 0°C, and the mixture was stirred at 0°C for 1 hr. 5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (2.0 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution (30 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 55:45, v/v) to give a colorless oil. Trifluoroacetic acid (15 mL) was added to this colorless oil, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (2.52 g, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.42 (s, 3 H), 3.53 (s, 3 H), 4.48 (s, 2 H), 5.88 (d, J = 15.5 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.09 - 7.17 (m, 2 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Reference Example 179 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

To a solution of (E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 178 (2.18 g) in a mixed solvent of tetrahydrofuran (31 mL) and ethanol (31 mL) was added 10% palladium carbon (218 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.65 g, yield 75%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.31 (s, 3 H), 2.71 - 2.82 (m, 2 H), 2.87 - 2.97 (m, 2 H), 3.47 (s, 3 H), 4.43 (br s, 2 H), 6.70 (d, J = 2.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Reference Example 180 (E)-2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 24 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.44 (s, 3 H), 3.55 (s, 3 H), 4.46 (br s, 2 H), 5.87 (d, J = 15.6 Hz, 1 H), 6.80 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.15 (d, J = 15.6 Hz, 1 H), 7.22 (dd, J = 8.5, 1.7 Hz, 1 H), 7.63 (d, J = 8.5 Hz, 1 H).

Reference Example 181 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 180.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.22 (s, 3 H), 2.44 - 2.56 (m, 1 H), 2.60 - 2.72 (m, 1 H), 2.75 - 2.92 (m, 2 H), 3.37 (s, 3 H), 6.77 (s, 2 H), 6.80 - 6.83 (m, 1 H), 7.04 - 7.07 (m, 1 H), 7.20 (dd,

J = 8.5, 1.9 Hz, 1 H), 7.57 (d, J = 3.4 Hz, 1 H), 7.71 (d, J = 8.5 Hz, 1 H).

Reference Example 182 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (2.91 g) in N,N-dimethylformamide (25 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 970 mg) with stirring, and the mixture was stirred at 0°C for 30 min. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (2.93 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 80°C for 30 min. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v) to give the title compound (1.55 g, yield 30%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.67 (s, 3 H), 6.74 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H), 9.60 (s, 1 H).

Reference Example 183 (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 182 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 3.49 (s, 3 H), 6.09 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 15.9 Hz, 1 H), 6.85 - 6.91 (m, 3 H), 7.81 (d, J = 3.4 Hz, 1 H), 8.28 - 8.33 (m, 2 H).

Reference Example 184 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the

title compound was obtained from (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 183.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.21 (s, 3 H), 2.53 - 2.60 (m, 2 H), 2.86 - 2.94 (m, 2 H), 3.41 (s, 3 H), 6.74 (s, 2 H), 6.80 (d, J = 3.8 Hz, 1 H), 7.80 (d, J = 3.8 Hz, 1 H), 8.27 (q, J = 2.3 Hz, 2 H).

Reference Example 185 (E)-2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 20 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.43 (s, 3 H), 3.54 (s, 3 H), 4.49 (s, 2 H), 5.87 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.2 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.96 - 7.04 (m, 1 H), 7.10 - 7.18 (m, 2 H), 7.36 (dd, J = 9.1, 2.4 Hz, 1 H).

Reference Example 186 2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 185.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.22 (s, 3 H), 2.55 - 2.71 (m, 2 H), 2.75 - 2.94 (m, 2 H), 3.37 (s, 3 H), 6.74 - 6.79 (m, 3 H), 7.01 - 7.07 (m, 2 H), 7.45 - 7.51 (m, 1 H), 7.60 (d, J = 3.4 Hz, 1 H).

Reference Example 187 (E)-2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 11 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.41 (s, 3 H), 3.58 (s, 3 H), 4.71 (s, 2

H), 6.07 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.12 (d, J = 15.6 Hz, 1 H), 7.17 - 7.23 (m, 2 H), 8.03 (dd, J = 7.9, 1.5 Hz, 1 H), 8.33 (dd, J = 4.7, 1.5 Hz, 1 H).

Reference Example 188 2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 187.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.35 (s, 3 H), 2.73 - 3.24 (m, 4 H), 3.46 (s, 3 H), 4.99 (s, 2 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.22 (dd, J = 7.9, 4.9 Hz, 1 H), 8.04 (dd, J = 7.8, 1.6 Hz, 1 H), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H).

Reference Example 189 (E)-2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 58 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.48 (s, 3 H), 3.71 (s, 3 H), 6.08 (d, J = 15.9 Hz, 1 H), 6.49 (d, J = 2.3 Hz, 1 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.81 - 6.89 (m, 4 H), 7.36 (d, J = 3.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H).

Reference Example 190 2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 189.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.30 (s, 3 H), 2.71 - 2.84 (m, 2 H), 2.86 - 2.97 (m, 2 H), 3.49 (s, 3 H), 3.77 (s, 3 H), 4.52 (s, 2 H), 6.43 (d, J = 2.1 Hz, 1 H), 6.64 - 6.67 (m, 1 H), 6.85 (dd, J = 8.7, 2.3 Hz, 1 H), 6.95 (d, J = 3.2 Hz, 1 H), 7.54 (d, J = 8.7 Hz, 1 H).

Reference Example 191 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde

To a solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (1.22 g) in N,N-dimethylformamide (25 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 340 mg) with stirring, and the mixture was stirred at 0°C for 20 min. 5-Chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde (1.51 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 100°C for 3.5 hr. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 80:20, v/v) to give the title compound (1.71 g, yield 73%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.81 (s, 3 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 9.87 (s, 1 H).

Reference Example 192 (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethylenesulfonamide

To a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (2.46 g) in N,N-dimethylformamide (50 mL) was added 60% sodium hydride (in oil, 645 mg) with stirring at 0°C, and the mixture was stirred at 0°C for 1 hr. 5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 191 (1.71 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution (50 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The

filtrate was concentrated, trifluoroacetic acid (52 mL) was added to the residue, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 65:35, v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.51 g, yield 72%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:3.66 (s, 3 H), 5.86 (d, J = 15.8 Hz, 1 H), 6.89 - 7.08 (m, 4 H), 7.91 (d, J = 3.8 Hz, 1 H), 8.32 - 8.38 (m, 2 H).

Reference Example 193 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethanesulfonamide

To a solution of (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 192 (1.36 g) in a mixed solvent of tetrahydrofuran (30 mL) and ethanol (30 mL) was added 10% palladium carbon (136 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 8 hr. The catalyst was removed by filtration, and the filtrate was concentrated. To a solution of this residue in a mixed solvent of tetrahydrofuran (30 mL) and ethanol (30 mL) was added 10% palladium carbon (136 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 24 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was crystallized from hexane-ethyl acetate to give the title compound (1.22 g, yield 90%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.67 - 2.75 (m, 2 H), 2.84 - 2.96 (m, 2 H), 3.61 (s, 3 H), 6.82 - 6.89 (m, 3 H), 7.92 (d, J = 3.8 Hz, 1 H), 8.32 (s, 2 H).

Reference Example 194 (E)-2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazole-4-carbaldehyde obtained in Reference Example 41 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.46 (s, 3 H), 3.55 (s, 3 H), 4.43 (s, 2 H), 5.88 (d, J = 15.6 Hz,1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.14 (d, J = 15.6 Hz, 1 H), 7.23 - 7.27 (m, 2 H), 7.50 (d, J = 8.5 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H).

Reference Example 195 2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethylenesulfonamide obtained in Reference Example 194.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.24 (s, 3 H), 2.42 - 2.54 (m, 1 H), 2.60 - 2.73 (m, 1 H), 2.77 - 2.95 (m, 2 H), 3.38 (s, 3 H), 6.76 (s, 2 H), 6.94 (d, J = 3.0 Hz, 1 H), 7.32 (s, 1 H), 7.49 (d, J = 8.3 Hz, 1 H), 7.80 (d, J = 3.4 Hz, 1 H), 7.93 (d, J = 8.3 Hz, 1 H).

Reference Example 196 butyl sulfamate

Formic acid (930 mg) was added to chlorosulfonyl isocyanate (2.86 g) cooled at 0°C in an ice bath, and the mixture was vigorously stirred for 5 min. Acetonitrile (10 mL) was added to the reaction mixture, and the mixture was stirred at 0°C for 1 hr, and then at room temperature for 7 hr. A solution of butanol (1.00 g) and pyridine (1.60 g) in acetonitrile (9 mL) was added to the reaction mixture, and the mixture was stirred at room temperature for 24 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated

to give the title compound (2.09 g, yield 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 - 0.99 (m, 3 H), 1.38 - 1.52 (m, 2 H), 1.67 - 1.79 (m, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.98 (br s, 2 H).

Reference Example 197 N-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}sulfamide

To a solution of 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (321 mg) in ethanol (5.8 mL) was added sulfamide (946 mg), and the mixture was heated under reflux for 24 hr. Sodium borohydride (48.8 mg) was added to the reaction mixture, and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 35:65, v/v), and crystallized from hexane-ethyl acetate to give the title compound (100 mg, yield 24%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.36 (s, 3 H), 3.51 (s, 3 H), 3.85 - 4.00 (m, 2 H), 4.04 - 4.15 (m, 3 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.15 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Reference Example 198 5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-chloro-6-methoxy-1H-indole and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.58 (s, 3 H), 3.59 (s, 3 H), 3.85 (s, 3 H), 6.55 (s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.70 (s, 1 H), 9.55 (s, 1 H).

Reference Example 199 (E)-2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the

title compound was obtained from 5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 198 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.45 (s, 3 H), 3.55 (s, 3 H), 3.83 (s, 3 H), 4.49 (s, 2 H), 5.92 (d, J = 15.6 Hz, 1 H), 6.44 (s, 1 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.98 (d, J = 3.2 Hz, 1 H), 7.17 (d, J = 15.6 Hz, 1 H), 7.70 (s, 1 H).

Reference Example 200 2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 199.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.23 (s, 3 H), 2.54 - 2.70 (m, 2 H), 2.78 - 2.93 (m, 2 H), 3.39 (s, 3 H), 3.80 (s, 3 H), 6.64 (s, 1 H), 6.68 (d, J = 3.4 Hz, 1 H), 6.77 (s, 2 H), 7.41 (d, J = 3.4 Hz, 1 H), 7.75 (s, 1 H).

Reference Example 201 1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazole-4-carbaldehyde

To a solution of 5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine (8.08 g) in N,N-dimethylformamide (80 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 1.89 g) with stirring, and the mixture was stirred at 0°C for 30 min. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (6.25 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 80°C for 8 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v), and crystallized from hexane-ethyl acetate to give the title compound (8.40 g, yield 69%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 3.68 (s, 3 H), 6.89 (d, J

= 3.8 Hz, 1 H), 7.46 (d, J = 3.6 Hz, 1 H), 8.30 (d, J = 1.5 Hz, 1 H), 8.62 (d, J = 1.3 Hz, 1 H), 9.63 (s, 1 H).

Reference Example 202 ethyl (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazole-4-carbaldehyde obtained in Reference Example 201 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.58 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.71 (d, J = 16.3 Hz, 1 H), 6.88 (d, J = 3.8 Hz, 1 H), 7.23 - 7.30 (m, 1 H), 7.35 (d, J = 3.8 Hz, 1 H), 8.31 (d, J = 1.9 Hz, 1 H), 8.62 (d, J = 1.9 Hz, 1 H).

Reference Example 203 (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylate obtained in Reference Example 202.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 3.51 (s, 3 H), 5.48 (d, J = 16.3 Hz, 1 H), 7.04 (d, J = 3.4 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.97 (d, J = 3.4 Hz, 1 H), 8.65 (d, J = 4.5 Hz, 2 H), 12.21 (br s, 1 H).

Reference Example 204 1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

To a solution of 5-methyl-1H-pyrrolo[2,3-b]pyridine (1.70 g) in N,N-dimethylformamide (30 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 561 mg) with stirring, and the mixture was stirred at 0°C for 30 min. 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (1.85 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 80°C for 6 hr. Water was added to the reaction

mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v), and crystallized from hexane-ethyl acetate to give the title compound (1.42 g, yield 48%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.46 (s, 3 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 7.25 - 7.29 (m, 1 H), 7.80 - 7.83 (m, 1 H), 8.19 (d, J = 2.1 Hz, 1 H), 9.57 (s, 1 H).

Reference Example 205 ethyl (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (diethoxyphosphoryl)acetate (1.38 g) in tetrahydrofuran (46 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 269 mg) with stirring, and the mixture was stirred at 0°C for 30 min. A solution of 1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 204 (1.42 g) in tetrahydrofuran (10 mL) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 0°C for 4 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (1.61 g, yield 89%) as pale-yellow crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.44 - 2.47 (m, 6 H), 3.58 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.69 (d, J = 16.3 Hz, 1 H), 6.68 (d, J = 3.4 Hz, 1 H), 7.15 (d, J = 3.8 Hz, 1 H), 7.30 (d, J = 16.3 Hz, 1 H), 7.81 (d, J = 1.5 Hz, 1 H), 8.18 (d, J = 1.5 Hz, 1 H).

Reference Example 206 (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

To a solution of ethyl (2E)-3-[1,3-dimethyl-5-(5-methyl-

1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 205 (1.59 g) in a mixed solvent of tetrahydrofuran (25 mL) and ethanol (25 mL) was added a 1N aqueous sodium hydroxide solution (9.8 mL), and the mixture was stirred with heating at 60°C for 3 hr. The reaction mixture was allowed to cool to room temperature, and concentrated. An aqueous solution (20 mL) of the residue was neutralized with an aqueous solution (15 mL) of potassium hydrogensulfate (1.33 g), and the precipitated crystals were collected by filtration. The crystals were dissolved in ethyl acetate, and the solution was dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (1.14 g, yield 79%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 2.41 (s, 3 H), 3.48 (s, 3 H), 5.47 (d, J = 16.3 Hz, 1 H), 6.79 (d, J = 3.8 Hz, 1 H), 7.06 (d, J = 16.3 Hz, 1 H), 7.65 (d, J = 3.4 Hz, 1 H), 7.95 (s, 1 H), 8.12 (d, J = 1.9 Hz, 1 H), 12.14 (br s, 1 H).

Reference Example 207 (E)-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethylenesulfonamide

A solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (8.92 g) in N,N-dimethylformamide (180 mL) was added 60% sodium hydride (in oil, 2.33 g) with stirring at 0°C, and the mixture was stirred at 0°C for 1 hr. 1,3-Dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazole-4-carbaldehyde obtained in Reference Example 201 (5.79 g) was added to the reaction mixture, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, trifluoroacetic acid (50 mL) was added to the residue, and the mixture was stirred at room

temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v), and crystallized from hexane-ethyl acetate to give the title compound (6.36 g, yield 88%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.50 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 15.9 Hz, 1 H), 6.86 (s, 2 H), 7.06 (d, J = 3.8 Hz, 1 H), 7.95 (d, J = 3.8 Hz, 1 H), 8.60 (s, 1 H), 8.65 (s, 1 H).

Reference Example 208 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide

To a solution of (E)-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethylenesulfonamide obtained in Reference Example 207 (6.31 g) in a mixed solvent of tetrahydrofuran (80 mL) and ethanol (80 mL) was added 10% palladium carbon (631 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 8 hr. The catalyst was removed by filtration, and the filtrate was concentrated. To a solution of this residue in a mixed solvent of tetrahydrofuran (80 mL) and ethanol (80 mL) was added 10% palladium carbon (631 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 5 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was crystallized from hexane-ethanol to give the title compound (6.11 g, yield 96%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.22 (s, 3 H), 2.53 - 2.63 (m, 2 H), 2.92 (t, J = 8.3 Hz, 2 H), 3.43 (s, 3 H), 6.74 (s, 2 H), 6.98 (d, J = 3.4 Hz, 1 H), 7.93 (d, J = 3.4 Hz, 1 H), 8.60 (s, 1 H), 8.65 (s, 1 H).

Reference Example 209 (E)-2-[1,3-dimethyl-5-(5-methyl-1H-

pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 204 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 2.41 (s, 3 H), 3.47 (s, 3 H), 6.12 (d, J = 15.6 Hz, 1 H), 6.76 - 6.89 (m, 4 H), 7.63 (d, J = 3.6 Hz, 1 H), 7.95 (d, J = 1.1 Hz, 1 H), 8.13 (d, J = 1.5 Hz, 1 H).

Reference Example 210 2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 209.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.20 (s, 3 H), 2.40 (s, 3 H), 2.53 - 2.62 (m, 2 H), 2.85 - 2.93 (m, 2 H), 3.39 (s, 3 H), 6.71 (d, J = 3.6 Hz, 1 H), 6.75 (s, 2 H), 7.63 (d, J = 3.8 Hz, 1 H), 7.89 - 7.93 (m, 1 H), 8.11 (d, J = 2.1 Hz, 1 H).

Reference Example 211 ethyl 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propanoate

By a method similar to that in Reference Example 65, the title compound was obtained from ethyl (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylate obtained in Reference Example 202.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.16 (t, J = 7.1 Hz, 3 H), 2.26 - 2.35 (m, 5 H), 2.54 - 2.63 (m, 2 H), 3.51 (s, 3 H), 3.99 (q, J = 7.0 Hz, 2 H), 6.82 (d, J = 3.6 Hz, 1 H), 7.37 (d, J = 3.6 Hz, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H).

Reference Example 212 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propan-1-ol

By a method similar to that in Reference Example 66, the title compound was obtained from ethyl 3-{1,3-dimethyl-5-[5-

(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propanoate obtained in Reference Example 211.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.53 - 1.65 (m, 2 H), 2.29 - 2.40 (m, 5 H), 3.43 - 3.52 (m, 5 H), 6.81 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.27 (d, J = 1.7 Hz, 1 H), 8.60 (d, J = 1.7 Hz, 1 H).

Reference Example 213 5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

1,3-Dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 11 (1.38 g) was dissolved in methanol (100 mL), 10% palladium carbon (530 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 78 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (ethyl acetate) to give the title compound (0.85 g, yield 61%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.47 (s, 3 H), 3.28 (t, J = 8.6 Hz, 2 H), 3.73 (s, 3 H), 4.04 (t, J = 8.6 Hz, 2 H), 6.67 (dd, J = 6.9, 5.5 Hz, 1 H), 7.40 (d, J = 6.9 Hz, 1 H), 7.89 (d, J = 5.5 Hz, 1 H), 9.78 (s, 1 H).

Reference Example 214 ethyl (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 213 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 - 1.32 (m, 3 H), 2.38 (s, 3 H), 3.23 - 3.35 (m, 2 H), 3.66 (s, 3 H), 3.75 - 3.95 (m, 2 H), 4.15 - 4.21 (m, 2 H), 5.96 (d, J = 16.2 Hz, 1 H), 6.65 (dd, J = 7.2, 5.3 Hz, 1 H), 7.39 (dd, J = 7.2, 1.5 Hz, 1 H), 7.45 (d, J = 16.2 Hz, 1 H), 7.90 (dd, J = 5.3, 1.5 Hz, 1 H).

Reference Example 215 (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 214.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.27 (s, 3 H), 3.26 (t, J = 8.5 Hz, 2 H), 3.56 (s, 3 H), 3.79 - 3.95 (m, 2 H), 5.80 (d, J = 16.1 Hz, 1 H), 6.68 (dd, J = 7.2, 4.5 Hz, 1 H), 7.24 (d, J = 16.1 Hz, 1 H), 7.50 (dd, J = 7.2, 1.5 Hz, 1 H), 7.76 (d, J = 4.5 Hz, 1 H), 12.08 (s, 1 H).

Reference Example 216 3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-pyrrolo[2,3-b]pyridine and 5-chloro-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 150.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.99 - 1.08 (m, 4 H), 2.45 - 2.55 (m, 1 H), 3.63 (s, 3 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.22 (dd, J = 7.8, 4.8 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.02 (dd, J = 7.8, 1.5 Hz, 1 H), 8.36 (dd, J = 4.8, 1.5 Hz, 1 H), 9.66 (s, 1 H).

Reference Example 217 ethyl (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 216 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.00 (d, J = 7.2 Hz, 4 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.91 - 2.05 (m, 1 H), 3.55 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.92 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.15 - 7.24 (m, 2 H), 7.40 (d, J = 16.1 Hz, 1 H), 8.02 (dd, J = 7.8, 1.7 Hz, 1 H), 8.35 (dd, J = 4.5, 1.7 Hz, 1 H).

Reference Example 218 (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-

yl]acrylate obtained in Reference Example 217.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.85 - 0.99 (m, 4 H), 2.00 - 2.10 (m, 1 H), 3.47 (s, 3 H), 5.59 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 16.2 Hz, 1 H), 7.28 (dd, J = 7.9, 4.7 Hz, 1 H), 7.72 (d, J = 3.6 Hz, 1 H), 8.17 (dd, J = 7.9, 1.6 Hz, 1 H), 8.28 (dd, J = 4.7, 1.6 Hz, 1 H), 12.14 (s, 1 H).

Reference Example 219 3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 213, the title compound was obtained from 3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 216.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 - 1.05 (m, 4 H), 2.03 - 2.31 (m, 1 H), 3.27 (t, J = 8.5 Hz, 2 H), 3.68 (s, 3 H), 3.94 - 4.10 (m, 2 H), 6.66 (dd, J = 7.2, 5.1 Hz, 1 H), 7.35 - 7.42 (m, 1 H), 7.88 (d, J = 5.1 Hz, 1 H), 9.91 (s, 1 H).

Reference Example 220 ethyl (2E)-3-[3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 219 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 - 0.96 (m, 4 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.87 - 1.96 (m, 1 H), 3.23 - 3.32 (m, 2 H), 3.62 (s, 3 H), 3.78 - 3.95 (m, 2 H), 4.18 (q, J = 7.1 Hz, 2 H), 6.18 (d, J = 16.1 Hz, 1 H), 6.64 (dd, J = 7.2, 5.3 Hz, 1 H), 7.38 (dd, J = 7.2, 1.5 Hz, 1 H), 7.54 (d, J = 16.1 Hz, 1 H), 7.90 (d, J = 5.3 Hz, 1 H).

Reference Example 221 (2E)-3-[3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[3-cyclopropyl-5-

(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 220.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.75 - 0.83 (m, 2 H), 0.85 - 0.94 (m, 2 H), 1.90 - 1.99 (m, 1 H), 3.25 (t, J = 8.3 Hz, 2 H), 3.54 (s, 3 H), 3.78 - 3.93 (m, 2 H), 5.98 (d, J = 16.3 Hz, 1 H), 6.68 (dd, J = 7.2, 5.3 Hz, 1 H), 7.34 (d, J = 16.3 Hz, 1 H), 7.45 - 7.53 (m, 1 H), 7.74 - 7.77 (m, 1 H), 12.08 (s, 1 H).

Reference Example 222 1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-pyrrolo[3,2-c]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 3.59 (s, 3 H), 6.93 (dd, J = 3.4, 0.8 Hz, 1 H), 7.05 (d, J = 5.7 Hz, 1 H), 7.24 (d, J = 3.4 Hz, 1 H), 8.44 (d, J = 5.7 Hz, 1 H), 9.06 (d, J = 0.8 Hz, 1 H), 9.56 (s, 1 H).

Reference Example 223 ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 222 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.92 (dd, J = 3.4, 0.9 Hz, 1 H), 6.97 (d, J = 5.8 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.26 (d, J = 16.2 Hz, 1 H), 8.40 (d, J = 5.8 Hz, 1 H), 9.05 (d, J = 0.9 Hz, 1 H).

Reference Example 224 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 223.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.38 (s, 3 H), 3.50 (s, 3 H), 5.37 (d, J = 16.2 Hz, 1 H), 7.02 - 7.08 (m, 2 H), 7.11 (d, J = 5.8 Hz, 1

H), 7.71 (d, J = 3.4 Hz, 1 H), 8.30 (d, J = 5.8 Hz, 1 H), 9.01 (s, 1 H), 12.19 (s, 1 H).

Reference Example 225 1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-pyrrolo[2,3-c]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.58 (s, 3 H), 3.62 (s, 3 H), 6.84 (d, J = 3.0 Hz, 1 H), 7.34 (d, J = 3.0 Hz, 1 H), 7.64 (d, J = 5.5 Hz, 1 H), 8.43 (d, J = 5.5 Hz, 1 H), 8.53 (s, 1 H), 9.59 (s, 1 H).

Reference Example 226 ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 225 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (t, J = 7.2 Hz, 3 H), 2.48 (s, 3 H), 3.54 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.63 (d, J = 16.4 Hz, 1 H), 6.84 (dd, J = 3.3, 0.9 Hz, 1 H), 7.24 (s, 1 H), 7.27 (d, J = 16.4 Hz, 1 H), 7.64 (dd, J = 5.5, 0.9 Hz, 1 H), 8.41 (d, J = 5.5 Hz, 1 H), 8.45 (s, 1 H).

Reference Example 227 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 226.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.39 (s, 3 H), 3.53 (s, 3 H), 5.36 (d, J = 16.2 Hz, 1 H), 6.95 (dd, J = 3.3, 0.8 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.74 (dd, J = 5.4, 0.8 Hz, 1 H), 7.85 (d, J = 3.3 Hz, 1 H), 8.31 (d, J = 5.4 Hz, 1 H), 8.41 (s, 1 H), 12.19 (s, 1 H).

Reference Example 228 1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the

title compound was obtained from 1H-pyrrolo[2,3-b]pyridine and 5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.82 (s, 3 H), 6.80 (d, J = 3.9 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.32 (d, J = 3.9 Hz, 1 H), 8.01 - 8.05 (m, 1 H), 8.32 - 8.35 (m, 1 H), 9.83 (s, 1 H).

Reference Example 229 ethyl (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 228 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.22 (d, J = 7.2 Hz, 3 H), 3.70 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.59 (d, J = 16.2 Hz, 1 H), 6.83 (d, J = 3.8 Hz, 1 H), 7.19 (d, J = 3.8 Hz, 1 H), 7.25 (dd, J = 8.1, 4.5 Hz, 1 H), 7.39 (d, J = 16.2 Hz, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 8.36 (d, J = 4.5 Hz, 1 H).

Reference Example 230 (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 229.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:3.66 (s, 3 H), 5.23 (d, J = 16.5 Hz, 1 H), 6.95 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 16.5 Hz, 1 H), 7.32 (dd, J = 8.0, 4.5 Hz, 1 H), 7.80 (d, J = 3.8 Hz, 1 H), 8.18 - 8.23 (m, 1 H), 8.28 - 8.32 (m, 1 H), 12.56 (s, 1 H).

Reference Example 231 3-(1-naphthyl)thiophene-2-carbaldehyde

To a mixture of 1-naphthylboronic acid (1.67 g), 3-bromothiophene-2-carbaldehyde (1.81 g), a 2.0M aqueous sodium carbonate solution (10.0 mL) and 1,2-dimethoxyethane (30 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.43 g), and the reaction mixture was heated under reflux under nitrogen atmosphere for 5 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 95:5, v/v) to give the title compound (2.28 g, yield 98%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:7.29 (d, J = 4.9 Hz, 1 H), 7.45 - 7.49 (m, 4 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.83 (dd, J = 4.9, 1.5 Hz, 1 H), 7.91 - 7.98 (m, 2 H), 9.60 (s, 1 H).

Reference Example 232 ethyl (2E)-3-[3-(1-naphthyl)-2-thienyl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 3-(1-naphthyl)thiophene-2-carbaldehyde obtained in Reference Example 231 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (d, J = 7.1 Hz, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 6.26 (d, J = 15.6 Hz, 1 H), 7.14 (d, J = 5.1 Hz, 1 H), 7.35 (dd, J = 7.0, 1.1 Hz, 1 H), 7.40 - 7.58 (m, 5 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.86 - 7.96 (m, 2 H).

Reference Example 233 (2E)-3-[3-(1-naphthyl)-2-thienyl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[3-(1-naphthyl)-2-thienyl]acrylate obtained in Reference Example 232.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:6.18 (d, J = 15.5 Hz, 1 H), 7.18 - 7.27 (m, 2 H), 7.41 (d, J = 6.1 Hz, 1 H), 7.47 - 7.68 (m, 4 H), 7.89 (d, J = 5.3 Hz, 1 H), 8.00 - 8.08 (m, 2 H), 12.33 (s, 1 H).

Reference Example 234 ethyl (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

To a solution of ethyl (diethoxyphosphoryl)acetate (2.54 g) in tetrahydrofuran (20 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 459 mg) with stirring, and the mixture was stirred at 0°C for 30 min. A solution of 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference

Example 182 (2.03 g) in tetrahydrofuran (25 mL) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 0°C for 3 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (2.54 g, yield 99%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.69 (d, J = 16.3 Hz, 1 H), 6.73 (d, J = 3.8 Hz, 1 H), 7.23 - 7.30 (m, 2 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H).

Reference Example 235 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

To a solution of ethyl (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 234 (2.50 g) in a mixed solvent of tetrahydrofuran (15 mL) and ethanol (15 mL) was added a 1N aqueous sodium hydroxide solution (15 mL), and the mixture was stirred with heating at 60°C for 2 hr. The reaction mixture was allowed to cool to room temperature, neutralized with an aqueous solution (80 mL) of potassium hydrogensulfate (2.1 g), and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (2.18 g, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.49 (s, 3 H), 5.46 (d, J = 16.3 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.83 (d, J = 3.6 Hz, 1 H), 8.29 - 8.33 (m, 2 H), 12.17 (s, 1 H).

Reference Example 236 5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-bromo-1H-pyrrolo[2,3-b]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.67 (s, 3 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.33 (d, J = 3.6 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H), 8.38 (d, J = 2.1 Hz, 1 H), 9.60 (s, 1 H).

Reference Example 237 ethyl (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 236 and ethyl (diethoxyphosphoryl)acetate.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.69 (d, J = 16.5 Hz, 1 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.22 (d, J = 3.6 Hz, 1 H), 7.28 (d, J = 16.5 Hz, 1 H), 8.16 (d, J = 2.3 Hz, 1 H), 8.37 (d, J = 2.3 Hz, 1 H).

Reference Example 238 (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 237.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 3.49 (s, 3 H), 5.46 (d, J = 16.3 Hz, 1 H), 6.87 (d, J = 3.4 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.81 (d, J = 3.4 Hz, 1 H), 8.36 (d, J = 2.3 Hz, 1 H), 8.44 (d, J = 2.3 Hz, 1 H), 12.17 (s, 1 H).

Reference Example 239 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate

To a solution of 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanol obtained in Reference Example 63 (630 mg) in tetrahydrofuran (10 mL) were added triethylamine (442 mg) and methanesulfonyl chloride (393 mg), and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl

acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated to give the title compound (797 mg, yield 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.31 (s, 3 H), 2.58 - 2.75 (m, 2 H), 2.77 (s, 3 H), 3.46 (s, 3 H), 4.04 (t, J = 6.6 Hz, 2 H), 6.69 (d, J = 3.2 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Reference Example 240 tert-butyl 4-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-3-oxopiperazine-1-carboxylate

To a solution of tert-butyl 3-oxopiperazine-1-carboxylate (466 mg) in N,N-dimethylformamide (5 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 120 mg) with stirring, and the mixture was stirred at room temperature for 15 min. A solution of 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate obtained in Reference Example 239 (642 mg) in N,N-dimethylformamide (5 mL) was added to this reaction mixture, and the reaction mixture was stirred at 60°C for 12 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 10:90, v/v) to give the title compound (486 mg, yield 59%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.44 (s, 9 H), 2.32 (s, 3 H), 2.40 - 2.53 (m, 2 H), 2.96 - 3.05 (m, 2 H), 3.18 - 3.28 (m, 2 H), 3.40 - 3.50 (m, 5 H), 3.96 (s, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 2.1 Hz, 1 H).

Reference Example 241 2-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethoxy}-1H-isoindole-1,3(2H)-dione

To a solution of 2-[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]ethanol obtained in Reference Example 63 (2.06 g) in tetrahydrofuran (50 mL) were added N-hydroxyphthalimide (1.29 g) and triphenylphosphine (2.23 g), and then diethyl azodicarboxylate (40% toluene solution, 5.57 g) was added, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the residue, and the insoluble material was filtered off. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (2.97 g, yield 96%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.32 (s, 3 H), 2.64 - 2.85 (m, 2 H), 3.47 (s, 3 H), 4.02 (t, J = 7.6 Hz, 2 H), 6.61 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.09 - 7.17 (m, 2 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.72 - 7.80 (m, 4 H).

Reference Example 242 1-{4-[2-(aminooxy)ethyl]-1,3-dimethyl-1H-pyrazol-5-yl}-5-chloro-1H-indole

To a solution of 2-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethoxy}-1H-isoindole-1,3(2H)-dione obtained in Reference Example 241 (1.26 g) in tetrahydrofuran (20 mL) was added a 35% aqueous hydrazine solution (2.91 g), and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated to give the title compound (919 mg, yield 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.30 (s, 3 H), 2.40 - 2.60 (m, 2 H), 3.44 (s, 3 H), 3.51 (t, J = 6.6 Hz, 2 H), 5.04 (s, 2 H), 6.64 - 6.69 (m, 1 H), 6.94 - 6.99 (m, 1 H), 7.12 - 7.22 (m, 2 H), 7.63 - 7.67 (m, 1 H).

Reference Example 243 (4R)-5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-4-isopropyl-2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

To a solution of (4R)-4-isopropyl-2-(4-methoxybenzyl)-

1,2,5-thiadiazolidin-3-one 1,1-dioxide obtained in Reference Example 273 (800 mg) in N,N-dimethylformamide (6 mL) was added 60% sodium hydride (in oil, 103 mg) with stirring at 0°C, and the mixture was stirred at room temperature for 10 min. A solution of 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate obtained in Reference Example 239 (783 mg) in N,N-dimethylformamide (6 mL) was added to this reaction mixture, and the reaction mixture was stirred at 100°C for 5 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v) to give the title compound (740 mg, yield 59%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.58 (dd, J = 17.6, 7.0 Hz, 3 H), 0.79 (dd, J = 7.0, 2.7 Hz, 3 H), 1.61 - 1.82 (m, 1 H), 2.30 (s, 3 H), 2.50 - 2.88 (m, 3 H), 3.08 - 3.32 (m, 1 H), 3.41 (d, J = 3.0 Hz, 1 H), 3.51 (d, J = 3.0 Hz, 3 H), 3.78 (s, 3 H), 4.53 - 4.66 (m, 2 H), 6.67 - 6.70 (m, 1 H), 6.83 (d, J = 8.3 Hz, 2 H), 6.89 - 6.93 (m, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.66 (s, 1 H).

Reference Example 244 5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde

To a solution of 5-chloro-1H-pyrrolo[2,3-b]pyridine (1.30 g) in N,N-dimethylformamide (25 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 380 mg) with stirring, and the mixture was stirred at 0°C for 20 min. 5-Chloro-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 150 (1.47 g) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 100°C for 4 hr. After the reaction mixture was allowed to cool to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic

layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (1.69 g, yield 70%) as colorless crystals. ^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.00 - 1.08 (m, 4 H), 2.40 - 2.52 (m, 1 H), 3.61 (s, 3 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 3.6 Hz, 1 H), 7.99 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H), 9.68 (s, 1 H).

Reference Example 245 (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethylenesulfonamide

To a solution of tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate (2.64 g) in N,N-dimethylformamide (20 mL) was added 60% sodium hydride (in oil, 676 mg) with stirring at 0°C, and the mixture was stirred at 0°C for 1 hr. 5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 244 (1.68 g) was added to the reaction mixture at 0°C, and the mixture was stirred at room temperature for 1.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give colorless crystals. Trifluoroacetic acid (20 mL) was added to the colorless crystals, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title

compound (1.49 g, yield 74%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.01 (d, J = 7.6 Hz, 4 H), 1.88 - 1.96 (m, 1 H), 3.55 (s, 3 H), 4.48 (s, 2 H), 6.34 (d, J = 15.5 Hz, 1 H), 6.74 (d, J = 3.8 Hz, 1 H), 7.20 - 7.26 (m, 2 H), 8.01 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H).

Reference Example 246 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide

To a solution of (E)-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 245 (935 mg) in a mixed solvent of tetrahydrofuran (25 mL) and ethanol (25 mL) was added 10% palladium carbon (200 mg), and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 3 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 30:70, v/v), and crystallized from hexane-ethyl acetate to give the title compound (758 mg, yield 80%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 - 1.00 (m, 4 H), 1.78 - 1.89 (m, 1 H), 2.78 - 2.90 (m, 1 H), 2.95 - 3.25 (m, 2 H), 3.30 - 3.40 (m, 1 H), 3.42 (s, 3 H), 4.83 (s, 2 H), 6.69 (d, J = 3.4 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Reference Example 247 5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

By a method similar to that in Reference Example 243, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate obtained in Reference Example 239 and 2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide obtained in Reference Example 269.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.30 (s, 3 H), 2.44 - 2.63 (m, 2 H), 3.02 (t, J = 6.8 Hz, 2 H), 3.19 - 3.34 (m, 2 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 4.59 (s, 2 H), 6.62 (d, J = 3.2 Hz, 1 H), 6.86 (d,

J = 8.3 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.2 Hz, 1 H), 7.11 (dd, J = 8.7, 1.7 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 2 H), 7.66 (s, 1 H).

Reference Example 248 1-benzyl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 85, the title compound was obtained from 2-benzyl-5-methyl-2,4-dihydro-3H-pyrazol-3-one.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.47 (s, 3 H), 5.30 (s, 2 H), 7.23 - 7.38 (m, 5 H), 9.87 (s, 1 H).

Reference Example 249 1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-pyrrolo[2,3-b]pyridine and 1-benzyl-5-chloro-3-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 248.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.57 (s, 3 H), 5.16 (s, 2 H), 6.66 (d, J = 3.8 Hz, 1 H), 6.85 - 6.92 (m, 2 H), 7.04 (d, J = 3.8 Hz, 1 H), 7.15 - 7.27 (m, 4 H), 7.98 - 8.01 (m, 1 H), 8.35 (d, J = 4.9 Hz, 1 H), 9.55 (s, 1 H).

Reference Example 250 ethyl (2E)-3-[1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 249 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 (t, J = 7.1 Hz, 3 H), 2.47 (s, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.95 (d, J = 15.0 Hz, 1 H), 5.15 (d, J = 15.0 Hz, 1 H), 5.68 (d, J = 16.2 Hz, 1 H), 6.64 (d, J = 3.6 Hz, 1 H), 6.82 - 6.95 (m, 3 H), 7.12 - 7.36 (m, 5 H), 7.97 - 8.00 (m, 1 H), 8.33 (dd, J = 4.9, 1.5 Hz, 1 H).

Reference Example 251 (2E)-3-[1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1-benzyl-3-

methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 250.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.38 (s, 3 H), 4.83 (d, J = 15.6 Hz, 1 H), 5.06 (d, J = 15.6 Hz, 1 H), 5.47 (d, J = 16.3 Hz, 1 H), 6.83 (d, J = 3.4 Hz, 1 H), 6.93 (dd, J = 5.7, 4.2 Hz, 2 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.16 - 7.22 (m, 3 H), 7.26 (dd, J = 8.0, 4.5 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 8.14 (dd, J = 8.0, 1.5 Hz, 1 H), 8.22 - 8.31 (m, 1 H), 12.15 (s, 1 H).

Reference Example 252 3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

To 1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 249 (2.32 g) was added trifluoroacetic acid (35 mL), and the mixture was heated under reflux for 150 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 55:45, v/v) to give the title compound (880 mg, yield 53%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.52 (s, 3 H), 6.68 (d, J = 3.8 Hz, 1 H), 7.22 (dd, J = 7.6, 4.9 Hz, 1 H), 7.98 - 8.14 (m, 2 H), 8.36 (d, J = 3.8 Hz, 1 H), 9.88 (s, 1 H).

Reference Example 253 ethyl (2E)-3-[3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

To a solution of 3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 252 (473 mg) in toluene (20 mL) was added ethyl (triphenylphosphoranylidene)acetate (1.16 g), and the mixture was heated under reflux for 15 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 10:90, v/v) to give the title compound (589 mg, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.32 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.56 - 5.62 (m, 1 H), 6.70 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 7.8, 4.6 Hz, 1 H), 7.37 (d, J = 3.4 Hz, 1 H), 7.41 - 7.49 (m, 1 H), 8.03 (dd, J = 7.8, 1.5 Hz, 1 H), 8.35 (dd, J = 4.6, 1.5 Hz, 1 H), 12.00 (s, 1 H).

Reference Example 254 (2E)-3-[3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

To a solution of ethyl (2E)-3-[3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 253 (1.75 g) in a mixed solvent of tetrahydrofuran (12 mL) and ethanol (12 mL) was added a 1N aqueous sodium hydroxide solution (18 mL), and the mixture was stirred with heating at 80°C for 4 hr. The reaction mixture was allowed to cool to room temperature, neutralized with an aqueous solution (50 mL) of potassium hydrogensulfate (2.5 g), and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (1.10 g, yield 69%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.46 (s, 3 H), 5.34 (d, J = 16.2 Hz, 1 H), 6.73 (d, J = 3.6 Hz, 1 H), 7.16 - 7.28 (m, 2 H), 7.60 (d, J = 3.6 Hz, 1 H), 8.09 (dd, J = 7.8, 1.6 Hz, 1 H), 8.22 (dd, J = 4.7, 1.5 Hz, 1 H), 12.00 (s, 1 H), 13.23 (s, 1 H).

Reference Example 255 (2E)-3-[1-(tert-butoxycarbonyl)-5-methyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

To a solution of (2E)-3-[3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 254 (715 mg) in a mixed solvent of tetrahydrofuran (10 mL) and water (5 mL) were added sodium carbonate (284 mg) and di-tert-butyl dicarbonate (6.24 g), and the mixture was stirred at room temperature for 72 hr. The reaction mixture was neutralized with potassium hydrogensulfate (0.73 g), and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium

sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v) to give the title compound (549 mg, yield 56%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.60 (s, 9 H), 2.69 (s, 3 H), 5.11 (d, J = 16.2 Hz, 1 H), 6.80 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.8, 4.6 Hz, 1 H), 7.33 (d, J = 16.2 Hz, 1 H), 7.68 (d, J = 3.6 Hz, 1 H), 8.13 (dd, J = 7.8, 1.5 Hz, 1 H), 8.24 (dd, J = 4.6, 1.5 Hz, 1 H), 12.28 (s, 1 H).

Reference Example 256 1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazole-5-carbaldehyde

By a method similar to that in Reference Example 9, the title compound was obtained from 1-benzyl-2-butyl-4-chloro-1H-imidazole-5-carbaldehyde and 1-naphthylboronic acid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.3 Hz, 3 H), 1.35 - 1.48 (m, 2 H), 1.70 - 1.84 (m, 2 H), 2.75 - 2.81 (m, 2 H), 5.72 (s, 2 H), 7.15 (d, J = 7.0 Hz, 2 H), 7.29 - 7.40 (m, 3 H), 7.49 - 7.60 (m, 4 H), 7.87 - 7.95 (m, 2 H), 8.09 - 8.15 (m, 1 H), 9.50 (s, 1 H).

Reference Example 257 ethyl (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazole-5-carbaldehyde obtained in Reference Example 256 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.4 Hz, 3 H), 1.11 (t, J = 7.0 Hz, 3 H), 1.34 - 1.46 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.73 - 2.79 (m, 2 H), 4.01 (q, J = 7.0 Hz, 2 H), 5.34 (s, 2 H), 5.56 (d, J = 16.3 Hz, 1 H), 7.11 (d, J = 6.8 Hz, 2 H), 7.30 - 7.56 (m, 8 H), 7.85 - 7.93 (m, 3 H).

Reference Example 258 (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]acrylate obtained in Reference

Example 257.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.83 (t, J = 7.4 Hz, 3 H), 1.28 - 1.42 (m, 2 H), 1.58 - 1.69 (m, 2 H), 2.77 (t, J = 7.6 Hz, 2 H), 5.39 (d, J = 16.3 Hz, 1 H), 5.51 (s, 2 H), 7.11 (d, J = 7.2 Hz, 2 H), 7.28 (d, J = 16.3 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.39 - 7.64 (m, 6 H), 7.81 (d, J = 8.3 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H), 12.02 (s, 1 H).

Reference Example 259 ethyl N-({[(benzyloxy)carbonyl]amino}sulfonyl)-β-alaninate

To a solution of benzyl alcohol (2.25 g) in acetonitrile (40 ml) was added chlorosulfonyl isocyanate (1.90 mL) with stirring at 0°C, and the mixture was stirred for 30 min. Pyridine (3.35 mL) was added to this reaction mixture, and the mixture was stirred at 0°C for 1 hr. β-Alanine ethyl ester hydrochloride (4.79 g) and N,N-diisopropylethylamine (7.13 mL) were added, and the mixture was stirred at room temperature for 3 hr. 1N Hydrochloric acid was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (6.55 g, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.27 (t, J = 7.2 Hz, 3 H), 2.59 (t, J = 6.1 Hz, 2 H), 3.24 - 3.45 (m, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.20 (s, 2 H), 5.76 (t, J = 6.2 Hz, 1 H), 7.30 - 7.38 (m, 5 H), 7.40 (br s, 1 H).

Reference Example 260 ethyl N-(aminosulfonyl)-β-alaninate

By a method similar to that in Reference Example 109, the title compound was obtained from ethyl N-({[(benzyloxy)carbonyl]amino}sulfonyl)-β-alaninate obtained in Reference Example 259.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.28 (t, J = 7.2 Hz, 3 H), 2.65 (t, J = 5.9 Hz, 2 H), 3.28 - 3.54 (m, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.61 (br s, 2 H), 5.05 (t, J = 5.7 Hz, 1 H).

Reference Example 261 5-(difluoromethyl)-2-methyl-2,4-dihydro-3H-pyrazol-3-one

By a method similar to that in Reference Example 84, the title compound was obtained from ethyl 4,4-difluoro-3-oxobutanoate and methylhydrazine.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:3.54 (s, 3 H), 5.55 (s, 1 H), 6.70 (t, J = 54.8 Hz, 1 H), 11.35 (s, 1 H).

Reference Example 262 5-chloro-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 85, the title compound was obtained from 5-(difluoromethyl)-2-methyl-2,4-dihydro-3H-pyrazol-3-one obtained in Reference Example 261.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.93 (s, 3 H), 6.90 (t, J = 53.6 Hz, 1 H), 9.96 (s, 1 H).

Reference Example 263 3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 1H-pyrrolo[2,3-b]pyridine and 5-chloro-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 262.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:3.81 (s, 3 H), 6.77 - 7.16 (m, 2 H), 7.24 (dd, J = 8.0, 4.7 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.03 (dd, J = 8.0, 1.5 Hz, 1 H), 8.35 (dd, J = 4.7, 1.5 Hz, 1 H), 9.79 (s, 1 H).

Reference Example 264 ethyl (2E)-3-[3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-4-carbaldehyde obtained in Reference Example 263 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (d, J = 7.2 Hz, 3 H), 3.67 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.86 (d, J = 16.3 Hz, 1 H), 6.58 - 6.93 (m, 2 H), 7.20 - 7.29 (m, 2 H), 7.37 (d, J = 16.3 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.36 (dd, J = 4.9, 1.5 Hz, 1 H).

Reference Example 265 (2E)-3-[3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylate obtained in Reference Example 264.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:3.62 (s, 3 H), 5.42 (d, J = 16.3 Hz, 1 H), 6.94 (d, J = 3.6 Hz, 1 H), 7.06 - 7.42 (m, 3 H), 7.81 (d, J = 3.6 Hz, 1 H), 8.20 (dd, J = 8.0, 1.5 Hz, 1 H), 8.30 (dd, J = 4.5, 1.5 Hz, 1 H), 12.41 (s, 1 H).

Reference Example 266 ethyl N-{[(tert-butoxycarbonyl)amino]sulfonyl}glycinate

To a solution of tert-butyl alcohol (10 g) in acetonitrile (200 mL), which was cooled at 0°C in an ice bath, was added dropwise chlorosulfonyl isocyanate (22.9 g), and the mixture was stirred at 0°C for 1 hr. Pyridine (33 mL) was added to the reaction mixture at 0°C, and the reaction mixture was further stirred at 0°C for 45 min to give a solution of tert-butyl N-chlorosulfonyl carbamate in acetonitrile. To a suspension of glycine ethyl ester hydrochloride (56.5 g) in acetonitrile (200 mL), which was cooled at 0°C in an ice bath, was added triethylamine (57 mL), and the mixture was stirred at 0°C for 20 min. The white precipitate was removed by filtration, and washed with a small amount of acetonitrile. The obtained filtrate was added to the aforementioned solution of tert-butyl N-chlorosulfonyl carbamate in acetonitrile, which was cooled at 0°C in an ice bath, and the mixture was stirred at room temperature for 14 hr. The reaction mixture was concentrated under reduced pressure, 1M hydrochloric acid (260 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was suspended in dichloromethane (100 mL) heated in advance, and the insoluble material was collected by filtration, and dried to give the title compound (30.3 g, yield

80%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.30 (t, J = 7.1 Hz, 3 H), 1.50 (s, 9 H), 3.95 (s, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 5.63 (br s, 1 H).

Reference Example 267 ethyl N-{[(tert-butoxycarbonyl)(4-methoxybenzyl)amino]sulfonyl}glycinate

To a solution of ethyl N-{[(tert-butoxycarbonyl)amino]sulfonyl}glycinate obtained in Reference Example 266 (20.0 g), triphenylphosphine (18.6 g) and 4-methoxybenzyl alcohol (9.79 g) in tetrahydrofuran (100 mL) were added diethyl azodicarboxylate (31.6 g) and tetrahydrofuran (20 mL) under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature for 24 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 75:25, v/v), and crystallized from hexane-isopropyl ether to give the title compound (17.7 g, yield 62%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.25 (t, J = 7.1 Hz, 3 H), 1.54 (s, 9 H), 3.55 (d, J = 5.4 Hz, 2 H), 3.80 (s, 3 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.76 (s, 2 H), 5.70 (t, J = 5.4 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H).

Reference Example 268 ethyl N-{[(4-methoxybenzyl)amino]sulfonyl}glycinate

To ethyl N-{[(tert-butoxycarbonyl)(4-methoxybenzyl)amino]sulfonyl}glycinate obtained in Reference Example 267 (10.0 g) was added a 4M hydrogen chloride-ethyl acetate solution (100 mL) at 0°C, and the mixture was stirred at 0°C for 1 hr, and then at room temperature for 3.5 hr. The reaction mixture was concentrated under reduced pressure, the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 80:20 - 60:40, v/v) to give the title

compound (6.48 g, yield 86%) as a white solid.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.28 (t, J = 7.2 Hz, 3 H), 3.79 (d, J = 5.1 Hz, 2 H), 3.80 (s, 3 H), 4.17 - 4.25 (m, 4 H), 4.52 (t, J = 5.9 Hz, 1 H), 4.82 (t, J = 5.6 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H).

Reference Example 269 2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

To a solution of ethyl N-{[(4-methoxybenzyl)amino]sulfonyl}glycinate obtained in Reference Example 268 (6.21 g) in methanol (60 mL) were added sodium methoxide (about 28% methanol solution: 11.9 g) and methanol (40 mL), and the mixture was stirred at room temperature for 6 hr. 1M Hydrochloric acid (70 mL) was added to the reaction mixture at 0°C, and the reaction mixture was concentrated under reduced pressure. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30 - 60:40, v/v), and crystallized from hexane-ethyl acetate to give the title compound (3.76 g, yield 71%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:3.79 (s, 3 H), 4.02 (d, J = 7.2 Hz, 2 H), 4.68 (s, 2 H), 4.83 (br s, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H).

Reference Example 270 methyl N-{[(tert-butoxycarbonyl)amino]sulfonyl}-D-valinate

By a method similar to that in Reference Example 266, the title compound was obtained from D-valine methyl ester hydrochloride, tert-butyl alcohol and chlorosulfonyl isocyanate.
^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.91 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.49 (s, 9 H), 2.09 - 2.19 (m, 1 H), 3.75 (s, 3 H), 4.03 (dd, J = 9.3, 4.8 Hz, 1 H), 5.63 (d, J = 9.3 Hz, 1 H).

Reference Example 271 methyl N-{[(tert-butoxycarbonyl)(4-methoxybenzyl)amino]sulfonyl}-D-valinate

By a method similar to that in Reference Example 267, the

title compound was obtained from methyl N-{[(tert-butoxycarbonyl)amino]sulfonyl}-D-valinate obtained in Reference Example 270 and 4-methoxybenzyl alcohol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.82 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 1.53 (s, 9 H), 1.97 - 2.04 (m, 1 H), 3.58 (dd, J = 8.7, 4.8 Hz, 1 H), 3.62 (s, 3 H), 3.80 (s, 3 H), 4.64 (d, J = 15.3 Hz, 1 H), 4.81 (d, J = 15.3 Hz, 1 H), 5.78 (d, J = 8.7 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 9.0 Hz, 2 H).

Reference Example 272 methyl N-{[(4-methoxybenzyl)amino]sulfonyl}-D-valinate

By a method similar to that in Reference Example 268, the title compound was obtained from methyl N-{[(tert-butoxycarbonyl)(4-methoxybenzyl)amino]sulfonyl}-D-valinate obtained in Reference Example 271.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.91 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 2.06 - 2.16 (m, 1 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 3.84 (dd, J = 9.9, 4.8 Hz, 1 H), 4.08 - 4.15 (m, 2 H), 4.32 (t, J = 6.0 Hz, 1 H), 4.97 (d, J = 9.9 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.4 Hz, 2 H).

Reference Example 273 (4R)-4-isopropyl-2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

By a method similar to that in Reference Example 269, the title compound was obtained from methyl N-{[(4-methoxybenzyl)amino]sulfonyl}-D-valinate obtained in Reference Example 272.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.92 (d, J = 6.9 Hz, 3 H), 1.04 (d, J = 6.9 Hz, 3 H), 2.30 - 2.40 (m, 1 H), 3.79 (s, 3 H), 4.07 (dd, J = 6.9, 3.6 Hz, 1 H), 4.64 (d, J = 15.0 Hz, 1 H), 4.69 (d, J = 15.0 Hz, 1 H), 4.75 (d, J = 6.9 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H).

Reference Example 274 methyl 2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrole-3-carboxylate

To a solution of methyl 4-bromo-2,5-dimethyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrole-3-carboxylate (827 mg) in toluene (22 mL) were added 1-naphthaleneboronic acid (785 mg)

and potassium carbonate (1.89 g) under argon atmosphere, and the mixture was stirred at room temperature for 30 min. Tris(dibenzylideneacetone)dipalladium(0) (52 mg) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (93 mg) were added to this reaction mixture, and the mixture was stirred at 100°C for 18 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10, v/v) to give the title compound (902 mg, yield 96%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.00 (s, 9 H), 0.90 - 0.97 (m, 2 H), 1.98 (s, 3 H), 2.67 (s, 3 H), 3.23 (s, 3 H), 3.53 - 3.60 (m, 2 H), 5.09 - 5.38 (m, 2 H), 7.22 - 7.48 (m, 5 H), 7.74 - 7.85 (m, 2 H).

Reference Example 275 2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrole-3-carbaldehyde

To a solution of methyl 2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrole-3-carboxylate obtained in Reference Example 274 (1.22 g) in diethyl ether (30 mL) was added diisobutylaluminum hydride (1.5M toluene solution, 4.9 mL) with stirred at 0°C, and the mixture was stirred at room temperature for 2 hr. Methanol and water were added to this reaction mixture, the mixture was filtrated through celite®, and the filtrate was concentrated. The residue was dissolved in dichloromethane (10 mL), the solution was added to a mixture of pyridinium dichromate (1.34 g) and celite® (1.34 g) in dichloromethane (30 mL) with stirring, and the mixture was stirred at room temperature for 7 hr. The reaction mixture was filtrated through celite®, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 85:15, v/v) to give the title compound (214 mg, yield 19%) as a pale-yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.00 (s, 9 H), 0.91 - 0.98 (m, 2 H), 2.03 (s, 3 H), 2.70 (s, 3 H), 3.55 - 3.61 (m, 2 H), 5.22 - 5.31 (m, 2 H), 7.32 - 7.51 (m, 4 H), 7.65 (d, J = 8.3 Hz, 1 H), 7.80 - 7.88 (m, 2 H), 9.40 (s, 1 H).

Reference Example 276 ethyl (2E)-3-(2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-3-yl)acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrole-3-carbaldehyde obtained in Reference Example 275 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.00 (s, 9 H), 0.90 - 0.97 (m, 2 H), 1.09 (t, J = 7.0 Hz, 3 H), 1.94 (s, 3 H), 2.47 (s, 3 H), 3.52 - 3.59 (m, 2 H), 3.93 - 4.02 (m, 2 H), 5.08 (d, J = 15.9 Hz, 1 H), 5.18 - 5.30 (m, 2 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.39 - 7.61 (m, 4 H), 7.80 - 7.88 (m, 2 H).

Reference Example 277 (2E)-3-(2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-3-yl)acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-(2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-3-yl)acrylate obtained in Reference Example 276.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.00 (s, 9 H), 0.85 - 0.93 (m, 2 H), 1.92 (s, 3 H), 2.43 (s, 3 H), 3.58 (t, J = 7.8 Hz, 2 H), 4.86 (d, J = 15.9 Hz, 1 H), 5.27 - 5.38 (m, 2 H), 7.28 - 7.61 (m, 6 H), 7.91 - 8.00 (m, 2 H).

Reference Example 278 benzyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

By a method similar to that in Reference Example 102, the title compound was obtained from benzyl alcohol, chlorosulfonyl isocyanate and 2-isopropoxyethanamine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.13 (d, J = 6.4 Hz, 6 H), 3.24 (q, J = 4.9 Hz, 2 H), 3.47 - 3.60 (m, 3 H), 5.19 (s, 2 H), 5.49 (br s, 1 H), 7.32 - 7.41 (m, 5 H).

Reference Example 279 N-(2-isopropoxyethyl)sulfamide

By a method similar to that in Reference Example 109, the title compound was obtained from benzyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate obtained in Reference Example 278.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 (d, J = 6.2 Hz, 6 H), 3.31 (q, J = 5.3 Hz, 2 H), 3.53 - 3.67 (m, 3 H), 4.80 (br s, 3 H).

Reference Example 280 5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

To a mixture of 5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 236 (1.52 g), cyclopropylboronic acid (818 mg), potasium carbonate (3.94 g) and toluene (50 mL) was stirred at room temperature for 30 min under argon atmosphere. Tris(dibenzylideneacetone)dipalladium(0) (109 mg) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (195 mg) was added to this reaction mixture at room temperature, and the reaction mixture was stirred at 100°C for 18 hr under Argon. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (1.31 g, yield 99%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.71 - 0.78 (m, 2 H), 1.00 - 1.08 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.68 (d, J = 3.8 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 7.65 (d, J = 2.3 Hz, 1 H), 8.21 (d, J = 1.9 Hz, 1 H), 9.57 (s, 1 H).

Reference Example 281 (E)-2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Reference Example 178, the title compound was obtained from 5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 280 and tert-butyl {[(diphenylphosphoryl)methyl]sulfonyl}carbamate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.72 - 0.79 (m, 2 H), 0.95 - 1.03 (m, 2 H), 2.02 - 2.13 (m, 1 H), 2.36 (s, 3 H), 3.47 (s, 3 H), 6.12 (d, J = 15.6 Hz, 1 H), 6.76 - 6.83 (m, 2 H), 6.87 (s, 2 H), 7.62 (d, J = 3.8 Hz, 1 H), 7.77 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H).

Reference Example 282 2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Reference Example 179, the title compound was obtained from (E)-2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 281.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.71 - 0.78 (m, 2 H), 0.95 - 1.02 (m, 2 H), 2.01 - 2.12 (m, 1 H), 2.20 (s, 3 H), 2.56 (dd, J = 7.5, 3.2 Hz, 2 H), 2.85 - 2.94 (m, 2 H), 3.39 (s, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 6.76 (s, 2 H), 7.62 (d, J = 3.6 Hz, 1 H), 7.73 (d, J = 2.1 Hz, 1 H), 8.13 (d, J = 2.1 Hz, 1 H).

Reference Example 283 5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

By a method similar to that in Reference Example 1, the title compound was obtained from 5-fluoro-1H-pyrrolo[2,3-b]pyridine and 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.55 (s, 3 H), 3.68 (s, 3 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.38 (d, J = 3.8 Hz, 1 H), 7.72 (dd, J = 8.5, 2.6 Hz, 1 H), 8.23 (dd, J = 2.4, 1.7 Hz, 1 H), 9.60 (s, 1 H).

Reference Example 284 ethyl (2E)-3-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate

By a method similar to that in Reference Example 12, the title compound was obtained from 5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 283 and ethyl (diethoxyphosphoryl)acetate.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.24 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.58 (s, 3 H), 4.14 (q, J = 7.0 Hz, 2 H), 5.70 (d, J = 16.2 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.25 - 7.31 (m, 2 H), 7.72 (dd, J = 8.5, 2.6 Hz, 1 H), 8.22 (dd, J = 2.5, 1.6 Hz, 1 H).

Reference Example 285 (2E)-3-[5-(5-fluoro-1H-pyrrolo[2,3-

b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

By a method similar to that in Reference Example 13, the title compound was obtained from ethyl (2E)-3-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylate obtained in Reference Example 284.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.37 (s, 3 H), 3.50 (s, 3 H), 5.47 (d, J = 16.2 Hz, 1 H), 6.90 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.2 Hz, 1 H), 7.84 (d, J = 3.6 Hz, 1 H), 8.09 (dd, J = 9.1, 2.7 Hz, 1 H), 8.29 (dd, J = 2.5, 1.6 Hz, 1 H), 12.20 (br s, 1 H).

Reference Example 286 benzyl [(pentylamino)sulfonyl]carbamate

To a solution of benzyl alcohol (3.06 g) in dichloromethane (150 mL) was added chlorosulfonyl isocyanate (2.55 mL) with stirring at 0°C, and the mixture was stirred at 0°C for 30 min. Pyridine (8.0 mL) was added to this reaction mixture, and the mixture was stirred at 0°C for 1 hr. 1-Pentylamine (16.0 mL) was added, and the mixture was stirred overnight at room temperature. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was diluted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, a saturated aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (8.18 g, yield 96%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.92 (m, 3 H), 1.25 - 1.34 (m, 4 H), 1.46 - 1.63 (m, 2 H), 2.98 - 3.07 (m, 2 H), 5.07 (s, 1 H), 5.19 (s, 2 H), 7.28 - 7.42 (m, 5 H).

Reference Example 287 N-pentylsulfamide

Benzyl [(pentylamino)sulfonyl]carbamate obtained in Reference Example 286 (5.83 g) was dissolved in a mixed solvent of tetrahydrofuran (50 mL) and ethanol (50 mL), 10% palladium carbon (3.11 g) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 4 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was crystallized from diisopropyl

ether-ethyl acetate to give the title compound (3.15 g, yield 98%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.95 (m, 3 H), 1.30 - 1.40 (m, 4 H), 1.52 - 1.63 (m, 2 H), 3.10 - 3.16 (m, 2 H), 4.51 (br s, 3 H).

Reference Example 288 3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid

By a method similar to that in Reference Example 65, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 206.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.28 (s, 3 H), 2.29 - 2.36 (m, 2 H), 2.45 (s, 3 H), 2.53 - 2.72 (m, 2 H), 3.45 (s, 3 H), 6.63 (d, J = 3.6 Hz, 1 H), 7.15 (d, J = 3.6 Hz, 1 H), 7.82 (d, J = 1.1 Hz, 1 H), 8.14 (d, J = 2.1 Hz, 1 H).

Reference Example 289 3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propan-1-ol

To a solution of 3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 288 (410 mg) and N,N-dimethylformamide (0.1 mL) in tetrahydrofuran (13 mL) was added dropwise oxalyl chloride (261.8 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, tetrahydrofuran (13 mL) and methanol (13 mL) were added to the residue. The mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated. Tetrahydrofuran (13 mL) was added to the residue, which was cooled at 0°C in an ice bath, was added diisobutylaluminum hydride (1.5M toluene solution, 13 mL) by small portions with stirring. The reaction mixture was stirred at room temperature for 2 hr, and was cooled again at 0°C in an ice bath. Methanol and water were added to the reaction mixture with stirring, the mixture was filtrated through celite®, and

the filtrate was concentrated. The residue was subjected to silica gel column chromatography (ethyl acetate-methanol 95:5, v/v) to give the title compound (291 mg, yield 74%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.54 - 1.72 (m, 2 H), 2.29 (s, 3 H), 2.33 - 2.40 (m, 2 H), 2.44 (s, 3 H), 3.42 - 3.53 (m, 5 H), 6.61 (d, J = 3.6 Hz, 1 H), 7.14 (d, J = 3.6 Hz, 1 H), 7.79 (d, J = 1.3 Hz, 1 H), 8.16 (d, J = 2.1 Hz, 1 H).

Example 1 (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

A mixture of (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 2 (400 mg), 2-methyl-6-nitrobenzoic anhydride (586 mg), pentane-1-sulfonamide (240 mg), triethylamine (465 mg), 4-dimethylaminopyridine (175 mg) and acetonitrile (8 mL) was stirred at room temperature for 24 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v) to give the title compound (579 mg, yield 98%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.1 Hz, 3 H), 1.25 - 1.40 (m, 4 H), 1.72 - 1.76 (m, 2 H), 2.44 (s, 3 H), 3.28 - 3.34 (m, 2 H), 3.54 (s, 3 H), 5.23 (d, J = 15.6 Hz, 1 H), 6.83 (d, J = 3.2 Hz, 1 H), 6.94 - 7.01 (m, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.23 - 7.27 (m, 2 H), 7.40 (s, 1 H), 7.48 (d, J = 15.6 Hz, 1 H), 7.73 - 7.75 (m, 1 H).

Example 2 3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)propanamide

(2E)-3-[5-(1H-Indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 1 (233 mg) was dissolved in a mixed solvent of tetrahydrofuran (10 mL) and

methanol (10 mL), 10% palladium carbon (25 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 6 hr. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 55:45, v/v), and crystallized from hexane-ethyl acetate to give the title compound (174 mg, yield 74%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.92 (m, 3 H), 1.25 - 1.40 (m, 4 H), 1.65 - 1.75 (m, 2 H), 2.01 - 2.15 (m, 2 H), 2.30 (s, 3 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.23 - 3.30 (m, 2 H), 3.47 (s, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.96 - 7.02 (m, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.20 - 7.27 (m, 2 H), 7.39 (s, 1 H), 7.70 - 7.73 (m, 1 H).

Example 3 (2E)-3-[5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 5 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.22 - 1.43 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.46 (s, 3 H), 3.31 - 3.36 (m, 2 H), 3.57 (s, 3 H), 5.45 (d, J = 15.9 Hz, 1 H), 7.14 (d, J = 8.3 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.44 - 7.51 (m, 2 H), 7.64 (s, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H).

Example 4 (2E)-3-[5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(2H-indazol-2-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 6 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.0 Hz, 3 H), 1.23 - 1.42 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 - 3.37 (m, 2 H), 3.69 (s, 3 H), 5.70 (d, J = 15.9 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.42 - 7.45 (m, 1 H), 7.49 (d, J = 15.9 Hz, 1 H), 7.73 -

7.78 (m, 2 H), 7.90 (s, 1 H), 8.13 (s, 1 H).

Example 5 (2E)-3-[5-(1H-benzimidazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(1H-benzimidazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 8 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.81 (t, J = 7.1 Hz, 3 H), 1.18 - 1.36 (m, 4 H), 1.58 - 1.67 (m, 2 H), 2.49 (s, 3 H), 3.30 - 3.36 (m, 2 H), 3.55 (s, 3 H), 5.67 (d, J = 16.0 Hz, 1 H), 7.12 (d, J = 7.5 Hz, 1 H), 7.26 - 7.40 (m, 2 H), 7.50 (d, J = 8.1 Hz, 1 H), 7.65 (d, J = 16.0 Hz, 1 H), 7.76 (s, 1 H), 10.30 (s, 1 H).

Example 6 (2E)-3-[5-(1-benzothien-3-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(1-benzothien-3-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 10 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.90 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.68 - 1.79 (m, 2 H), 2.47 (s, 3 H), 3.31 - 3.37 (m, 2 H), 3.64 (s, 3 H), 5.75 (d, J = 15.8 Hz, 1 H), 7.35 - 7.50 (m, 3 H), 7.50 - 7.58 (m, 2 H), 7.68 (s, 1 H), 7.96 - 7.99 (m, 1 H).

Example 7 potassium {(2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

To a solution of (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 1 (445 mg) in methanol (4 mL) was added an aqueous solution (1 mL) of potassium hydrogencarbonate (108 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether-methanol to give the title compound (483 mg, yield 99%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.82 (m, 3 H), 1.15 - 1.23 (m, 4 H), 1.37 - 1.47 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.41 (s, 3 H), 5.57 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz,

1 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.95 - 6.99 (m, 1 H), 7.14 - 7.22 (m, 2 H), 7.51 (d, J = 3.4 Hz, 1 H), 7.68 - 7.71 (m, 1 H).

Example 8 potassium {(2E)-3-[5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 3.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.76 - 0.84 (m, 3 H), 1.15 - 1.24 (m, 4 H), 1.35 - 1.47 (m, 2 H), 2.36 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.44 (s, 3 H), 5.58 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 7.22 (dd, J = 8.5, 0.9 Hz, 1 H), 7.29 - 7.35 (m, 1 H), 7.45 - 7.50 (m, 1 H), 7.95 (d, J = 8.1 Hz, 1 H), 8.55 (d, J = 0.9 Hz, 1 H).

Example 9 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

A mixture of (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 (473 mg), 2-methyl-6-nitrobenzoic anhydride (689 mg), pentane-1-sulfonamide (269 mg), triethylamine (525 mg), 4-dimethylaminopyridine (206 mg) and acetonitrile (8 mL) was stirred at room temperature for 72 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (590 mg, yield 85%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.92 (m, 3 H), 1.23 - 1.44 (m, 4 H), 1.71 - 1.83 (m, 2 H), 2.29 (s, 3 H), 3.37 - 3.43 (m, 2 H), 3.56 (s, 3 H), 5.57 (d, J = 15.7 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.34 (d, J = 15.7 Hz, 1 H), 8.05 (dd, J = 7.8, 1.5 Hz, 1 H), 8.32 (dd, J = 4.7, 1.5 Hz, 1 H), 8.88 (s, 1 H).

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Recrystallization of the crude crystals obtained under the same conditions as in Example 9 from hexane-diisopropyl ether-ethanol gave colorless crystals. melting point 149-163°C

Recrystallization of the crude crystals obtained under the same conditions as in Example 9 from H_2O-95%ethanol(ethanol-H_2O 95:5, v/v) gave colorless crystals. melting point 194-197°C

Example 10 (2E)-3-[1,3-dimethyl-5-(1-naphthyl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1-naphthyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 15 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.2 Hz, 3 H), 1.23 - 1.34 (m, 4 H), 1.67 - 1.75 (m, 2 H), 2.49 (s, 3 H), 3.26 - 3.31 (m, 2 H), 3.51 (s, 3 H), 5.60 (d, J = 15.5 Hz, 1 H), 7.31 - 7.65 (m, 7 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H).

Example 11 potassium {(2E)-3-[1,3-dimethyl-5-(1-naphthyl)-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1-naphthyl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 10.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.75 - 0.82 (m, 3 H), 1.12 - 1.23 (m, 4 H), 1.35 - 1.48 (m, 2 H), 2.37 (s, 3 H), 2.78 - 2.85 (m, 2 H), 3.40 (s, 3 H), 5.70 (d, J = 16.1 Hz, 1 H), 6.77 (d, J = 16.1 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.48 - 7.63 (m, 3 H), 7.64 - 7.73 (m, 1 H), 8.07 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H).

Example 12 (2E)-3-[1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 17 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.2 Hz, 3 H), 1.15 - 1.36

(m, 4 H), 1.52 - 1.62 (m, 2 H), 2.40 (s, 3 H), 2.56 (s, 3 H), 3.28 - 3.33 (m, 2 H), 3.46 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.89 (d, J = 3.4 Hz, 1 H), 6.97 - 7.15 (m, 3 H), 7.55 (d, J = 3.4 Hz, 1 H), 11.59 (s, 1 H).

Example 13 potassium {(2E)-3-[1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(4-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 12.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.82 (m, 3 H), 1.15 - 1.25 (m, 4 H), 1.38 - 1.52 (m, 2 H), 2.33 (s, 3 H), 2.55 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.39 (s, 3 H), 5.58 (d, J = 16.2 Hz, 1 H), 6.74 - 6.85 (m, 3 H), 6.97 (d, J = 7.2 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 7.48 (d, J = 3.2 Hz, 1 H).

Example 14 (2E)-3-[5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 19 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.92 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.34 (m, 2 H), 3.52 (s, 3 H), 5.35 (d, J = 15.5 Hz, 1 H), 6.89 (d, J = 8.0 Hz, 1 H), 6.95 (d, J = 3.4 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.16 - 7.21 (m, 1 H), 7.25 - 7.29 (m, 1 H), 7.46 (d, J = 15.5 Hz, 1 H), 7.74 (s, 1 H).

Example 15 potassium {(2E)-3-[5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(4-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 14.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.76 - 0.84 (m, 3 H), 1.16 - 1.25 (m, 4 H), 1.38 - 1.47 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H),

3.42 (s, 3 H), 5.54 (d, J = 16.2 Hz, 1 H), 6.74 (d, J = 16.2 Hz, 1 H), 6.85 (dd, J = 3.4, 0.9 Hz, 1 H), 6.99 (d, J = 7.9 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.24 - 7.29 (m, 1 H), 7.68 (d, J = 3.4 Hz, 1 H).

Example 16 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.84 (m, 3 H), 1.18 - 1.35 (m, 4 H), 1.51 - 1.63 (m, 2 H), 2.39 (s, 3 H), 3.27 - 3.37 (m, 2 H), 3.47 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.86 (d, J = 3.4 Hz, 1 H), 7.00 - 7.11 (m, 3 H), 7.49 - 7.54 (m, 1 H), 7.66 (d, J = 3.4 Hz, 1 H), 11.60 (s, 1 H).

Example 17 potassium {(2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 16.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.83 (m, 3 H), 1.17 - 1.25 (m, 4 H), 1.37 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.41 (s, 3 H), 5.56 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.95 - 7.07 (m, 2 H), 7.48 (dd, J = 9.6, 1.9 Hz, 1 H), 7.61 (d, J = 3.4 Hz, 1 H).

Example 18 (2E)-3-[5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 23 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.89 (m, 3 H), 1.21 - 1.38 (m, 4 H), 1.65 - 1.78 (m, 2 H), 2.42 (s, 3 H), 3.30 - 3.35 (m, 2 H), 3.53 (s, 3 H), 3.88 (s, 3 H), 5.24 (d, J = 15.7 Hz, 1 H), 6.75

(d, J = 3.4 Hz, 1 H), 6.84 - 6.93 (m, 2 H), 7.04 (d, J = 3.4 Hz, 1 H), 7.17 (s, 1 H), 7.48 (d, J = 15.7 Hz, 1 H), 7.68 (s, 1 H).

Example 19 potassium {(2E)-3-[5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(5-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 18.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.83 (m, 3 H), 1.18 - 1.22 (m, 4 H), 1.40 - 1.48 (m, 2 H), 2.33 (s, 3 H), 2.84 - 2.89 (m, 2 H), 3.41 (s, 3 H), 3.79 (s, 3 H), 5.58 (d, J = 16.3 Hz, 1 H), 6.69 - 6.89 (m, 4 H), 7.20 (d, J = 2.3 Hz, 1 H), 7.45 (d, J = 3.4 Hz, 1 H).

Example 20 (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 25 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.91 (m, 3 H), 1.24 - 1.39 (m, 4 H), 1.68 - 1.78 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.34 (m, 2 H), 3.53 (s, 3 H), 5.33 (d, J = 15.9 Hz, 1 H), 6.81 (d, J = 3.0 Hz, 1 H), 6.97 (d, J = 1.7 Hz, 1 H), 7.06 (d, J = 3.0 Hz, 1 H), 7.23 (dd, J = 8.4, 1.7 Hz, 1 H), 7.45 (d, J = 15.9 Hz, 1 H), 7.47 (s, 1 H), 7.65 (d, J = 8.4 Hz, 1 H).

Example 21 (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 28 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.89 (m, 3 H), 1.27 - 1.38 (m, 4 H), 1.67 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 - 3.35 (m, 2 H), 3.47 (s, 3 H), 5.01 (s, 2 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.47 (d, J = 2.3 Hz, 1 H), 6.72 - 6.75 (m, 1 H), 6.94 (d, J = 3.2 Hz,

1 H), 6.99 (dd, J = 8.7, 2.3 Hz, 1 H), 7.29 - 7.51 (m, 7 H), 7.60 (d, J = 8.7 Hz, 1 H).

Example 22 (2E)-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

To a solution of (2E)-3-{5-[6-(benzyloxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}-N-(pentylsulfonyl)acrylamide obtained in Example 21 (300 mg) in dichloromethane (4 mL) was added dropwise boron tribromide (1M dichloromethane solution, 1.2 mL) with stirring at -78°C, and the mixture was stirred at -78°C for 20 min. The reaction mixture was quenched with methanol (2 mL), and concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (233 mg, yield 93%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.24 - 1.43 (m, 4 H), 1.70 - 1.81 (m, 2 H), 2.35 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.51 (s, 3 H), 5.36 - 5.43 (m, 1 H), 6.15 - 6.31 (m, 2 H), 6.73 (d, J = 3.6 Hz, 1 H), 6.83 (dd, J = 8.5, 2.1 Hz, 1 H), 6.92 - 6.93 (m, 1 H), 7.43 (d, J = 15.5 Hz, 1 H), 7.55 (d, J = 8.5 Hz, 1 H), 8.02 (s, 1 H).

Example 23 (2E)-3-[1,3-dimethyl-5-(2-naphthyl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(2-naphthyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 30 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.0 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.69 - 1.83 (m, 2 H), 2.45 (s, 3 H), 3.32 - 3.41 (m, 2 H), 3.72 (s, 3 H), 5.87 (d, J = 15.5 Hz, 1 H), 7.37 (dd, J = 8.3, 1.9 Hz, 1 H), 7.56 - 7.67 (m, 4 H), 7.79 (s, 1 H), 7.87 - 7.96 (m, 2 H), 8.00 (d, J = 8.7 Hz, 1 H).

Example 24 (2E)-3-[1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(quinolin-8-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 33 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.1 Hz, 3 H), 1.23 - 1.44 (m, 4 H), 1.70 - 1.85 (m, 2 H), 2.28 (s, 3 H), 3.43 - 3.49 (m, 2 H), 3.53 (s, 3 H), 5.72 (d, J = 15.6 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 7.52 (dd, J = 8.3, 4.1 Hz, 1 H), 7.62 - 7.76 (m, 2 H), 8.03 (dd, J = 7.6, 2.0 Hz, 1 H), 8.31 (dd, J = 8.3, 1.6 Hz, 1 H), 8.78 - 8.87 (m, 1 H), 8.92 (dd, J = 4.1, 1.6 Hz, 1 H).

Example 25 (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 36 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.91 (m, 3 H), 1.27 - 1.40 (m, 4 H), 1.69 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.32 - 3.39 (m, 2 H), 3.53 (s, 3 H), 5.36 (d, J = 15.9 Hz, 1 H), 6.73 - 6.81 (m, 2 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.38 - 7.58 (m, 3 H).

Example 26 potassium {(2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(5,6-difluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 25.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 - 0.83 (m, 3 H), 1.14 - 1.25 (m, 4 H), 1.38 - 1.50 (m, 2 H), 2.33 (s, 3 H), 2.82 - 2.90 (m, 2 H), 3.43 (s, 3 H), 5.52 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 6.82 (d, J = 3.0 Hz, 1 H), 7.09 (dd, J = 10.8, 7.0 Hz, 1 H), 7.61 (d, J = 3.0 Hz, 1 H), 7.72 (dd, J = 10.8, 8.0 Hz, 1 H).

Example 27 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

A mixture of 4-dimethylaminopyridine (643 mg), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (875 mg) and acetonitrile (10 mL) was stirred at room temperature for 10 min. Pentane-1-sulfonamide (541 mg) and (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 (1.11 g) were successively added to the reaction mixture, and the mixture was stirred at room temperature for 15 hr. 1M Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50 - 40:60, v/v) to give the title compound (927 mg, yield 59%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.93 (m, 3 H), 1.27 - 1.41 (m, 4 H), 1.67 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.27 - 3.36 (m, 2 H), 3.53 (s, 3 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.78 (dd, J = 3.3, 0.8 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz, 1 H), 7.39 (br s, 1 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H).

Example 28 sodium {(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

To a solution of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 27 (173 mg) in methanol (1 mL) was added an aqueous solution (0.5 mL) of sodium hydrogencarbonate (35 mg), and the mixture was stirred at room temperature for 6 hr. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from diethyl ether-methanol to give the title compound (174 mg, yield 95%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.83 (m, 3 H), 1.15 - 1.23 (m, 4 H), 1.39 - 1.49 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H),

3.41 (s, 3 H), 5.56 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz, 1 H), 6.81 (dd, J = 3.2, 0.8 Hz, 1 H), 7.01 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.62 (d, J = 3.2 Hz, 1 H), 7.77 (d, J = 1.9 Hz, 1 H).

Example 29 (2E)-3-[5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 40 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.87 (t, J = 7.2 Hz, 3 H), 1.27 - 1.37 (m, 4 H), 1.68 - 1.75 (m, 2 H), 2.44 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.58 (s, 3 H), 5.64 (d, J = 15.6 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 7.36 - 7.45 (m, 2 H), 7.50 - 7.56 (m, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 8.19 (br s, 1 H).

Example 30 (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 42 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.66 - 0.90 (m, 3 H), 1.17 - 1.38 (m, 4 H), 1.42 - 1.68 (m, 2 H), 2.41 (s, 3 H), 3.25 - 3.30 (m, 2 H), 3.49 (s, 3 H), 5.82 - 6.15 (m, 1 H), 6.93 - 7.14 (m, 2 H), 7.29 - 7.40 (m, 1 H), 7.52 (dd, J = 8.7, 1.5 Hz, 1 H), 7.85 (d, J = 3.4 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 11.58 (s, 1 H).

Example 31 potassium ((2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}prop-2-enoyl)(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}-N-(pentylsulfonyl)acrylamide obtained in Example 30.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.61 - 0.95 (m, 3 H), 1.19 - 1.29 (m, 4 H), 1.32 - 1.51 (m, 2 H), 2.36 (s, 3 H), 2.69 - 2.98 (m, 2 H),

3.22 - 3.33 (m, 2 H), 3.43 (s, 1 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 6.98 (d, J = 3.4 Hz, 1 H), 7.28 (s, 1 H), 7.49 (d, J = 8.3 Hz, 1 H), 7.81 (d, J = 3.0 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H).

Example 32 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)propanamide

By a method similar to that in Example 1, the title compound was obtained from 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 45 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 - 0.95 (m, 3 H), 1.32 - 1.45 (m, 4 H), 1.50 - 1.62 (m, 1 H), 1.64 - 1.80 (m, 1 H), 1.99 - 2.13 (m, 1 H), 2.26 (s, 3 H), 2.31 - 2.38 (m, 1 H), 2.54 - 2.66 (m, 1 H), 2.86 - 3.00 (m, 1 H), 3.03 - 3.16 (m, 1 H), 3.23 - 3.37 (m, 4 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 3.8 Hz, 1 H), 7.29 (dd, J = 7.9, 4.9 Hz, 1 H), 8.11 (dd, J = 7.9, 1.4 Hz, 1 H), 8.43 (dd, J = 4.9, 1.4 Hz, 1 H), 12.12 (s, 1 H).

Example 33 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

A mixture of (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 (300 mg), 2-methyl-6-nitrobenzoic anhydride (440 mg), 4-methylbenzenesulfonamide (184 mg), triethylamine (329 mg), 4-dimethylaminopyridine (138 mg) and acetonitrile (8 mL) was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from diisopropyl ether-methanol to give the title compound (420 mg, yield 91%) as colorless crystals. melting point 236.9-238.3°C.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.35 (s, 3 H), 2.35 (s, 3 H), 3.47 (s, 3 H), 6.04 (d, J = 16.1 Hz, 1 H), 6.86 (d, J = 3.4 Hz, 1 H),

6.93 (d, J = 16.1 Hz, 1 H), 7.27 (dd, J = 8.0, 4.6 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.67 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 2 H), 8.15 (dd, J = 8.0, 1.5 Hz, 1 H), 8.25 (dd, J = 4.6, 1.5 Hz, 1 H), 12.01 (s, 1 H).

Example 34 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-2-methyl-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-2-methylacrylic acid obtained in Reference Example 48 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.28 - 1.45 (m, 4 H), 1.75 - 1.84 (m, 2 H), 2.30 (s, 3 H), 3.40 - 3.50 (m, 2 H), 3.67 (s, 3 H), 6.69 (d, J = 3.8 Hz, 1 H), 7.09 (d, J = 3.8 Hz, 1 H), 7.16 - 7.23 (m, 2 H), 7.77 (s, 1 H), 8.00 (dd, J = 8.0, 1.5 Hz, 1 H), 8.37 (dd, J = 4.5, 1.5 Hz, 1 H).

Example 35 (2E)-2-methyl-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-2-methyl-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 53 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.1 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.68 - 1.83 (m, 2 H), 2.12 (s, 3 H), 3.39 - 3.46 (m, 2 H), 3.66 (s, 3 H), 6.74 - 6.76 (m, 1 H), 6.81 (s, 1 H), 7.16 - 7.23 (m, 2 H), 7.89 (s, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 8.05 - 8.18 (m, 1 H), 8.28 - 8.34 (m, 1 H).

Example 36 (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 57 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.92 (m, 3 H), 1.28 - 1.44 (m, 4 H), 1.69 - 1.84 (m, 2 H), 2.37 (s, 3 H), 3.16 - 3.28 (m, 2 H), 3.29 - 3.40 (m, 2 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 3.80 - 3.89

(m, 2 H), 5.73 (d, J = 2.3 Hz, 1 H), 5.84 (d, J = 15.5 Hz, 1 H), 6.33 (dd, J = 8.0, 2.3 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 15.5 Hz, 1 H), 7.63 - 7.71 (m, 1 H).

Example 37 potassium {(2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(6-methoxy-2,3-dihydro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 36.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.80 - 0.87 (m, 3 H), 1.16 - 1.30 (m, 4 H), 1.45 - 1.55 (m, 2 H), 2.25 (s, 3 H), 2.85 - 2.95 (m, 2 H), 3.10 - 3.17 (m, 2 H), 3.55 (s, 3 H), 3.59 (s, 3 H), 3.70 - 3.80 (m, 1 H), 3.81 - 3.92 (m, 1 H), 5.58 (d, J = 2.3 Hz, 1 H), 5.86 (d, J = 16.2 Hz, 1 H), 6.25 (dd, J = 8.0, 2.3 Hz, 1 H), 6.94 (d, J = 16.2 Hz, 1 H), 7.05 (d, J = 8.0 Hz, 1 H).

Example 38 (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 60 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.91 (m, 3 H), 1.26 - 1.40 (m, 4 H), 1.67 - 1.82 (m, 2 H), 2.44 (s, 3 H), 3.28 - 3.37 (m, 2 H), 3.55 (s, 3 H), 3.77 (s, 3 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.40 (d, J = 2.3 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.33 (s, 1 H), 7.50 (d, J = 15.6 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H).

Example 39 potassium {(2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 38.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.76 - 0.86 (m, 3 H), 1.15 - 1.26 (m,

4 H), 1.40 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.79 - 2.91 (m, 2 H), 3.42 (s, 3 H), 3.69 (s, 3 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.44 (d, J = 2.1 Hz, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.74 - 6.86 (m, 2 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Example 40 3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)propanamide

By a method similar to that in Example 1, the title compound was obtained from 3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 46 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 - 0.94 (m, 3 H), 1.32 - 1.47 (m, 4 H), 1.49 - 1.59 (m, 1 H), 1.60 - 1.75 (m, 1 H), 2.17 (s, 3 H), 2.17 - 2.28 (m, 1 H), 2.37 - 2.47 (m, 1 H), 2.59 - 2.70 (m, 1 H), 2.82 - 3.03 (m, 2 H), 3.17 - 3.35 (m, 3 H), 3.55 (s, 3 H), 3.76 - 3.98 (m, 2 H), 6.69 (dd, J = 7.2, 5.5 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.94 (dd, J = 5.5, 1.5 Hz, 1 H), 12.27 (s, 1 H).

Example 41 N-[({2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethyl}amino)carbonyl]pentane-1-sulfonamide

3-[1,3-Dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 45 (302 mg), diphenyl azidophosphate (438 mg) and triethylamine (165 mg) were dissolved in N,N-dimethylformamide (5 mL), and the solution was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was dissolved in toluene (8 mL). The solution was heated under reflux for 2 hr, 1,8-diazabicyclo[5.4.0]undec-7-ene (330 mg) and pentane-1-sulfonamide (165 mg) were added to the reaction mixture, and the mixture was further heated under reflux for 4 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel chromatography (ethyl acetate-methanol 95:5, v/v), and crystallized from hexane-ethanol to give the title compound (196 mg, yield 42%) as colorless

crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.1 Hz, 3 H), 1.28 - 1.48 (m, 4 H), 1.65 - 1.80 (m, 2 H), 2.31 (s, 3 H), 2.32 - 2.43 (m, 1 H), 2.58 - 2.72 (m, 1 H), 3.09 - 3.20 (m, 1 H), 3.23 - 3.30 (m, 2 H), 3.33 - 3.48 (m, 4 H), 5.92 (s, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.19 (d, J = 3.8 Hz, 1 H), 7.27 (dd, J = 7.9, 4.7 Hz, 1 H), 7.79 (s, 1 H), 8.07 (dd, J = 7.9, 1.5 Hz, 1 H), 8.40 (dd, J = 4.7, 1.5 Hz, 1 H).

Example 42 N-[({2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethyl}amino)carbonyl]butane-1-sulfonamide

By a method similar to that in Example 41, the title compound was obtained from 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 45 and butane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.3 Hz, 3 H), 1.37 - 1.50 (m, 2 H), 1.65 - 1.80 (m, 2 H), 2.31 (s, 3 H), 2.32 - 2.40 (m, 1 H), 2.61 - 2.71 (m, 1 H), 3.07 - 3.22 (m, 1 H), 3.22 - 3.29 (m, 2 H), 3.35 - 3.47 (m, 4 H), 5.89 (s, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 7.26 (dd, J = 7.8, 4.8 Hz, 1 H), 7.91 (s, 1 H), 8.07 (dd, J = 7.8, 1.5 Hz, 1 H), 8.40 (dd, J = 4.8, 1.5 Hz, 1 H).

Example 43 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(phenylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and benzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.37 (s, 3 H), 3.47 (s, 3 H), 5.39 (d, J = 15.9 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 1.9 Hz, 1 H), 7.36 (d, J = 15.5 Hz, 1 H), 7.44 - 7.66 (m, 4 H), 7.90 - 7.98 (m, 2 H), 8.21 (br s, 1 H).

Example 44 potassium {(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(phenylsulfonyl)azanide

By a method similar to that in Example 7, the title

compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(phenylsulfonyl)acrylamide obtained in Example 43.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.32 (s, 3 H), 3.39 (s, 3 H), 5.52 (d, J = 15.9 Hz, 1 H), 6.70 (d, J = 16.3 Hz, 1 H), 6.80 (d, J = 3.4 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.34 (m, 3 H), 7.59 (d, J = 3.4 Hz, 1 H), 7.64 - 7.70 (m, 2 H), 7.75 (d, J = 1.9 Hz, 1 H).

Example 45 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.36 (s, 3 H), 2.41 (s, 3 H), 3.47 (s, 3 H), 5.40 (d, J = 15.6 Hz, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.84 (d, J = 8.9 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.16 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.30 (m, 2 H), 7.35 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 1.9 Hz, 1 H), 7.82 (d, J = 8.3 Hz, 2 H), 8.34 (br s, 1 H).

Example 46 potassium {(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}[(4-methylphenyl)sulfonyl]azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide obtained in Example 45.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.27 (s, 3 H), 2.31 (s, 3 H), 3.40 (s, 3 H), 5.51 (d, J = 16.3 Hz, 1 H), 6.68 (d, J = 16.3 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.50 - 7.61 (m, 3 H), 7.75 (d, J = 1.9 Hz, 1 H).

Example 47 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-chlorophenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title

compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 2-chlorobenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.51 (s, 3 H), 5.40 (d, J = 15.8 Hz, 1H), 6.75 (dd, J = 3.2, 0.8 Hz, 1 H), 6.86 (d, J = 8.9 Hz, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.30 - 7.57 (m, 4 H), 7.68 (d, J = 1.7 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H).

Example 48 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(3-chlorophenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 3-chlorobenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.36 (s, 3 H), 3.47 (s, 3 H), 5.36 (d, J = 15.8 Hz, 1 H), 6.73 (d, J = 3.2 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 2.1 Hz, 1 H), 7.37 (d, J = 15.6 Hz, 1 H), 7.43 (d, J = 7.9 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 7.63 (d, J = 1.9 Hz, 1 H), 7.82 - 7.88 (m, 1 H), 7.91 - 7.96 (m, 1 H).

Example 49 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-chlorophenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-chlorobenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.37 (s, 3 H), 3.48 (s, 3 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.71 - 6.75 (m, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 7.43 - 7.49 (m, 2 H), 7.64 (d, J = 1.9 Hz, 1 H), 7.86 - 7.93 (m, 2 H), 8.19 (br s, 1 H).

Example 50 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2,4-dichlorophenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-

1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 2,4-dichlorobenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.37 (s, 3 H), 3.48 (s, 3 H), 6.71 (s, 1 H), 6.87 (d, J = 8.9 Hz, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.14 - 7.45 (m, 5 H), 7.64 (d, J = 1.1 Hz, 1 H), 7.91 - 8.06 (m, 1 H).

Example 51 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[3-(trifluoromethyl)phenyl]sulfonyl}acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 3-(trifluoromethyl)benzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.48 (s, 3 H), 5.31 (d, J = 15.6 Hz, 1 H), 6.74 (dd, J = 3.3, 0.8 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.8, 2.0 Hz, 1 H), 7.38 (d, J = 15.6 Hz, 1 H), 7.62 - 7.70 (m, 2 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.18 - 8.24 (m, 2 H).

Example 52 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[4-(trifluoromethyl)phenyl]sulfonyl}acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-(trifluoromethyl)benzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.37 (s, 3 H), 3.48 (s, 3 H), 5.29 (d, J = 15.8 Hz, 1 H), 6.74 (dd, J = 3.2, 0.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 2.1 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 8.09 (d, J = 8.3 Hz, 2 H).

Example 53 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-methoxybenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H),

6.86 (d, J = 8.9 Hz, 1 H), 6.90 - 6.96 (m, 2 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.36 (d, J = 15.6 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 7.84 - 7.90 (m, 2 H).

Example 54 (2E)-N-[(4-butylphenyl)sulfonyl]-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-butylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.95 (m, 3 H), 1.24 - 1.43 (m, 2 H), 1.53 - 1.66 (m, 2 H), 2.37 (s, 3 H), 2.61 - 2.70 (m, 2 H), 3.48 (s, 3 H), 5.38 (d, J = 15.6 Hz, 1 H), 6.73 (dd, J = 3.2, 0.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.2 Hz, 1 H), 7.17 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.31 (m, 2 H), 7.36 (d, J = 15.6 Hz, 1 H), 7.64 (d, J = 1.5 Hz, 1 H), 7.80 - 7.88 (m, 2 H).

Example 55 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(2-furylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and furan-2-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.41 (s, 3 H), 3.50 (s, 3 H), 5.50 (d, J = 15.8 Hz, 1 H), 6.48 (dd, J = 3.5, 1.8 Hz, 1 H), 6.75 - 6.79 (m, 1 H), 6.88 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.40 (d, J = 15.6 Hz, 1 H), 7.51 (d, J = 0.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Example 56 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(2-thienylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and thiophene-2-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.39 (s, 3 H), 3.48 (s, 3 H), 5.41 (d, J

= 15.6 Hz, 1 H), 6.73 - 6.76 (m, 1 H), 6.87 (d, J = 8.7 Hz, 1 H), 7.02 - 7.09 (m, 2 H), 7.18 (dd, J = 8.8, 2.0 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.62 (dd, J = 5.1, 1.3 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H), 7.75 (dd, J = 3.8, 1.3 Hz, 1 H).

Example 57 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(2,3-dihydro-1-benzofuran-5-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 2,3-dihydro-1-benzofuran-5-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.24 (t, J = 8.8 Hz, 2 H), 3.49 (s, 3 H), 4.66 (t, J = 8.8 Hz, 2 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.73 - 6.89 (m, 3 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.8, 2.0 Hz, 1 H), 7.36 (d, J = 15.8 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 7.72 (dd, J = 8.6, 2.2 Hz, 1 H), 7.81 (d, J = 1.9 Hz, 1 H).

Example 58 (2E)-N-(benzylsulfonyl)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 1-phenylmethanesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.38 (s, 3 H), 3.47 - 3.52 (m, 3 H), 4.49 (br s, 2 H), 5.31 (d, J = 15.3 Hz, 1 H), 6.71 (d, J = 2.1 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.2 Hz, 1 H), 7.15 - 7.49 (m, 7 H), 7.65 (s, 1 H).

Example 59 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(cyclopropylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and cyclopropanesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.01 - 1.09 (m, 2 H), 1.25 - 1.33 (m, 2 H), 2.43 (s, 3 H), 2.72 - 2.84 (m, 1 H), 3.52 (s, 3 H), 5.42 (d,

J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Example 60 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(cyclopropylmethyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 1-cyclopropylmethanesulfonamide obtained in Reference Example 100.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.28 (d, J = 4.5 Hz, 2 H), 0.55 - 0.68 (m, 2 H), 1.01 (d, J = 8.0 Hz, 1 H), 2.44 (s, 3 H), 3.22 (dd, J = 7.2, 1.9 Hz, 2 H), 3.53 (s, 3 H), 5.32 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.46 (d, J = 15.9 Hz, 1 H), 7.71 (s, 1 H).

Example 61 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylpentyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 4-methylpentane-1-sulfonamide obtained in Reference Example 101.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (d, J = 6.6 Hz, 6 H), 1.18 - 1.29 (m, 2 H), 1.45 - 1.58 (m, 1 H), 1.66 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 (dd, J = 8.7, 7.2 Hz, 2 H), 3.52 (s, 3 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.78 (dd, J = 3.3, 0.8 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H).

Example 62 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide

A mixture of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 (353 mg), 2-methyl-6-nitrobenzoic anhydride (462 mg), N-pentylsulfamide obtained in Reference Example 287 (195 mg),

triethylamine (339 mg), 4-dimethylaminopyridine (137 mg) and acetonitrile (11 mL) was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (299 mg, yield 58%) as colorless crystals. melting point 184.3-184.4°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.78 - 0.94 (m, 3 H), 1.19 - 1.35 (m, 4 H), 1.49 (d, J = 6.4 Hz, 2 H), 2.42 (s, 3 H), 2.90 (q, J = 6.6 Hz, 2 H), 3.52 (s, 3 H), 5.11 - 5.21 (m, 1 H), 5.31 (d, J = 15.5 Hz, 1 H), 6.74 - 6.96 (m, 2 H), 7.06 - 7.29 (m, 2 H), 7.40 (d, J = 15.9 Hz, 1 H), 7.69 (s, 1 H), 8.12 (br s, 1 H).

Example 63 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(2-isopropoxyethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(2-isopropoxyethyl)sulfamide obtained in Reference Example 279.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.10 (d, J = 6.1 Hz, 6 H), 2.43 (s, 3 H), 3.13 (t, J = 4.9 Hz, 2 H), 3.42 - 3.57 (m, 6 H), 5.26 (d, J = 15.9 Hz, 1 H), 5.44 (br s, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.42 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H).

Example 64 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[methyl(pentyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference

Example 38 and N-methyl-N-pentylsulfamide obtained in Reference Example 110.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.79 - 0.92 (m, 3 H), 1.19 - 1.40 (m, 4 H), 1.47 - 1.60 (m, 2 H), 2.42 (s, 3 H), 2.87 (s, 3 H), 3.20 (t, J = 7.4 Hz, 2 H), 3.50 (s, 3 H), 5.41 (d, J = 15.5 Hz, 1 H), 6.76 (d, J = 2.7 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.38 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H), 8.13 (br s, 1 H).

Example 65 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl (pentylsulfonyl)carbamate

To a solution of [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 (358 mg) in N,N-dimethylformamide (13 mL) was added N,N'-carbonyldiimidazole (252 mg), and the mixture was stirred at 50°C for 1 hr. Pentane-1-sulfonamide (294 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (336 mg) and 4-dimethylaminopyridine (206 mg) were added to this reaction mixture, and the mixture was stirred at 50°C for 4 hr. After the reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 60:40, v/v), and crystallized from hexane-ethyl acetate to give the title compound (233 mg, yield 38%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.94 (m, 3 H), 1.25 - 1.46 (m, 4 H), 1.72 - 1.85 (m, 2 H), 2.35 (s, 3 H), 3.25 - 3.33 (m, 2 H), 3.50 (s, 3 H), 4.78 - 4.95 (m, 2 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 66 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl (pentylsulfonyl)carbamate

By a method similar to that in Example 65, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]ethanol obtained in Reference Example 63 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.0 Hz, 3 H), 1.23 - 1.47 (m, 4 H), 1.70- 1.82 (m, 2 H), 2.29 (s, 3 H), 2.51 - 2.69 (m, 2 H), 3.22 - 3.31 (m, 2 H), 3.49 (s, 3 H), 3.92 - 4.17 (m, 2 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.18 - 7.27 (m, 1 H), 7.69 (d, J = 2.3 Hz, 1 H).

Example 67 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl (pentylsulfonyl)carbamate

By a method similar to that in Example 65, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.94 (m, 3 H), 1.28 - 1.47 (m, 4 H), 1.56 - 1.70 (m, 2 H), 1.73 - 1.86 (m, 2 H), 2.20 - 2.42 (m, 5 H), 3.25 - 3.33 (m, 2 H), 3.47 (s, 3 H), 3.93 - 4.03 (m, 2 H), 6.69 - 6.72 (m, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Example 68 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl (phenylsulfonyl)carbamate

By a method similar to that in Example 65, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 and benzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.24 (s, 3 H), 3.49 (s, 3 H), 4.65 - 4.83 (m, 2 H), 6.66 (d, J = 2.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.15 (dd, J = 8.8, 2.0 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 7.60 - 7.68 (m, 2 H), 7.91 - 7.98 (m, 2 H).

Example 69 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl [(4-methylphenyl)sulfonyl]carbamate

By a method similar to that in Example 65, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.25 (s, 3 H), 2.44 (s, 3 H), 3.49 (s, 3 H), 4.64 - 4.81 (m, 2 H), 6.66 (d, J = 2.6 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.15 (dd, J = 8.7, 1.9 Hz, 1 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 2 H).

Example 70 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl [(4-methoxyphenyl)sulfonyl]carbamate

By a method similar to that in Example 65, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 and 4-methoxybenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.26 (s, 3 H), 3.49 (s, 3 H), 3.87 (s, 3 H), 4.65 - 4.83 (m, 2 H), 6.64 - 6.69 (m, 1 H), 6.84 - 7.02 (m, 3 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.16 (dd, J = 8.7, 1.9 Hz, 1 H), 7.65 (d, J = 1.9 Hz, 1 H), 7.83 - 7.90 (m, 2 H).

Example 71 [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

To a solution of [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanol obtained in Reference Example 61 (355 mg) in acetonitrile (13 mL) was added chlorosulfonyl isocyanate (191 mg) with stirring at 0°C, and the mixture was stirred at 0°C for 30 min. Pyridine (306 mg) was added to this reaction mixture, and the mixture stirred at 0°C for 1 hr. 2-Aminoethyl isopropyl ether (797 mg) was added, and the mixture was stirred at room temperature for 17 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v) to give the title compound (141 mg, yield 23%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.09 (dd, J = 6.0, 0.9 Hz, 6 H), 2.36 (s, 3 H), 3.17 (br s, 2 H), 3.44 - 3.56 (m, 6 H), 4.77 - 4.92 (m, 2 H), 5.35 (br s, 1 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.15 - 7.23 (m, 2 H), 7.67 (d, J = 1.5 Hz, 1

H).

Example 72 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

By a method similar to that in Example 71, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanol obtained in Reference Example 63, chlorosulfonyl isocyanate and 2-aminoethyl isopropyl ether.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.10 (d, J = 6.2 Hz, 6 H), 2.31 (s, 3 H), 2.50 - 2.68(m, 2 H), 3.08 - 3.18 (m, 2 H), 3.45 - 3.58 (m, 6 H), 3.93 - 4.17 (m, 2 H), 5.34 (br s, 1 H), 6.71 (dd, J = 3.2, 0.8 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.9, 2.1 Hz, 1 H), 7.69 (d, J = 1.5 Hz, 1 H).

Example 73 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

By a method similar to that in Example 71, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66, chlorosulfonyl isocyanate and 2-aminoethyl isopropyl ether.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.12 (dd, J = 6.1, 1.0 Hz, 6 H), 1.52 - 1.68 (m, 2 H), 2.19 - 2.41 (m, 5 H), 3.17 (br s, 2 H), 3.44 - 3.62 (m, 6 H), 3.90 - 4.04 (m, 2 H), 5.34 (br s, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m,1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Example 74 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl {[(4-methoxybenzyl)amino]sulfonyl}carbamate

By a method similar to that in Example 71, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66, chlorosulfonyl isocyanate and 4-methoxybenzylamine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.50 - 1.62 (m, 2 H), 2.16 - 2.37 (m, 5 H), 3.47 (s, 3 H), 3.76 (s, 3 H), 3.82 - 3.95 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.30 (br s, 1 H), 6.69 (dd, J = 3.2, 0.8 Hz, 1 H), 6.79 - 6.85 (m, 2 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.10 (d, J

= 3.2 Hz, 1 H), 7.14 - 7.22 (m, 3 H), 7.68 (d, J = 1.9 Hz, 1 H).

Example 75 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acetamide

By a method similar to that in Example 1, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetic acid obtained in Reference Example 67 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.93 (m, 3 H), 1.19 - 1.38 (m, 4 H), 1.52 - 1.70 (m, 2 H), 2.29 (s, 3 H), 3.09 - 3.32 (m, 4 H), 3.52 (s, 3 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Example 76 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)propanamide

By a method similar to that in Example 1, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 68 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 - 0.93 (m, 3 H), 1.21 - 1.43 (m, 4 H), 1.64 - 1.77 (m, 2 H), 2.10 - 2.19 (m, 2 H), 2.29 (s, 3 H), 2.53 - 2.66 (m, 2 H), 3.24 - 3.32 (m, 2 H), 3.44 (s, 3 H), 6.69 (dd, J = 3.3, 0.8 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 77 (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)but-2-enamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]but-2-ene acid obtained in Reference Example 70 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.94 (m, 3 H), 1.22 - 1.45 (m, 4 H), 1.67 - 1.81 (m, 2 H), 2.39 (s, 3 H), 3.02 (dd, J = 7.3, 1.1 Hz, 2 H), 3.28 - 3.37 (m, 2 H), 3.51 (s, 3 H), 5.15 - 5.27 (m, 1 H), 6.09 (d, J = 16.2 Hz, 1 H), 6.72 - 6.76 (m, 1 H), 6.90 - 6.99 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz,

1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Example 78 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acetamide

By a method similar to that in Example 62, the title compound was obtained from [5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acetic acid obtained in Reference Example 67 and N-pentylsulfamide obtained in Reference Example 287.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 6.9 Hz, 3 H), 1.16 - 1.33 (m, 4 H), 1.37 - 1.49 (m, 2 H), 2.28 (s, 3 H), 2.71 (d, J = 6.2 Hz, 2 H), 3.14 - 3.31 (m, 2 H), 3.51 (s, 3 H), 5.08 (br s, 1 H), 6.67 - 6.71 (m, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Example 79 4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]butanamide

By a method similar to that in Example 62, the title compound was obtained from 4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]butanoic acid obtained in Reference Example 71 and N-pentylsulfamide obtained in Reference Example 287.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 6.6 Hz, 3 H), 1.24 - 1.32 (m, 4 H), 1.43 - 1.67 (m, 4 H), 2.00 - 2.09 (m, 2 H), 2.16 - 2.36 (m, 5 H), 2.81 - 2.91 (m, 2 H), 3.48 (s, 3 H), 5.05 (br s, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Example 80 N-[({[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}amino)carbonyl]pentane-1-sulfonamide

To a solution of 1-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanamine obtained in Reference Example 75 (508 mg) in N,N-dimethylformamide (18 mL) was added N,N'-carbonyldiimidazole (449 mg), and the mixture was stirred at 50°C for 2 hr. Pentane-1-sulfonamide (419 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (478 mg) and 4-

dimethylaminopyridine (384 mg) were added to this reaction mixture, and the mixture was stirred at 50°C for 4 hr. After the reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (612 mg, yield 73%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.93 (m, 3 H), 1.23 - 1.38 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.33 (s, 3 H), 2.92 - 3.00 (m, 2 H), 3.47 (s, 3 H), 3.99 - 4.12 (m, 2 H), 6.33 - 6.42 (m, 1 H), 6.69 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Example 81 N-[({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}amino)carbonyl]pentane-1-sulfonamide

By a method similar to that in Example 80, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanamine obtained in Reference Example 76 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.0 Hz, 3 H), 1.24 - 1.45 (m, 4 H), 1.70 - 1.83 (m, 2 H), 2.30 (s, 3 H), 2.34 - 2.57 (m, 2 H), 3.06 - 3.18 (m, 4 H), 3.46 (s, 3 H), 6.31 (br s, 1 H), 6.68 (d, J = 3.2 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.15 - 7.22 (m, 2 H), 7.65 (d, J = 1.9 Hz, 1 H)

Example 82 N-[({3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl}amino)carbonyl]pentane-1-sulfonamide

By a method similar to that in Example 80, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-amine obtained in Reference Example 77 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 - 0.93 (m, 3 H), 1.29 - 1.40 (m, 4 H), 1.42 - 1.54 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.14 - 2.34 (m,

5 H), 3.02 - 3.12 (m, 4 H), 3.45 (s, 3 H), 6.24 (t, J = 5.3 Hz, 1 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Example 83 N-[({[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}amino)carbonyl]-4-methylbenzenesulfonamide

By a method similar to that in Example 80, the title compound was obtained from 1-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methanamine obtained in Reference Example 75 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.23 (s, 3 H), 2.42 (s, 3 H), 3.48 (s, 3 H), 3.98 (d, J = 4.9 Hz, 2 H), 6.56 (br s, 1 H), 6.68 (d, J = 3.0 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 - 7.30 (m, 4 H), 7.53 - 7.70 (m, 3 H).

Example 84 (5Z)-5-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methylene}-1,3-thiazolidine-2,4-dione

To a solution of 5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazole-4-carbaldehyde obtained in Reference Example 37 (560 mg) in ethanol (6.8 mL) were added 1,3-thiazolidine-2,4-dione (719 mg) and piperidine (382 mg), and the mixture was heated under reflux for 20 hr. After the reaction mixture was allowed to cool to room temperature, 1N hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 70:30, v/v), and crystallized from hexane-ethyl acetate to give the title compound (213 mg, yield 28%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.43 (s, 3 H), 3.45 (s, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.0 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (s, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.07 (br s, 1 H).

Example 85 (5Z)-5-{3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propylidene}-1,3-thiazolidine-2,4-dione

By a method similar to that in Example 84, the title compound was obtained from 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propanal obtained in Reference Example 78 and 1,3-thiazolidine-2,4-dione.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.14 (q, J = 7.3 Hz, 2 H), 2.30 (s, 3 H), 2.37 - 2.57 (m, 2 H), 3.48 (s, 3 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.76 (t, J = 7.6 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 8.20 (br s, 1 H).

Example 86 5-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}-1,3-thiazolidine-2,4-dione

(5Z)-5-{[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methylene}-1,3-thiazolidine-2,4-dione obtained in Example 84 (86 mg) was dissolved in a mixed solvent of tetrahydrofuran (2 mL) and ethanol (2 mL), 10% palladium carbon (30 mg) was added, and the mixture was stirred under 1 atom of hydrogen atmosphere at room temperature for 6 days. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v), and crystallized from hexane-ethanol to give the title compound (33 mg, yield 37%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 2.50 (br s, 3 H), 2.67 (br s, 1 H), 3.13 (br s, 1 H), 3.38 (s, 3 H), 4.29 (br s, 1 H), 6.77 (br s, 1 H), 6.96 - 7.10 (m, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.59 (br s, 1 H), 7.75 (br s, 1 H), 11.94 (d, J = 1.5 Hz, 1 H).

Example 87 5-{3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl}-1,3-thiazolidine-2,4-dione

By a method similar to that in Example 86, the title compound was obtained from (5Z)-5-{3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propylidene}-1,3-thiazolidine-2,4-dione obtained in Example 85.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.39 (d, J = 0.9 Hz, 2 H), 1.64 - 1.78 (m, 1 H), 1.93 (br s, 1 H), 2.20 - 2.36 (m, 5 H), 3.47 (d, J = 2.4 Hz, 3 H), 4.02 - 4.10 (m, 1 H), 6.68 (d, J = 3.2 Hz, 1 H),

6.93 (d, J = 8.7 Hz, 1 H), 7.08 (dd, J = 3.2, 1.3 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.67 (s, 1 H), 8.02 (br s, 1 H).

Example 88 (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 81 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.91 (m, 3 H), 1.23 - 1.46 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.46 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.53 (s, 3 H), 5.45 (d, J = 15.6 Hz, 1 H), 6.93 (d, J = 3.2 Hz, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.51 (dd, J = 8.5, 1.3 Hz, 1 H), 8.10 (d, J = 0.9 Hz, 1 H).

Example 89 (2E)-3-[5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 83 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.90 (m, 3 H), 1.19 - 1.44 (m, 4 H), 1.66 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.53 (s, 3 H), 5.40 (d, J = 15.8 Hz, 1 H), 6.67 (dd, J = 9.1, 2.4 Hz, 1 H), 6.80 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 7.08 (m, 2 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.65 (dd, J = 8.8, 5.2 Hz, 1 H).

Example 90 potassium {(2E)-3-[5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(6-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 89.

^{1}H-NMR (300 MHz, DMSO-d_6)δ: 0.76 - 0.85 (m, 3 H), 1.15 - 1.26 (m, 4 H), 1.37 - 1.49 (m, 2 H), 2.34 (s, 3 H), 2.81 - 2.91 (m, 2 H), 3.43 (s, 3 H), 5.55 (d, J = 15.9 Hz, 1 H), 6.71 - 6.85 (m, 3 H), 6.99 - 7.09 (m, 1 H), 7.52 (d, J = 3.0 Hz, 1 H), 7.71 (dd, J =

8.7, 5.3 Hz, 1 H).

Example 91 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-3-(methoxymethyl)-1-methyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 88 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.91 (m, 3 H), 1.25 - 1.41 (m, 4 H), 1.68 - 1.81 (m, 2 H), 3.30 - 3.39 (m, 2 H), 3.46 (s, 3 H), 3.57 (s, 3 H), 4.54 - 4.65 (m, 2 H), 5.76 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.34 - 7.47 (m, 2 H).

Example 92 3-{(E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]vinyl}-1,2,4-oxadiazol-5(4H)-one

To a solution of (1Z,2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N'-hydroxyprop-2-enimidamide obtained in Reference Example 90 (152 mg) in tetrahydrofuran (4.6 mL) were added N,N'-carbonyldiimidazole (112 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (281 mg), and the mixture was stirred at room temperature for 4 hr. 1N Hydrochloric acid was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (109 mg, yield 67%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.47 (s, 3 H), 3.54 (s, 3 H), 5.75 (d, J = 17.0 Hz, 1 H), 6.73 (d, J = 17.0 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.6, 2.0 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Example 93 2-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methoxy}-N-(pentylsulfonyl)acetamide

By a method similar to that in Example 1, the title compound was obtained from {[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]methoxy}acetic acid obtained in Reference Example 93 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.94 (m, 3 H), 1.27 - 1.45 (m, 4 H), 1.73 - 1.86 (m, 2 H), 2.35 (s, 3 H), 3.31 - 3.40 (m, 2 H), 3.53 (s, 3 H), 3.82 (s, 2 H), 4.14 - 4.32 (m, 2 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.0 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Example 94 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(1-propylbutyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(1-propylbutyl)sulfamide obtained in Reference Example 112.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.82 (t, J = 7.0 Hz, 6 H), 1.18 - 1.46 (m, 8 H), 2.43 (s, 3 H), 3.20 - 3.31 (m, 1 H), 3.53 (s, 3 H), 4.86 (d, J = 8.0 Hz, 1 H), 5.27 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.83 (br s, 1 H).

Example 95 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(cyclohexylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-cyclohexylsulfamide obtained in Reference Example 114.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.10 - 1.30 (m, 6 H), 1.62 - 1.72 (m, 2 H), 1.77 - 1.88 (m, 2 H), 2.44 (s, 3 H), 3.08 - 3.22 (m, 1 H), 3.53 (s, 3 H), 4.94 (d, J = 7.2 Hz, 1 H), 5.23 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.9 Hz, 1 H), 7.72 (d, J = 1.9 Hz, 1 H).

Example 96 (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxo-N-(pentylsulfonyl)but-3-enamide

By a method similar to that in Example 1, the title compound was obtained from (3E)-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-2-oxobut-3-enoic acid obtained in Reference Example 94 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.1 Hz, 3 H), 1.27 - 1.45 (m, 4 H), 1.75 - 1.88 (m, 2 H), 2.53 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.55 (s, 3 H), 6.76 - 6.83 (m, 2 H), 6.88 - 6.94 (m, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (d, J = 16.2 Hz, 1 H), 7.72 (d, J = 1.9 Hz, 1 H), 9.11 (br s, 1 H).

Example 97 5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-1,3-thiazolidine-2,4-dione

To a solution of ethyl 2-chloro-4-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]butanoate obtained in Reference Example 97 (99 mg) in ethanol (2.5 mL) were added thiourea (76 mg) and sodium acetate (82 mg), and the mixture was heated under reflux for 36 hr. 6N Hydrochloric acid (10 mL) was added to this reaction mixture, and the mixture was heated under reflux for 8 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 70:30, v/v) to give the title compound (59 mg, yield 61%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.75 - 1.92 (m, 1 H), 2.06 - 2.21 (m, 1 H), 2.25 - 2.54 (m, 5 H), 3.48 (s, 3 H), 3.95 - 4.06 (m, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.08 - 7.12 (m, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.16 (br s, 1 H).

Example 98 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(morpholin-4-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-

1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and morpholine-4-sulfonamide obtained in Reference Example 109.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.43 (s, 3 H), 3.25 - 3.32 (m, 4 H), 3.52 (s, 3 H), 3.65 - 3.73 (m, 4 H), 5.35 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 7.67 - 7.75 (m, 2 H).

Example 99 (2E)-N-[(butylamino)sulfonyl]-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.2 Hz, 3 H), 1.23 - 1.39 (m, 2 H), 1.40 - 1.54 (m, 2 H), 2.44 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.53 (s, 3 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 2.6 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.75 (br s, 1 H).

Example 100 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.2 Hz, 3 H), 1.24 - 1.40 (m, 2 H), 1.41 - 1.55 (m, 2 H), 2.38 (s, 3 H), 2.97 (q, J = 6.8 Hz, 2 H), 3.59 (s, 3 H), 5.12 (t, J = 6.2 Hz, 1 H), 5.45 (d, J = 15.6 Hz, 1 H), 6.80 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 8.06 (dd, J = 7.9, 1.5 Hz, 1 H), 8.16 (br s, 1 H), 8.35 (dd, J = 4.7, 1.5

Hz, 1 H).

Example 101 N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanamide

By a method similar to that in Example 62, the title compound was obtained from 3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propanoic acid obtained in Reference Example 45 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.2 Hz, 3 H), 1.31 - 1.44 (m, 2 H), 1.45 - 1.55 (m, 2 H), 2.01 - 2.16 (m, 1 H), 2.26 (s, 3 H), 2.29 - 2.40 (m, 1 H), 2.53 - 2.68 (m, 2 H), 2.72 - 3.00 (m, 2 H), 3.30 (s, 3 H), 4.96 (s, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 7.29 (dd, J = 7.9, 4.8 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H), 8.42 (dd, J = 4.8, 1.5 Hz, 1 H), 11.87 (s, 1 H).

Example 102 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.17 (m, 2 H), 0.46 - 0.54 (m, 2 H), 0.84 - 1.00 (m, 1 H), 2.43 (s, 3 H), 2.78 - 2.83 (m, 2 H), 3.53 (s, 3 H), 5.17 - 5.22 (m, 2 H), 6.78 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.9, 2.0 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.70 (s, 1 H), 7.71 (d, J = 2.0 Hz, 1 H).

Example 103 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(1-ethylpropyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(1-ethylpropyl)sulfamide obtained in Reference Example 113.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.81 - 0.86 (m, 6 H), 1.30 - 1.55 (m, 4 H), 2.43 (s, 3 H), 3.08 - 3.20 (m, 1 H), 3.53 (s, 3 H), 4.86 (d, J = 7.6 Hz, 1 H), 5.25 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 2.3 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.42 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.77 (s, 1 H).

Example 104 ethyl N-[({(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}amino)sulfonyl]glycinate

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and ethyl N-(aminosulfonyl)glycinate obtained in Reference Example 117.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.42 (s, 3 H), 3.52 (s, 3 H), 3.87 (s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 15.6 Hz, 1 H), 5.59 (s, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.88 - 6.95 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.43 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.80 (br s, 1 H).

Example 105 (2E)-N-[(butylamino)sulfonyl]-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 2 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.2 Hz, 3 H), 1.07 - 1.30 (m, 2 H), 1.30 - 1.41 (m, 2 H), 2.40 (s, 3 H), 2.71 - 2.85 (m, 2 H), 3.47 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.85 (d, J = 3.0 Hz, 1 H), 6.92 - 7.06 (m, 2 H), 7.11 - 7.25 (m, 2 H), 7.52 (t, J = 5.7 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.68 - 7.81 (m, 1 H), 11.31 (s, 1 H).

Example 106 (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 2 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 (t, J = 7.4 Hz, 3 H), 1.25 - 1.52 (m, 2 H), 2.40 (s, 3 H), 2.63 - 2.86 (m, 2 H), 3.47 (s, 3 H), 6.12 (d, J = 16.3 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.92 - 7.07 (m, 2 H), 7.13 - 7.25 (m, 2 H), 7.52 (br s, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.65 - 7.78 (m, 1 H), 11.31 (s, 1 H).

Example 107 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 2 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.05 - 0.15 (m, 2 H), 0.24 - 0.39 (m, 2 H), 0.72 - 0.94 (m, 1 H), 2.40 (s, 3 H), 2.71 (t, J = 6.4 Hz, 2 H), 3.47 (s, 3 H), 6.11 (d, J = 16.0 Hz, 1 H), 6.85 (dd, J = 3.3, 0.8 Hz, 1 H), 6.99 (d, J = 16.0 Hz, 1 H), 6.98 - 7.04 (m, 1 H), 7.15 - 7.25 (m, 2 H), 7.52 - 7.64 (m, 2 H), 7.67 - 7.82 (m, 1 H), 11.32 (s, 1 H).

Example 108 (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 130 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.1 Hz, 3 H), 1.10 - 1.42 (m, 4 H), 1.46 - 1.65 (m, 2 H), 2.40 (s, 3 H), 3.24 - 3.32 (m, 2 H), 3.50 (s, 3 H), 6.07 (d, J = 16.0 Hz, 1 H), 6.91 - 7.13 (m, 2 H), 7.20 - 7.41 (m, 2 H), 7.60 - 7.73 (m, 1 H), 7.92 (s, 1 H), 11.62 (s, 1 H).

Example 109 (2E)-N-[(butylamino)sulfonyl]-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title

compound was obtained from (2E)-3-[5-(3-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 130 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.3 Hz, 3 H), 1.12 - 1.28 (m, 2 H), 1.28 - 1.42 (m, 2 H), 2.40 (s, 3 H), 2.67 - 2.87 (m, 2 H), 3.49 (s, 3 H), 6.08 (d, J = 16.2 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.04 - 7.12 (m, 1 H), 7.19 - 7.41 (m, 2 H), 7.54 (t, J = 5.6 Hz, 1 H), 7.57 - 7.71 (m, 1 H), 7.92 (s, 1 H), 11.32 (s, 1 H).

Example 110 (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 60 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 2.37 (s, 3 H), 3.46 (s, 3 H), 3.66 (s, 3 H), 6.05 (d, J = 16.0 Hz, 1 H), 6.44 (d, J = 1.9 Hz, 1 H), 6.73 (d, J = 2.8 Hz, 1 H), 6.83 (dd, J = 8.5, 2.3 Hz, 1 H), 6.95 (d, J = 16.0 Hz, 1 H), 7.25 - 7.39 (m, 3 H), 7.58 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 12.02 (s, 1 H).

Example 111 potassium {(2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}[(4-methylphenyl)sulfonyl]azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide obtained in Example 110.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.27 (s, 3 H), 2.32 (s, 3 H), 3.41 (s, 3 H), 3.67 (s, 3 H), 5.56 (d, J = 16.0 Hz, 1 H), 6.41 (d, J = 2.3 Hz, 1 H), 6.66 - 6.76 (m, 2 H), 6.81 (dd, J = 8.5, 2.3 Hz, 1 H), 7.09 (d, J = 7.9 Hz, 2 H), 7.29 (d, J = 3.2 Hz, 1 H), 7.48 - 7.60 (m, 3 H).

Example 112 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 136 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.1 Hz, 3 H), 0.97 - 1.41 (m, 4 H), 1.49 - 1.68 (m, 2 H), 2.36 (d, J = 1.1 Hz, 3 H), 2.38 (s, 3 H), 3.27 - 3.35 (m, 2 H), 3.48 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 7.03 (d, J = 15.9 Hz, 1 H), 7.27 (dd, J = 7.8, 4.7 Hz, 1 H), 7.47 (d, J = 0.8 Hz, 1 H), 8.13 (dd, J = 8.0, 1.5 Hz, 1 H), 8.25 (dd, J = 4.5, 1.5 Hz, 1 H), 11.59 (s, 1 H).

Example 113 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 136 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.3 Hz, 3 H), 1.13 - 1.28 (m, 2 H), 1.29 - 1.43 (m, 2 H), 2.36 (d, J = 0.9 Hz, 3 H), 2.38 (s, 3 H), 2.79 (q, J = 6.8 Hz, 2 H), 3.48 (s, 3 H), 6.13 (d, J = 16.0 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.26 (dd, J = 7.9, 4.7 Hz, 1 H), 7.47 (d, J = 1.1 Hz, 1 H), 7.48 - 7.51 (m, 1 H), 8.13 (dd, J = 7.8, 1.6 Hz, 1 H), 8.25 (dd, J = 4.7, 1.3 Hz, 1 H), 11.29 (s, 1 H).

Example 114 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 136 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.34 (d, J = 1.1 Hz, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 3.46 (s, 3 H), 6.07 (d, J = 16.0 Hz, 1 H), 6.92 (d, J = 16.0 Hz, 1 H), 7.25 (dd, J = 7.9, 4.7 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 2 H), 7.43 (d, J = 1.1 Hz, 1 H), 7.74 (d, J

= 8.3 Hz, 2 H), 8.12 (dd, J = 7.8, 1.6 Hz, 1 H), 8.23 (dd, J = 4.7, 1.5 Hz, 1 H), 12.00 (s, 1 H).

Example 115 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 136 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.04 - 0.16 (m, 2 H), 0.26 - 0.46 (m, 2 H), 0.70 - 0.97 (m, 1 H), 2.36 (d, J = 1.1 Hz, 3 H), 2.37 (s, 3 H), 2.72 (t, J = 6.4 Hz, 2 H), 3.48 (s, 3 H), 6.12 (d, J = 16.0 Hz, 1 H), 6.99 (d, J = 16.0 Hz, 1 H), 7.26 (dd, J = 7.8, 4.8 Hz, 1 H), 7.47 (d, J = 1.1 Hz, 1 H), 7.62 (t, J = 6.1 Hz, 1 H), 8.13 (dd, J = 7.9, 1.5 Hz, 1 H), 8.25 (dd, J = 4.7, 1.5 Hz, 1 H), 11.30 (s, 1 H).

Example 116 (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 140 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.82 (t, J = 7.0 Hz, 3 H), 1.17 - 1.40 (m, 4 H), 1.53 - 1.66 (m, 2 H), 2.38 (s, 3 H), 3.26 - 3.40 (m, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 6.29 (d, J = 16.0 Hz, 1 H), 7.08 - 7.17 (m, 1 H), 7.25 - 7.31 (m, 2 H), 7.35 (d, J = 16.0 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 7.68 (s, 1 H), 11.49 (s, 1 H).

Example 117 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1-methyl-1H-indol-3-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 140 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.3 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.31 - 1.44 (m, 2 H), 2.37 (s, 3 H), 2.75 - 2.85 (m, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 6.27 (d, J = 15.8 Hz, 1 H), 7.02 - 7.17 (m, 1 H), 7.23 - 7.36 (m, 3 H), 7.39 - 7.52 (m, 1 H), 7.59 (d, J = 8.9 Hz, 1 H), 7.67 (s, 1 H), 11.20 (s, 1 H).

Example 118 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 143 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.87 (t, J = 7.0 Hz, 3 H), 1.29 - 1.40 (m, 4 H), 1.56 - 1.78 (m, 2 H), 2.45 (s, 3 H), 2.63 (s, 3 H), 3.24 - 3.38 (m, 2 H), 3.56 (s, 3 H), 5.45 - 5.62 (m, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.28 - 7.36 (m, 1 H), 7.40 - 7.53 (m, 2 H), 7.78 (d, J = 8.1 Hz, 1 H), 7.86 (br s, 1 H).

Example 119 potassium {(2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 118.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.80 (t, J = 6.6 Hz, 3 H), 1.14 - 1.24 (m, 4 H), 1.32 - 1.50 (m, 2 H), 2.35 (s, 3 H), 2.62 (s, 3 H), 2.85 (t, J = 7.8 Hz, 2 H), 3.44 (s, 3 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.75 (d, J = 16.2 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 1 H), 7.20 - 7.35 (m, 1 H), 7.42 - 7.52 (m, 1 H), 7.89 (d, J = 8.1 Hz, 1 H).

Example 120 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 143 and N-butylsulfamide obtained in Reference Example

111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.3 Hz, 3 H), 1.11 - 1.27 (m, 2 H), 1.27 - 1.43 (m, 2 H), 2.40 (s, 3 H), 2.63 (s, 3 H), 2.68 - 2.88 (m, 2 H), 3.52 (s, 3 H), 6.09 (d, J = 16.4 Hz, 1 H), 7.04 (d, J = 16.0 Hz, 1 H), 7.20 (d, J = 8.3 Hz, 1 H), 7.25 - 7.37 (m, 1 H), 7.42 - 7.59 (m, 2 H), 7.92 (d, J = 7.9 Hz, 1 H), 11.28 (s, 1 H).

Example 121 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-indazol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 143 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.04 - 0.16 (m, 2 H), 0.25 - 0.44 (m, 2 H), 0.71 - 0.93 (m, 1 H), 2.39 (s, 3 H), 2.62 (s, 3 H), 2.67 - 2.74 (m, 2 H), 3.52 (s, 3 H), 6.06 (d, J = 16.6 Hz, 1 H), 7.02 (d, J = 16.2 Hz, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 7.32 (t, J = 7.1 Hz, 1 H), 7.44 - 7.52 (m, 1 H), 7.53 - 7.68 (m, 1 H), 7.92 (d, J = 7.7 Hz, 1 H), 11.30 (s, 1 H).

Example 122 (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 145 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 6.8 Hz, 3 H), 1.21 - 1.47 (m, 4 H), 1.69 - 1.86 (m, 2 H), 2.45 (s, 3 H), 3.28 - 3.48 (m, 2 H), 3.66 (s, 3 H), 3.83 (s, 3 H), 5.51 (d, J = 15.8 Hz, 1 H), 6.65 - 6.75 (m, 2 H), 6.95 (d, J = 3.2 Hz, 1 H), 7.50 (d, J = 15.8 Hz, 1 H), 7.89 (d, J = 8.7 Hz, 1 H).

Example 123 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title

compound was obtained from (2E)-3-[5-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 145 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.80 (t, J = 7.3 Hz, 3 H), 1.14 - 1.30 (m, 2 H), 1.31 - 1.47 (m, 2 H), 2.38 (s, 3 H), 2.75 - 2.85 (m, 2 H), 3.57 (s, 3 H), 3.73 (s, 3 H), 6.16 (d, J = 16.0 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.11 (d, J = 16.0 Hz, 1 H), 7.44 (d, J = 3.6 Hz, 1 H), 7.50 (t, J = 5.5 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 11.34 (br s, 1 H).

Example 124 (2E)-N-[(butylamino)sulfonyl]-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 155 and N-butylsulfamide obtained in Reference Example 111 .

1H NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.3 Hz, 3 H), 0.92 - 1.08 (m, 4 H), 1.25 - 1.38 (m, 2 H), 1.41 - 1.53 (m, 2 H), 1.91 - 2.02 (m, 1 H), 2.92 (q, J = 6.6 Hz, 2 H), 3.50 (s, 3 H), 5.02 - 5.11 (m, 1 H), 5.40 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.87 - 6.94 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.38 (dd, J = 9.0, 2.4 Hz, 1 H), 7.55 (d, J = 15.8 Hz, 1 H).

Example 125 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 218 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.16 - 0.21 (m, 2 H), 0.48 - 0.54 (m, 3 H), 0.77 - 0.81 (m, 2 H), 0.90 - 1.02 (m, 2 H), 1.63 - 1.72 (m, 1 H), 2.87 - 2.93 (m, 2 H), 3.54 (s, 3 H), 5.27 (t, J = 6.0 Hz,

1 H), 5.75 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.18 - 7.24 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.03 - 8.07 (m, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H).

Example 126 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 230 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.07 - 0.09 (m, 2 H), 0.27 - 0.33 (m, 2 H), 0.75 - 0.87 (m, 1 H), 2.70 (t, J = 6.6 Hz, 2 H), 3.63 (s, 3 H), 5.88 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.9 Hz, 1 H), 7.15 (d, J = 15.9 Hz, 1 H), 7.30 (dd, J = 7.8, 4.5 Hz, 1 H), 7.69 - 7.71 (m, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.19 (dd, J = 7.8, 1.5 Hz, 1 H), 8.28 (dd, J = 4.8, 1.5 Hz, 1 H).

Example 127 (2E)-N-[(butylamino)sulfonyl]-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 230 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 (t, J = 7.2 Hz, 3 H), 1.14 - 1.38 (m, 4 H), 2.74 - 2.80 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 16.2 Hz, 1 H), 6.93 (d, J = 3.3 Hz, 1 H), 7.16 (d, J = 15.3 Hz, 1 H), 7.31 (dd, J = 8.1, 4.8 Hz, 1 H), 7.58 - 7.60 (m, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.19 (dd, J = 7.8, 1.5 Hz, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H).

Example 128 (2E)-N-{[(3-methylbutyl)amino]sulfonyl}-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title

compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 230 and N-(3-methylbutyl)sulfamide obtained in Reference Example 125.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.76 (d, J = 6.6 Hz, 6 H), 1.20 - 1.28 (m, 2 H), 1.46 - 1.58 (m, 1 H), 2.76 - 2.82 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 15.9 Hz, 1 H), 7.31 (dd, J = 7.8, 4.8 Hz, 1 H), 7.60 (br s, 1 H), 7.78 (d, J = 3.9 Hz, 1 H), 8.19 (dd, J = 7.8, 1.8 Hz, 1 H), 8.29 (dd, J = 4.8, 1.8 Hz, 1 H).

Example 129 (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 230 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 (t, J = 7.2 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 2.70 - 2.77 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.9 Hz, 1H), 7.16 (d, J = 15.9 Hz, 1 H), 7.31 (dd, J = 8.1, 5.1 Hz, 1 H), 7.63 (t, J = 5.7 Hz, 1 H), 7.78 (d, J = 3.9 Hz, 1 H), 8.19 (dd, J = 8.1, 1.8 Hz, 1 H), 8.29 (dd, J = 5.1, 1.8 Hz, 1 H).

Example 130 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.2 Hz, 3 H), 1.46 - 1.58 (m, 2 H), 2.43 (s, 3 H), 2.85 - 2.92 (m, 2 H), 3.52 (s, 3 H), 5.10 (t, J = 6.3 Hz, 1 H), 5.25 (d, J = 15.9 Hz, 1 H), 6.77 (d, J = 3.3 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.3 Hz,

1 H), 7.20 (dd, J = 8.7, 1.8 Hz, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 7.70 (d, J = 1.8 Hz, 1 H), 7.81 (br s, 1 H).

Example 131 (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 218 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.60 - 0.67 (m, 1 H), 0.81 - 0.95 (m, 6 H), 1.49 - 1.62 (m, 2 H), 1.68 - 1.78 (m, 1 H), 2.93 - 3.02 (m, 2 H), 3.55 (s, 3 H), 5.16 (t, J = 6.0 Hz, 1 H), 5.75 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.9 Hz, 1 H), 6.99 - 7.23 (m, 2 H), 7.38 (d, J = 15.6 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.31 (d, J = 4.8 Hz, 1 H), 9.14 (br s, 1 H).

Example 132 (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-{[(3-methylbutyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 218 and N-(3-methylbutyl)sulfamide obtained in Reference Example 125.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.50 - 0.57 (m, 1 H), 0.78 - 0.94 (m, 9 H), 1.40 (q, J = 7.2 Hz, 2 H), 1.60 - 1.69 (m, 2 H), 3.02 - 3.05 (m, 2 H), 3.55 (s, 3 H), 5.14 (t, J = 6.0 Hz, 1 H), 5.79 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.29 (d, J = 4.8 Hz, 1 H), 9.56 (br s, 1 H).

Example 133 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[3-(difluoromethyl)-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-(difluoromethyl)-1-methyl-

5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 265 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.06 - 0.10 (m, 2 H), 0.28 - 0.35 (m, 2 H), 0.78 - 0.85 (m, 1 H), 2.70 (t, J = 6.3 Hz, 2 H), 3.59 (s, 3 H), 5.96 (d, J = 15.9 Hz, 1 H), 6.91 (d, J = 3.6 Hz, 1 H), 7.01 - 7.36 (m, 3 H), 7.67 (t, J = 6.3 Hz, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.17 - 8.20 (m, 1 H), 8.27 (dd, J = 4.8, 1.5 Hz, 1 H).

Example 134 (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 218 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.44 - 0.50 (m, 1 H), 0.73 - 0.76 (m, 2 H), 0.87 - 0.94 (m, 4 H), 1.28 - 1.42 (m, 4 H), 1.58 - 1.65 (m, 1 H), 1.76 - 1.86 (m, 2 H), 3.43 (q, J = 7.8 Hz, 2 H), 3.52 (s, 3 H), 5.83 (d, J = 15.6 Hz, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.04 (dd, J = 7.8, 1.5 Hz, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H), 9.87 (br s, 1 H).

Example 135 (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 230 and N-pentylsulfamide obtained in Reference Example 287.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.70 - 0.85 (m, 3 H), 1.05 - 1.24 (m, 4 H), 1.25 - 1.44 (m, 2 H), 2.68 - 2.83 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 16.0 Hz, 1 H), 6.94 (d, J = 3.8 Hz, 1 H), 7.17 (d, J = 16.0 Hz, 1 H), 7.31 (dd, J = 7.8, 4.8 Hz, 1 H), 7.60 (br s, 1 H), 7.78 (d, J = 3.6 Hz, 1 H), 8.20 (dd, J = 7.8, 1.6 Hz, 1 H),

8.30 (dd, J = 4.7, 1.5 Hz, 1 H), 11.53 (s, 1 H).

Example 136 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-pentylsulfamide obtained in Reference Example 287.

^{1}H-NMR (300 MHz, DMSO-d_6) δ:0.70 - 0.83 (m, 3 H), 1.09 - 1.26 (m, 4 H), 1.28 - 1.44 (m, 2 H), 2.39 (s, 3 H), 2.79 (q, J = 6.8 Hz, 2 H), 3.49 (s, 3 H), 6.11 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.27 (dd, J = 7.9, 4.7 Hz, 1 H), 7.51 (br s, 1 H), 7.71 (d, J = 3.8 Hz, 1 H), 8.16 (dd, J = 7.8, 1.6 Hz, 1 H), 8.27 (dd, J = 4.7, 1.5 Hz, 1 H), 11.29 (s, 1 H).

Example 137 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(ethylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-ethylsulfamide obtained in Reference Example 152.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:1.13 (t, J = 7.3 Hz, 3 H), 2.42 (s, 3 H), 2.92 - 3.04 (m, 2 H), 3.52 (s, 3 H), 5.13 (br s, 1 H), 5.29 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.7 Hz, 1 H), 8.04 (br s, 1 H).

Example 138 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and 1,4-dioxa-8-azaspiro[4.5]decane-8-sulfonamide

obtained in Reference Example 120.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.66 - 1.80 (m, 4 H), 2.42 (s, 3 H), 3.33 - 3.55 (m, 7 H), 3.93 (s, 4 H), 5.43 (d, J = 15.9 Hz, 1 H), 6.73 - 6.78 (m, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 1 H), 7.40 (d, J = 15.5 Hz, 1 H), 7.68 (s, 1 H), 8.14 (br s, 1 H).

Example 139 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(3-methylbutyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(3-methylbutyl)sulfamide obtained in Reference Example 125.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 (d, J = 6.6 Hz, 6 H), 1.37 (q, J = 7.0 Hz, 2 H), 1.52 - 1.68 (m, 1 H), 2.42 (s, 3 H), 2.92 (q, J = 7.1 Hz, 2 H), 3.52 (s, 3 H), 5.15 (t, J = 6.1 Hz, 1 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.69 (d, J = 1.7 Hz, 1 H), 8.19 (br s, 1 H).

Example 140 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclohexylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(cyclohexylmethyl)sulfamide obtained in Reference Example 123.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.80 - 0.94 (m, 2 H), 1.09 - 1.19 (m, 2 H), 1.37 - 1.49 (m, 1 H), 1.61 - 1.74 (m, 6 H), 2.42 (s, 3 H), 2.74 (t, J = 6.6 Hz, 2 H), 3.51 (s, 3 H), 5.21 (t, J = 6.3 Hz, 1 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.69 (d, J = 1.7 Hz, 1 H), 8.13 (br s, 1 H).

Example 141 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(3-isopropoxypropyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-(3-isopropoxypropyl)sulfamide obtained in Reference Example 121.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.12 (d, J = 6.0 Hz, 6 H), 1.70 - 1.80 (m, 2 H), 2.45 (s, 3 H), 3.02 - 3.12 (m, 2 H), 3.42 - 3.60 (m, 6 H), 5.31 (d, J = 15.8 Hz, 1 H), 5.72 (br s, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H), 7.90 (br s, 1 H).

Example 142 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-oxopiperidin-1-yl)sulfonyl]acrylamide

To a solution of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)acrylamide obtained in Example 138 (2.53 g) in tetrahydrofuran (10 mL) was added 1N hydrochloric acid (10 mL), and the mixture was stirred with heating at 70°C for 3 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 35:65, v/v) to give the title compound (2.23 g, yield 96%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.43 (s, 3 H), 2.52 (t, J = 6.2 Hz, 4 H), 3.52 (s, 3 H), 3.66 (t, J = 6.1 Hz, 4 H), 5.28 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.81 (br s, 1 H).

Example 143 ethyl N-[({(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}amino)sulfonyl]-β-alaninate

By a method similar to that in Example 62, the title

compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and ethyl N-(aminosulfonyl)-β-alaninate obtained in Reference Example 260.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 - 1.25 (m, 3 H), 2.40 (s, 3 H), 2.53 (t, J = 6.4 Hz, 2 H), 3.23 (q, J = 5.7 Hz, 2 H), 3.50 (s, 3 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.81 (br s, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.18 (dd, J = 8.7, 2.3 Hz, 1 H), 7.36 - 7.43 (m, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.60 (br s, 1 H).

Example 144 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-{[(1-propylbutyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-(1-propylbutyl)sulfamide obtained in Reference Example 112.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.82 (t, J = 6.8 Hz, 6 H), 1.19 - 1.47 (m, 8 H), 2.37 (s, 3 H), 3.24 - 3.37 (m, 1 H), 3.59 (s, 3 H), 4.95 (d, J = 7.6 Hz, 1 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.36 (d, J = 15.9 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.33 (dd, J = 4.9, 1.5 Hz, 1 H).

Example 145 (2E)-N-[(cyclohexylamino)sulfonyl]-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-cyclohexylsulfamide obtained in Reference Example 114.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.17 - 1.32 (m, 5 H), 1.49 - 1.57 (m, 1 H), 1.63 - 1.73 (m, 2 H), 1.79 - 1.91 (m, 2 H), 2.37 (s, 3 H), 3.15 - 3.26 (m, 1 H), 3.59 (s, 3 H), 5.05 (d, J = 6.8 Hz, 1 H), 5.47 (d, J = 15.9 Hz, 1 H), 6.80 (d, J = 3.8 Hz, 1 H), 7.19 (d,

J = 3.8 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.37 (d, J = 15.5 Hz, 1 H), 8.06 (dd, J = 7.6, 1.5 Hz, 1 H), 8.32 - 8.36 (m, 1 H).

Example 146 (2E)-N-{[(cyclohexylmethyl)amino]sulfonyl}-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-(cyclohexylmethyl)sulfamide obtained in Reference Example 123.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.82 - 0.96 (m, 2 H), 1.08 - 1.29 (m, 4 H), 1.65 - 1.77 (m, 5 H), 2.31 (s, 3 H), 2.83 (t, J = 6.4 Hz, 2 H), 3.56 (s, 3 H), 5.26 (t, J = 6.2 Hz, 1 H), 5.49 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 8.0, 4.5 Hz, 1 H), 7.33 (d, J = 15.9 Hz, 1 H), 8.03 - 8.07 (m, 1 H), 8.30 - 8.34 (m, 1 H), 8.82 (br s, 1 H).

Example 147 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.4 Hz, 3 H), 1.47 - 1.58 (m, 2 H), 2.31 (s, 3 H), 2.97 (q, J = 6.3 Hz, 2 H), 3.56 (s, 3 H), 5.23 (br s, 1 H), 5.50 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.21 - 7.27 (m, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 8.05 (d, J = 7.6 Hz, 1 H), 8.32 (d, J = 4.2 Hz, 1 H), 8.86 (br s, 1 H).

Example 148 (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid

obtained in Reference Example 133 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.10 (d, J = 4.5 Hz, 2 H), 0.33 (d, J = 7.6 Hz, 2 H), 0.84 (t, J = 7.4 Hz, 1 H), 2.38 (s, 3 H), 2.72 (t, J = 6.1 Hz, 2 H), 3.50 (s, 3 H), 6.05 (d, J = 15.9 Hz, 1 H), 7.01 (d, J = 16.3 Hz, 1 H), 7.40 (dd, J = 7.8, 4.7 Hz, 1 H), 7.63 (br s, 1 H), 8.06 (s, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 11.31 (br s, 1 H).

Example 149 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-{[(3-methylbutyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-(3-methylbutyl)sulfamide obtained in Reference Example 125.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (d, J = 6.8 Hz, 6 H), 1.40 (q, J = 6.9 Hz, 2 H), 1.56 - 1.70 (m, 1 H), 2.27 (s, 3 H), 2.98 - 3.09 (m, 2 H), 3.55 (s, 3 H), 5.22 (t, J = 6.1 Hz, 1 H), 5.53 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.0, 4.5 Hz, 1 H), 7.30 (d, J = 15.9 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 8.30 (d, J = 3.4 Hz, 1 H), 9.27 (br s, 1 H).

Example 150 (2E)-N-[(butylamino)sulfonyl]-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 81 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.4 Hz, 3 H), 1.27 - 1.38 (m, 2 H), 1.42 - 1.51 (m, 2 H), 2.46 (s, 3 H), 2.93 (q, J = 6.8 Hz, 2 H), 3.53 (s, 3 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.33 (d, J = 15.5 Hz, 1 H), 6.93 (d, J = 3.4 Hz, 1 H), 7.07 (d, J = 8.7 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.5 Hz, 1 H), 7.51

(dd, J = 8.3, 1.5 Hz, 1 H), 8.10 (s, 1 H).

Example 151 (2E)-N-[(butylamino)sulfonyl]-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 133 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.2 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.30 - 1.43 (m, 2 H), 2.38 (s, 3 H), 2.79 (q, J = 6.4 Hz, 2 H), 3.50 (s, 3 H), 6.07 (d, J = 15.9 Hz, 1 H), 7.02 (d, J = 15.9 Hz, 1 H), 7.40 (dd, J = 7.6, 4.5 Hz, 1 H), 7.48 - 7.56 (m, 1 H), 8.06 (s, 1 H), 8.16 (d, J = 8.0 Hz, 1 H), 8.38 (d, J = 4.2 Hz, 1 H), 11.30 (br s, 1 H).

Example 152 (2E)-N-[(butylamino)sulfonyl]-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.90 (m, 3 H), 1.24 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.42 (s, 3 H), 2.91 (q, J = 6.7 Hz, 2 H), 3.53 (s, 3 H), 5.13 (t, J = 6.1 Hz, 1 H), 5.29 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.04 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.34 - 7.45 (m, 2 H), 7.97 (br s, 1 H).

Example 153 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.18 (m, 2 H), 0.44 - 0.53 (m, 2 H), 0.86 - 1.00 (m, 1 H), 2.43 (s, 3 H), 2.81 (t, J = 6.1 Hz, 2 H), 3.54 (s, 3 H), 5.18 - 5.26 (m, 2 H), 6.80 (d, J = 3.4 Hz, 1 H), 6.86 - 6.92 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.35 - 7.46 (m, 2 H).

Example 154 (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 81 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.11 - 0.17 (m, 2 H), 0.50 (d, J = 7.9 Hz, 2 H), 0.86 - 0.99 (m, 1 H), 2.45 (s, 3 H), 2.81 (t, J = 6.1 Hz, 2 H), 3.53 (s, 3 H), 5.23 (br s, 1 H), 5.31 (d, J = 15.8 Hz, 1 H), 6.93 (d, J = 3.4 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 7.50 (dd, J = 8.6, 1.4 Hz, 1 H), 8.10 (s, 1 H).

Example 155 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-hydroxypiperidin-1-yl)sulfonyl]acrylamide

To a solution of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-oxopiperidin-1-yl)sulfonyl]acrylamide obtained in Example 142 (301 mg) in a mixed solvent of tetrahydrofuran (5 mL) and methanol (1 mL) was added sodium borohydride (26.3 mg), and the mixture was stirred at room temperature for 1 hr. Water was added to this reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 20:80, v/v) to give the title compound (176 mg, yield 58%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.55 - 1.67 (m, 2 H), 1.83 - 1.94 (m, 2 H), 2.43 (s, 3 H), 3.09 - 3.19 (m, 2 H), 3.51 (s, 3 H), 3.53 -

3.62 (m, 2 H), 3.83 (br s, 1 H), 5.36 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H), 7.76 (br s, 1 H).

Example 156 (2E)-N-[(butylamino)sulfonyl]-3-[5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-indazol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 40 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.2 Hz, 3 H), 1.25 - 1.39 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.45 (s, 3 H), 2.93 (q, J = 6.4 Hz, 2 H), 3.60 (s, 3 H), 5.11 (t, J = 6.2 Hz, 1 H), 5.53 (d, J = 15.9 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 7.36 - 7.45 (m, 2 H), 7.54 (t, J = 7.4 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H).

Example 157 (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-5-(5-fluoro-1H-indol-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 155 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.18 (m, 2 H), 0.43 - 0.54 (m, 2 H), 0.86 - 1.07 (m, 5 H), 1.90 - 2.02 (m, 1 H), 2.75 - 2.86 (m, 2 H), 3.50 (s, 3 H), 5.25 (br s, 1 H), 5.40 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 3.2 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.03 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.38 (dd, J = 9.0, 2.1 Hz, 1 H), 7.54 (d, J = 15.8 Hz, 1 H).

Example 158 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference

Example 21 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.3 Hz, 3 H), 1.45 - 1.56 (m, 2 H), 2.44 (s, 3 H), 2.85 - 2.92 (m, 2 H), 3.54 (s, 3 H), 5.08 (br s, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.80 (d, J = 3.2 Hz, 1 H), 6.87 - 6.94 (m, 1 H), 6.96 - 7.04 (m, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.34 - 7.48 (m, 2 H).

Example 159 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 60 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.2 Hz, 3 H), 1.24 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.44 (s, 3 H), 2.91 (q, J = 6.8 Hz, 2 H), 3.55 (s, 3 H), 3.77 (s, 3 H), 5.00 (br s, 1 H), 5.22 (d, J = 15.5 Hz, 1 H), 6.40 (d, J = 1.9 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.90 (dd, J = 8.5, 2.1 Hz, 1 H), 6.95 (d, J = 3.0 Hz, 1 H), 7.47 (d, J = 15.5 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H).

Example 160 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-hydroxy-4-methylpiperidin-1-yl)sulfonyl]acrylamide

To a solution of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-oxopiperidin-1-yl)sulfonyl]acrylamide obtained in Example 142 (308 mg) in tetrahydrofuran (6 mL) was added methylmagnesium bromide (1M diethyl ether solution, 1.4 mL) with stirring, and the mixture was stirred at room temperature for 1 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 25:75, v/v) to give the

title compound (155 mg, yield 49%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.25 (s, 3 H), 1.58 - 1.73 (m, 4 H), 2.44 (s, 3 H), 3.15 - 3.32 (m, 2 H), 3.43 - 3.58 (m, 5 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.8, 1.8 Hz, 1 H), 7.38 - 7.47 (m, 2 H), 7.71 (d, J = 1.9 Hz, 1 H).

Example 161 (2E)-N-[(butylamino)sulfonyl]-3-[5-(3-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

To a solution of (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide obtained in Example 159 (248 mg) in acetonitrile (2.5 mL) was added N-chlorosuccinimide (76 mg), and the mixture was stirred at room temperature for 24 hr. Ethyl acetate was added to the reaction mixture, and the organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 95:5 - 60:40, v/v). The obtained solid was crystallized from hexane-ethyl acetate, and then water-ethanol. The obtained crystals were purified by preparative HPLC (tool and preparative conditions were the same as those in Reference Example 97), and the eluate was concentrated. The obtained oil was dissolved in ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (43 mg, yield 16%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.2 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.29 - 1.44 (m, 2 H), 2.39 (s, 3 H), 2.78 (q, J = 6.8 Hz, 2 H), 3.50 (s, 3 H), 3.70 (s, 3 H), 6.10 (d, J = 16.3 Hz, 1 H), 6.52 (d, J = 1.9 Hz, 1 H), 6.95 (dd, J = 8.7, 1.9 Hz, 1 H), 7.03 (d, J = 15.9 Hz, 1 H), 7.44 - 7.59 (m, 1 H), 7.54 (d, J = 8.7 Hz, 1 H), 7.72 (s, 1 H), 11.33 (s, 1 H)

Example 162 (2E)-N-[(butylamino)sulfonyl]-3-{1,3-dimethyl-5-[6-(2-oxopropoxy)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylamide

To a solution of ethyl (2E)-3-{1,3-dimethyl-5-[6-(2-oxopropoxy)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylate obtained in Reference Example 157 (2.25 g) in a mixed solvent of tetrahydrofuran (10 mL) and ethanol (10 mL) was added a 1N aqueous sodium hydroxide solution (12 mL), and the mixture was stirred with heating at 50°C for 5 hr. The reaction mixture was allowed to cool to room temperature, and concentrated under reduced pressure. The residue was neutralized with an aqueous solution (10 mL) of potassium hydrogensulfate (1.6 g), and the precipitated crystals were collected by filtration. The obtained crystals were dissolved in ethyl acetate and tetrahydrofuran, and the solution was dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (methanol-ethyl acetate 5:95, v/v) to give a pale-yellow amorphous solid.

The obtained amorphous solid was dissolved in acetonitrile (40 mL), 2-methyl-6-nitrobenzoic anhydride (1.68 g), N-butylsulfamide obtained in Reference Example 111 (651 mg), triethylamine (1.23 g) and 4-dimethylaminopyridine (497 mg) were added, and the mixture was stirred at room temperature for 48 hr. A saturated aqueous ammonium chloride solution (20 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 35:65, v/v), and crystallized from hexane-ethyl acetate to give the title compound (245 mg, yield 85%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.2 Hz, 3 H), 1.23 - 1.37 (m, 2 H), 1.40 - 1.51 (m, 2 H), 2.26 (s, 3 H), 2.45 (s, 3 H), 2.93 (d, J = 6.6 Hz, 2 H), 3.54 (s, 3 H), 4.53 (s, 2 H), 5.02 (br s, 1 H), 5.27 (d, J = 15.8 Hz, 1 H), 6.39 - 6.43 (m, 1 H), 6.76 (d, J = 3.0 Hz, 1 H), 6.91 (dd, J = 8.6, 2.2 Hz, 1 H), 6.98 (d, J = 3.2 Hz, 1 H), 7.44 (d, J = 15.8 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 1 H).

Example 163 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(3-hydroxy-3-methylbutyl)amino]sulfonyl}acrylamide

To a solution of ethyl N-[({(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}amino)sulfonyl]-β-alaninate obtained in Example 143 (380 mg) in tetrahydrofuran (8 mL) was added methylmagnesium bromide (1M diethyl ether solution, 5 mL) with stirring, and the mixture was stirred at room temperature for 16 hr. A saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 35:65, v/v) to give the title compound (130 mg, yield 35%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.19 (d, J = 2.7 Hz, 6 H), 1.65 (t, J = 6.6 Hz, 2 H), 2.43 (s, 3 H), 3.09 - 3.18 (m, 2 H), 3.52 (s, 3 H), 5.28 - 5.35 (m, 1 H), 6.03 (br s, 1 H), 6.78 (d, J = 2.7 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Example 164 (2E)-N-[(butylamino)sulfonyl]-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 159 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.42 (s, 3 H), 2.91 (q, J = 6.7 Hz, 2 H), 3.42 (s, 3 H), 3.53 (s, 3 H), 3.68 - 3.78 (m, 2 H), 4.02 - 4.10 (m, 2 H), 5.05 (br s, 1 H), 5.26 (d, J = 15.8 Hz, 1 H), 6.46 (d, J = 1.3 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.88 -

6.98 (m, 2 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.91 (br s, 1 H).

Example 165 (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{5-[6-(2-methoxyethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 159 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.3 Hz, 3 H), 1.46 - 1.54 (m, 2 H), 2.43 (s, 3 H), 2.89 (q, J = 6.8 Hz, 2 H), 3.43 (s, 3 H), 3.54 (s, 3 H), 3.70 - 3.75 (m, 2 H), 4.03 - 4.11 (m, 2 H), 5.03 (br s, 1 H), 5.20 (d, J = 15.8 Hz, 1 H), 6.46 (d, J = 1.7 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.91 - 6.97 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.70 (br s, 1 H).

Example 166 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

To a solution of (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide obtained in Example 159 (1.65 g) in dichloromethane (30 mL) was added dropwise boron tribromide (1M dichloromethane solution, 7.4 mL) with stirring at -78°C, and the mixture was stirred at -78°C for 1 hr, and then at room temperature for 17 hr. The reaction mixture was quenched with methanol (10 mL), and concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethanol to give the title compound (1.44 g, yield 91%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.80 (t, J = 7.3 Hz, 3 H), 1.16 - 1.29 (m, 2 H), 1.31 - 1.42 (m, 2 H), 2.39 (s, 3 H), 2.80 (q, J = 6.8

Hz, 2 H), 3.46 (s, 3 H), 6.15 (d, J = 16.0 Hz, 1 H), 6.30 (d, J = 1.9 Hz, 1 H), 6.67 - 6.72 (m, 1 H), 7.02 (d, J = 16.0 Hz, 1 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.45 - 7.55 (m, 2 H), 9.22 (s, 1 H), 11.32 (s, 1 H).

Example 167 (2E)-N-[(butylamino)sulfonyl]-3-{5-[6-(cyclopropylmethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{5-[6-(cyclopropylmethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 161 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.33 (d, J = 4.7 Hz, 2 H), 0.63 (d, J = 7.3 Hz, 2 H), 0.87 (t, J = 7.2 Hz, 3 H), 1.20 - 1.37 (m, 3 H), 1.45 (d, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.85 - 2.97 (m, 2 H), 3.54 (s, 3 H), 3.74 (d, J = 6.8 Hz, 2 H), 5.02 (br s, 1 H), 5.23 (d, J = 15.8 Hz, 1 H), 6.40 (s, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.87 - 6.97 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.5 Hz, 1 H), 7.72 (br s, 1 H).

Example 168 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 163 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.14 (d, J = 4.7 Hz, 2 H), 0.45 - 0.53 (m, 2 H), 0.86 - 0.98 (m, 1 H), 1.27 - 1.32 (m, 6 H), 2.43 (s, 3 H), 2.80 (t, J = 6.2 Hz, 2 H), 3.55 (s, 3 H), 4.43 - 4.54 (m, 1 H), 5.18 - 5.25 (m, 2 H), 6.42 (d, J = 1.9 Hz, 1 H), 6.72 - 6.75 (m, 1 H), 6.88 (dd, J = 8.7, 2.1 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 15.8 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H).

Example 169 1-[4-((1E)-3-{[(butylamino)sulfonyl]amino}-3-oxoprop-1-en-1-yl)-1,3-dimethyl-1H-pyrazol-5-yl]-1H-indol-6-yl

methanesulfonate

To a solution of (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-hydroxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide obtained in Example 166 (335 mg) in tetrahydrofuran (2 ml) were added triethylamine (118 mg) and methanesulfonyl chloride (124 mg), and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from diethyl ether-ethanol to give the title compound (284 mg, yield 72%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.2 Hz, 3 H), 1.24 - 1.38 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.42 (s, 3 H), 2.94 (q, J = 6.4 Hz, 2 H), 3.15 (s, 3 H), 3.57 (s, 3 H), 5.15 (t, J = 6.1 Hz, 1 H), 5.48 (d, J = 15.9 Hz, 1 H), 6.85 (d, J = 2.7 Hz, 1 H), 7.01 (d, J = 1.5 Hz, 1 H), 7.12 - 7.18 (m, 2 H), 7.34 (d, J = 15.9 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 1 H), 8.24 (br s, 1 H).

Example 170 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-isopropoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 163 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.3 Hz, 3 H), 1.25 - 1.38 (m, 8 H), 1.42 - 1.53 (m, 2 H), 2.43 (s, 3 H), 2.91 (q, J = 6.8 Hz, 2 H), 3.55 (s, 3 H), 4.43 - 4.54 (m, 1 H), 5.00 - 5.08 (m, 1 H), 5.25 (d, J = 15.8 Hz, 1 H), 6.43 (d, J = 1.9 Hz, 1 H), 6.74 (d, J = 3.2 Hz, 1 H), 6.88 (dd, J = 8.6, 2.2 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 15.8 Hz, 1 H).

Example 171 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propoxyamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and N-propoxysulfamide obtained in Reference Example 165.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.3 Hz, 3 H), 1.58 - 1.64 (m, 2 H), 2.44 (s, 3 H), 3.53 (s, 3 H), 3.88 (t, J = 6.8 Hz, 2 H), 5.28 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.20 - 7.25 (m, 1 H), 7.46 (d, J = 15.8 Hz, 1 H), 7.72 (d, J = 1.5 Hz, 1 H), 7.81 (br s, 1 H).

Example 172 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[5-(6-ethoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-ethoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 167 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.11 - 0.17 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.86 - 0.98 (m, 1 H), 1.39 (t, J = 7.0 Hz, 3 H), 2.44 (s, 3 H), 2.80 (t, J = 6.4 Hz, 2 H), 3.55 (s, 3 H), 3.96 (q, J = 7.0 Hz, 2 H), 5.13 - 5.24 (m, 2 H), 6.40 (d, J = 1.7 Hz, 1 H), 6.74 (d, J = 3.4 Hz, 1 H), 6.86 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.68 (br s, 1 H).

Example 173 (2E)-N-[(butylamino)sulfonyl]-3-{5-[6-(2-methoxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{5-[6-(2-methoxy-1-methylethoxy)-1H-indol-1-yl]-1,3-dimethyl-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 172 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 5 H), 1.41 - 1.53 (m, 2 H), 2.42 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.37 (d, J = 0.9 Hz, 3 H), 3.42 - 3.60 (m, 5 H), 4.43

- 4.54 (m, 1 H), 5.04 (br s, 1 H), 5.25 (dd, J = 15.8, 2.8 Hz, 1 H), 6.50 (d, J = 1.7 Hz, 1 H), 6.73 (d, J = 3.0 Hz, 1 H), 6.89 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.88 (br s, 1 H).

Example 174 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 175 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.11 - 0.17 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.86 - 0.96 (m, 1 H), 2.43 (s, 3 H), 2.48 (s, 3 H), 2.80 (t, J = 6.5 Hz, 2 H), 3.54 (s, 3 H), 5.10 - 5.21 (m, 2 H), 6.73 - 6.76 (m, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 7.02 (d, J = 3.4 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.52 (s, 1 H).

Example 175 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-indol-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 175 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.2 Hz, 3 H), 1.25 - 1.37 (m, 2 H), 1.45 (d, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 2.48 (s, 3 H), 2.90 (q, J = 6.3 Hz, 2 H), 3.53 (s, 3 H), 5.04 (br s, 1 H), 5.22 (d, J = 15.8 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 7.02 (d, J = 3.0 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.51 (s, 1 H), 7.75 (br s, 1 H).

Example 176 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-ethoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-ethoxy-1H-indol-1-yl)-

1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 167 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 (t, J = 7.3 Hz, 3 H), 1.24 - 1.52 (m, 7 H), 2.43 (s, 3 H), 2.91 (q, J = 6.6 Hz, 2 H), 3.54 (s, 3 H), 3.96 (q, J = 7.0 Hz, 2 H), 5.00 - 5.10 (m, 1 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.40 (s, 1 H), 6.74 (d, J = 3.0 Hz, 1 H), 6.85 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.84 (br s, 1 H).

Example 177 (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 42 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.3 Hz, 3 H), 1.44 - 1.55 (m, 2 H), 2.47 (s, 3 H), 2.87 (q, J = 6.8 Hz, 2 H), 3.54 (s, 3 H), 5.09 - 5.17 (m, 1 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.22 - 7.27 (m, 2 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.48 - 7.53 (m, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Example 178 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(cyclohexylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and N-cyclohexylsulfamide obtained in Reference Example 114.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.01 - 1.20 (m, 5 H), 1.42 - 1.52 (m, 1 H), 1.57 - 1.74 (m, 4 H), 2.38 (s, 3 H), 3.01 (br s, 1 H), 3.48 (s, 3 H), 6.01 (d, J = 16.0 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.56 (br s, 1 H), 7.83 (d, J = 3.6 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H), 8.32 (d, J = 2.1 Hz, 1 H), 11.27 (s, 1 H).

Example 179 (2E)-N-[(butylamino)sulfonyl]-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 42 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.3 Hz, 3 H), 1.23 - 1.37 (m, 2 H), 1.40 - 1.52 (m, 2 H), 2.46 (s, 3 H), 2.90 (q, J = 6.7 Hz, 2 H), 3.54 (s, 3 H), 5.04 - 5.13 (m, 1 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.91 (d, J = 3.2 Hz, 1 H), 7.22 - 7.28 (m, 2 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Example 180 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 42 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.16 (m, 2 H), 0.42 - 0.52 (m, 2 H), 0.83 - 0.98 (m, 1 H), 2.47 (s, 3 H), 2.75 - 2.86 (m, 2 H), 3.54 (s, 3 H), 5.18 - 5.29 (m, 2 H), 6.91 (d, J = 3.4 Hz, 1 H), 7.22 - 7.27 (m, 2 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Example 181 (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 25 and N-propylsulfamide obtained in Reference Example 127.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.93 (m, 3 H), 1.45 - 1.56 (m, 2 H), 2.45 (s, 3 H), 2.85 - 2.94 (m, 2 H), 3.54 (s, 3 H), 5.09 (br

s, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.82 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.5, 1.9 Hz, 1 H), 7.42 (d, J = 15.6 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H).

Example 182 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(piperidin-1-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and piperidine-1-sulfonamide obtained in Reference Example 177.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.50 (br s, 2 H), 1.56 - 1.63 (m, 4 H), 2.43 (s, 3 H), 3.22 - 3.30 (m, 4 H), 3.52 (s, 3 H), 5.37 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 2.6 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.35 - 7.46 (m, 2 H), 7.68 (br s, 1 H).

Example 183 (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 25 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.12 - 0.18 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.84 - 0.98 (m, 1 H), 2.44 (s, 3 H), 2.78 - 2.86 (m, 2 H), 3.54 (s, 3 H), 5.18 - 5.27 (m, 2 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.97 (s, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.5, 1.7 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H).

Example 184 (2E)-N-[(butylamino)sulfonyl]-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 25 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.91 (m, 3 H), 1.24 - 1.38 (m, 2 H), 1.41 - 1.53 (m, 2 H), 2.44 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.54 (s, 3 H), 5.10 (br s, 1 H), 5.27 (d, J = 15.8 Hz, 1 H), 6.81 (dd, J = 3.3, 0.8 Hz, 1 H), 6.96 - 6.99 (m, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.23 (dd, J = 8.4, 1.8 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 1 H).

Example 185 (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(piperidin-1-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 and piperidine-1-sulfonamide obtained in Reference Example 177.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.48 - 1.55 (m, 2 H), 1.56 - 1.65 (m, 4 H), 2.43 (s, 3 H), 3.25 (t, J = 5.2 Hz, 4 H), 3.51 (s, 3 H), 5.38 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 2.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.66 - 7.73 (m, 2 H).

Example 186 butyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

To a solution of butanol (88.2 mg) in N,N-dimethylformamide (10 mL) was added N,N'-carbonyldiimidazole (209 mg), and the mixture was stirred at 60°C for 1 hr. 2-[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179 (350 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (226 mg) and 4-dimethylaminopyridine (181 mg) were added to the reaction mixture, and the mixture was stirred at 60°C for 20 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 50:50, v/v), and crystallized from hexane-ethyl acetate to give the

title compound (299 mg, yield 67%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (t, J = 7.4 Hz, 3 H), 1.22 - 1.41 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.46 (s, 3 H), 4.05 (t, J = 6.8 Hz, 2 H), 6.70 (d, J = 3.4 Hz, 1 H), 6.89 - 6.94 (m, 2 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 187 3,3,3-trifluoropropyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 3,3,3-trifluoropropan-1-ol and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.20 (s, 3 H), 2.38 - 2.47 (m, 1 H), 2.54 - 2.72 (m, 3 H), 3.21 - 3.29 (m, 2 H), 3.38 (s, 3 H), 4.19 (t, J = 5.9 Hz, 2 H), 6.77 (d, J = 3.2 Hz, 1 H), 7.04 (d, J = 8.9 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.59 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 11.69 (br s, 1 H).

Example 188 butyl ({2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 181, butanol and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.93 (t, J = 7.3 Hz, 3 H), 1.25 - 1.41 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.90 (m, 2 H), 3.32 (t, J = 7.9 Hz, 2 H), 3.47 (s, 3 H), 4.07 (t, J = 6.7 Hz, 2 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.5, 1.9 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Example 189 cyclopropylmethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

To a solution of cyclopropylmethanol (78.4 mg) in N,N-dimethylformamide (9 mL) was added N,N'-carbonyldiimidazole (191

mg), and the mixture was stirred at 60°C for 1 hr. 2-[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179 (320 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (207 mg) and 4-dimethylaminopyridine (166 mg) were added to this reaction mixture, and the mixture was stirred at 60°C for 20 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 45:55, v/v), and crystallized from hexane-ethyl acetate to give the title compound (182 mg, yield 45%) as colorless crystals.
melting point 169.8-170.4°C.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.24 - 0.30 (m, 2 H), 0.54 - 0.62 (m, 2 H), 0.98 - 1.11 (m, 1 H), 2.32 (s, 3 H), 2.66 - 2.87 (m, 2 H), 3.32 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 3.87 (d, J = 7.3 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.25 - 7.27 (m, 1 H), 7.66 (d, J = 2.1 Hz, 1 H).

Example 190 butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184, butanol and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (t, J = 7.3 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.53 - 1.64 (m, 2 H), 2.31 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.11 - 3.20 (m, 1 H), 3.36 (s, 3 H), 3.90 - 4.04 (m, 2 H), 4.06 - 4.18 (m, 1 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.1 Hz, 1 H), 8.28 (d, J = 2.1 Hz, 1 H), 10.57 (br s, 1 H).

Example 191 butyl ({(E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]vinyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from (E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 178, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.4 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.50 - 1.62 (m, 2 H), 2.45 (s, 3 H), 3.54 (s, 3 H), 4.00 - 4.15 (m, 2 H), 5.86 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Example 192 butyl ({2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 186, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.96 (m, 3 H), 1.25 - 1.40 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H), 2.66 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 4.06 (t, J = 6.6 Hz, 2 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.95 - 7.03 (m, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.34 (dd, J = 9.1, 2.3 Hz, 1 H).

Example 193 propyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, propanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.4 Hz, 3 H), 1.53 - 1.67 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.46 (s, 3 H), 4.01 (t, J = 6.7 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 194 butyl ({2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-

1-yl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 188, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.4 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.53 - 1.64 (m, 2 H), 2.32 (s, 3 H), 2.79 - 2.87 (m, 2 H), 3.08 - 3.18 (m, 1 H), 3.34 (s, 3 H), 3.87 - 3.98 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.74 (d, J = 3.8 Hz, 1 H), 7.11 (d, J = 3.8 Hz, 1 H), 7.22 - 7.28 (m, 1 H), 8.07 (dd, J = 8.0, 1.5 Hz, 1 H), 8.31 (dd, J = 4.9, 1.5 Hz, 1 H), 11.71 (br s, 1 H).

Example 195 isobutyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 2-methylpropan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (d, J = 6.8 Hz, 6 H), 1.79 - 1.92 (m, 1 H), 2.31 (s, 3 H), 2.65 - 2.88 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.83 (d, J = 6.8 Hz, 2 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 196 butyl ({2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 190, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.41 (m, 2 H), 1.50 - 1.62 (m, 2 H), 2.32 (s, 3 H), 2.67 - 2.89 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.48 (s, 3 H), 3.78 (s, 3 H), 4.05 (t, J = 6.7 Hz, 2 H), 6.43 (d, J = 2.3 Hz, 1 H), 6.64 - 6.68 (m, 1 H), 6.86 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H).

Example 197 butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

To a solution of butanol (109 mg) in N,N-dimethylformamide (10 mL) was added N,N'-carbonyldiimidazole (254 mg), and the mixture was stirred at 60°C for 1 hr. 2-[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 193 (400 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (209 mg) and 4-dimethylaminopyridine (168 mg) were added to this reaction mixture, and the mixture was stirred at 60°C for 22 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v), and crystallized from hexane-ethyl acetate to give the title compound (150 mg, yield 30%) as colorless crystals.
melting point 136.1-137.3°C.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.95 (t, J = 7.2 Hz, 3 H), 1.30 - 1.44 (m, 2 H), 1.54 - 1.66 (m, 2 H), 2.87 - 3.08 (m, 2 H), 3.21 - 3.31 (m, 1 H), 3.54 (s, 3 H), 3.83 - 3.96 (m, 1 H), 4.08 (t, J = 6.6 Hz, 2 H), 6.76 (d, J = 3.4 Hz, 1 H), 7.21 (d, J = 3.8 Hz, 1 H), 8.06 (d, J = 2.3 Hz, 1 H), 8.30 (d, J = 2.3 Hz, 1 H), 9.32 (br s, 1 H).

Example 198 butyl [(2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 195, butanol and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.34 (s, 3 H), 2.64 - 2.76 (m, 1

H), 2.79 - 2.91 (m, 1 H), 3.33 (t, J = 7.9 Hz, 2 H), 3.47 (s, 3 H), 4.06 (t, J = 6.7 Hz, 2 H), 6.83 (dd, J = 3.3, 0.8 Hz, 1 H), 7.24 - 7.28 (m, 2 H), 7.47 (dd, J = 8.3, 0.9 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H).

Example 199 N-({(E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]vinyl}sulfonyl)hexanamide

A mixture of (E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 178 (213 mg), hexanoic acid (74.1 mg), 2-methyl-6-nitrobenzoic anhydride (251 mg), triethylamine (184 mg), 4-dimethylaminopyridine (74.3 mg) and acetonitrile (6 mL) was stirred at room temperature for 24 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (198 mg, yield 73%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 6.9 Hz, 3 H), 1.20 - 1.35 (m, 4 H), 1.49 - 1.62 (m, 2 H), 2.14 (t, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 3.55 (s, 3 H), 5.79 (d, J = 15.6 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.35 (d, J = 15.6 Hz, 1 H), 7.61 (br s, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Example 200 N-({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)hexanamide

By a method similar to that in Example 199, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179 and hexanoic acid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 6.9 Hz, 3 H), 1.17 - 1.34 (m, 4 H), 1.42 - 1.55 (m, 2 H), 1.98 - 2.06 (m, 2 H), 2.30 (s, 3 H), 2.58 - 2.70 (m, 1 H), 2.71 - 2.84 (m, 1 H), 3.33 (t, J = 7.7

Hz, 2 H), 3.46 (s, 3 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Example 201 N-({2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethyl}sulfonyl)hexanamide

By a method similar to that in Example 199, the title compound was obtained from 2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 188 and hexanoic acid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.93 (m, 3 H), 1.23 - 1.39 (m, 4 H), 1.53 - 1.66 (m, 2 H), 1.81 - 1.92 (m, 1 H), 2.03 - 2.16 (m, 1 H), 2.29 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.07 - 3.16 (m, 1 H), 3.36 (s, 3 H), 3.98 - 4.14 (m, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.13 (d, J = 3.6 Hz, 1 H), 7.25 - 7.30 (m, 1 H), 8.10 (dd, J = 7.9, 1.5 Hz, 1 H), 8.29 (dd, J = 4.9, 1.5 Hz, 1 H), 11.49 (br s, 1 H).

Example 202 N-({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)hexanamide

By a method similar to that in Example 199, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184 and hexanoic acid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 6.8 Hz, 3 H), 1.23 - 1.39 (m, 4 H), 1.52 - 1.65 (m, 2 H), 1.80 - 1.92 (m, 1 H), 2.00 - 2.13 (m, 1 H), 2.28 (s, 3 H), 2.80 - 2.87 (m, 2 H), 3.09 - 3.19 (m, 1 H), 3.38 (s, 3 H), 3.95 - 4.12 (m, 1 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 8.07 (d, J = 2.1 Hz, 1 H), 8.26 (d, J = 2.3 Hz, 1 H), 10.61 (br s, 1 H).

Example 203 butyl {(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}sulfamate

A mixture of (2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 38 (342 mg), 2-methyl-6-nitrobenzoic anhydride (448 mg), butyl sulfamate obtained in Reference Example 196 (174 mg), triethylamine (329 mg), 4-dimethylaminopyridine (132 mg) and

acetonitrile (10 mL) was stirred at room temperature for 16 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 40:60, v/v) to give the title compound (187 mg, yield 38%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.4 Hz, 3 H), 1.28 - 1.43 (m, 2 H), 1.59 - 1.70 (m, 2 H), 2.44 (s, 3 H), 3.52 (s, 3 H), 4.26 (t, J = 6.6 Hz, 2 H), 5.56 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.47 (d, J = 15.9 Hz, 1 H), 7.70 (d, J = 1.5 Hz, 1 H).

Example 204 butyl {(2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}sulfamate

By a method similar to that in Example 203, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 133 and butyl sulfamate obtained in Reference Example 196.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.82 (t, J = 7.2 Hz, 3 H), 1.20 - 1.33 (m, 2 H), 1.50 - 1.63 (m, 2 H), 2.39 (s, 3 H), 3.51 (s, 3 H), 4.16 (t, J = 5.9 Hz, 2 H), 6.06 (d, J = 16.3 Hz, 1 H), 7.08 (d, J = 15.9 Hz, 1 H), 7.37 - 7.45 (m, 1 H), 8.07 (s, 1 H), 8.18 (d, J = 7.2 Hz, 1 H), 8.38 (d, J = 3.0 Hz, 1 H), 12.07 (br s, 1 H).

Example 205 butyl {(2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}sulfamate

By a method similar to that in Example 203, the title compound was obtained from (2E)-3-[5-(5-cyano-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 81 and butyl sulfamate obtained in Reference Example 196.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.3 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 1.59 - 1.71 (m, 2 H), 2.46 (s, 3 H), 3.52 (s, 3 H),

4.28 (t, J = 6.6 Hz, 2 H), 5.68 (d, J = 15.8 Hz, 1 H), 6.90 - 6.94 (m, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 7.24 (d, J = 3.4 Hz, 1 H), 7.42 (d, J = 15.6 Hz, 1 H), 7.47 - 7.52 (m, 1 H), 8.07 (d, J = 0.8 Hz, 1 H), 8.26 (br s, 1 H).

Example 206 butyl {(2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}sulfamate

By a method similar to that in Example 203, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and butyl sulfamate obtained in Reference Example 196.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.3 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.59 - 1.71 (m, 2 H), 2.44 (s, 3 H), 3.52 (s, 3 H), 4.27 (t, J = 6.5 Hz, 2 H), 5.56 (d, J = 15.8 Hz, 1 H), 6.77 - 6.80 (m, 1 H), 6.87 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.37 (dd, J = 9.0, 2.4 Hz, 1 H), 7.47 (d, J = 15.8 Hz, 1 H), 7.93 (br s, 1 H).

Example 207 N-[({[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}amino)sulfonyl]hexanamide

A mixture of N-{[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]methyl}sulfamide obtained in Reference Example 197 (63.3 mg), 2-methyl-6-nitrobenzoic anhydride (70.4 mg), hexanoic acid (19.7 mg), triethylamine (51.7 mg), 4-dimethylaminopyridine (20.8 mg) and acetonitrile (2 mL) was stirred at room temperature for 48 hr. A saturated aqueous ammonium chloride solution (5 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 50:50, v/v) to give the title compound (53.3 mg, yield 66%) as colorless crystals.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 6.8 Hz, 3 H), 1.15 - 1.33 (m, 4 H), 1.39 - 1.51 (m, 2 H), 1.96 - 2.07 (m, 2 H), 2.35 (s, 3 H), 3.47 (s, 3 H), 3.63 - 3.94 (m, 2 H), 5.15 (br s, 1 H), 6.69 (d, J = 2.7 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.15 - 7.24 (m,

2 H), 7.62 - 7.78 (m, 2 H)..

Example 208 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(2,2,2-trifluoroethyl)amino]carbonyl}ethanesulfonamide

To a solution of 2,2,2-trifluoroethanamine (134 mg) in N,N-dimethylformamide (11 mL) was added N,N'-carbonyldiimidazole (238 mg), and the mixture was stirred at 60°C for 1 hr. 2-[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179 (400 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (241 mg) and 4-dimethylaminopyridine (193 mg) were added to the reaction mixture, and the mixture was stirred at 60°C for 16 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 30:70, v/v), and crystallized from hexane-ethyl acetate to give the title compound (207 mg, yield 38 %) as colorless crystals.
^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.18 (s, 3 H), 2.37 - 2.47 (m, 1 H), 2.54 - 2.65 (m, 1 H), 3.23 - 3.30 (m, 2 H), 3.37 (s, 3 H), 3.73 - 3.88 (m, 2 H), 6.77 (d, J = 2.6 Hz, 1 H), 6.98 - 7.07 (m, 2 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 10.48 (br s, 1 H).

Example 209 N-[(butylamino)carbonyl]-2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 181, butylamine and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.95 (m, 3 H), 1.23 - 1.34 (m, 2 H), 1.35 - 1.49 (m, 2 H), 2.31 (s, 3 H), 2.68 - 2.90 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.17 (br s, 1 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 (d, J = 0.8 Hz, 1 H), 7.08 (d, J =

3.4 Hz, 1 H), 7.19 (dd, J = 8.5, 1.7 Hz, 1 H), 7.59 - 7.63 (m, 1 H).

Example 210 N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.2 Hz, 3 H), 1.22 - 1.35 (m, 2 H), 1.36 - 1.48 (m, 2 H), 2.30 (s, 3 H), 2.69 - 2.89 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.47 (s, 3 H), 6.13 (br s, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (1 H, d, J = 3.4 Hz), 7.20 (dd, J = 8.8, 1.8 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Example 211 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, cyclopropylmethylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.12 - 0.19 (m, 2 H), 0.44 - 0.52 (m, 2 H), 0.79 - 0.91 (m, 1 H), 2.30 (s, 3 H), 2.73 - 2.89 (m, 2 H), 2.93 - 3.10 (m, 4 H), 3.47 (s, 3 H), 6.21 (br s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Example 212 (E)-N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide

By a method similar to that in Example 208, the title compound was obtained from (E)-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethylenesulfonamide obtained in Reference Example 178, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.2 Hz, 3 H), 1.22 - 1.31 (m, 2 H), 1.33 - 1.43 (m, 2 H), 2.43 (s, 3 H), 3.03 - 3.21 (m, 2 H), 3.54 (s, 3 H), 5.85 (d, J = 15.6 Hz, 1 H), 6.18 (br s, 1 H),

6.78 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.16 (d, J = 15.4 Hz, 1 H), 7.23 (dd, J = 8.9, 1.9 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Example 213 N-[(butylamino)carbonyl]-2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 188, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (t, J = 7.2 Hz, 3 H), 1.25 - 1.37 (m, 2 H), 1.39 - 1.51 (m, 2 H), 2.33 (s, 3 H), 2.79 - 2.89 (m, 2 H), 2.95 - 3.07 (m, 1 H), 3.11 - 3.25 (m, 2 H), 3.38 (s, 3 H), 3.92 (br s, 1 H), 5.39 - 5.49 (m, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.15 (d, J = 3.6 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 8.10 (dd, J = 7.8, 1.4 Hz, 1 H), 8.29 - 8.33 (m, 1 H).

Example 214 N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.96 (m, 3 H), 1.25 - 1.37 (m, 2 H), 1.40 - 1.52 (m, 2 H), 2.31 (s, 3 H), 2.77 - 2.88 (m, 2 H), 3.04 - 3.25 (m, 3 H), 3.42 (s, 3 H), 3.75 (br s, 1 H), 5.54 (br s, 1 H), 6.71 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 8.05 (d, J = 2.1 Hz, 1 H), 8.27 (d, J = 2.1 Hz, 1 H).

Example 215 N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 193,

butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.2 Hz, 3 H), 1.24 - 1.39 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.84 - 3.05 (m, 2 H), 3.10 - 3.21 (m, 2 H), 3.30 (br s, 1 H), 3.49 - 3.63 (m, 4 H), 6.05 (br s, 1 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.23 (d, J = 3.8 Hz, 1 H), 8.05 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H).

Example 216 N-[(butylamino)carbonyl]-2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 190, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 - 0.94 (m, 3 H), 1.24 - 1.34 (m, 2 H), 1.35 - 1.48 (m, 2 H), 2.31 (s, 3 H), 2.74 - 2.89 (m, 2 H), 3.00 - 3.16 (m, 4 H), 3.50 (s, 3 H), 3.78 (s, 3 H), 6.07 (br s, 1 H), 6.43 (d, J = 2.1 Hz, 1 H), 6.67 (dd, J = 3.2, 0.8 Hz, 1 H), 6.87 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H).

Example 217 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)carbonyl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, propylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.4 Hz, 3 H), 1.38 - 1.51 (m, 2 H), 2.30 (s, 3 H), 2.68 - 2.88 (m, 2 H), 2.99 - 3.12 (m, 4 H), 3.48 (s, 3 H), 6.15 (br s, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 218 N-[(butylamino)carbonyl]-2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 186, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.95 (m, 3 H), 1.23 - 1.48 (m, 4 H), 2.30 (s, 3 H), 2.68 - 2.89 (m, 2 H), 2.99 - 3.16 (m, 4 H), 3.48 (s, 3 H), 6.13 (br s, 1 H), 6.72 (d, J = 2.7 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 6.94 - 7.03 (m, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.34 (dd, J = 9.1, 2.3 Hz, 1 H).

Example 219 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(isobutylamino)carbonyl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, isobutylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (d, J = 6.6 Hz, 6 H), 1.67 (dd, J = 13.6, 6.6 Hz, 1 H), 2.30 (s, 3 H), 2.69 - 2.89 (m, 2 H), 2.95 (t, J = 6.4 Hz, 2 H), 2.99 - 3.11 (m, 2 H), 3.47 (s, 3 H), 6.22 (br s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.3 Hz, 1 H), 7.67 (d, J = 1.3 Hz, 1 H).

Example 220 N-[(butylamino)carbonyl]-2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-{1,3-dimethyl-5-[6-(trifluoromethyl)-1H-indol-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 195, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.94 (m, 3 H), 1.22 - 1.34 (m, 2 H), 1.36 - 1.47 (m, 2 H), 2.33 (s, 3 H), 2.66 - 2.78 (m, 1 H), 2.79 - 2.91 (m, 1 H), 2.98 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.16 (br s, 1 H), 6.83 (dd, J = 3.4, 0.8 Hz, 1 H), 7.23 - 7.28 (m, 2 H), 7.47 (dd, J = 8.3, 1.1 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H).

Example 221 propyl ({2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference

Example 181, propanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.4 Hz, 3 H), 1.54 - 1.67 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.90 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.02 (t, J = 6.8 Hz, 2 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.4, 1.8 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Example 222 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(3-methylbutyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 3-methylbutan-1-amine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (d, J = 6.6 Hz, 6 H), 1.33 (q, J = 7.0 Hz, 2 H), 1.50 - 1.63 (m, 1 H), 2.30 (s, 3 H), 2.70 - 2.89 (m, 2 H), 2.94 - 3.08 (m, 2 H), 3.09 - 3.20 (m, 2 H), 3.45 - 3.50 (m, 3 H), 6.09 (br s, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.8, 1.8 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 223 benzyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, benzyl alcohol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.26 (s, 3 H), 2.62 - 2.86 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.45 (s, 3 H), 5.07 (s, 2 H), 6.66 (dd, J = 3.3, 0.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.28 - 7.33 (m, 2 H), 7.36 - 7.40 (m, 3 H), 7.64 (d, J = 1.7 Hz, 1 H).

Example 224 2,2,2-trifluoroethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference

Example 179, 2,2,2-trifluoroethanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.29 (s, 3 H), 2.67 - 2.84 (m, 2 H), 3.26 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.32 - 4.43 (m, 2 H), 6.70 (dd, J = 3.3, 0.8 Hz, 1 H), 6.89 - 6.93 (m, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (t, J = 1.7 Hz, 1 H).

Example 225 N-[(butylamino)carbonyl]-2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 200, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.87 - 0.95 (m, 3 H), 1.22 - 1.48 (m, 4 H), 2.32 (s, 3 H), 2.68 - 2.93 (m, 2 H), 3.02 - 3.16 (m, 4 H), 3.49 (s, 3 H), 3.83 (s, 3 H), 6.10 (br s, 1 H), 6.46 (s, 1 H), 6.63 (d, J = 3.2 Hz, 1 H), 6.99 (d, J = 3.4 Hz, 1 H), 7.67 (s, 1 H).

Example 226 butyl ({2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 200, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.96 (m, 3 H), 1.27 - 1.40 (m, 2 H), 1.50 - 1.61 (m, 2 H), 2.33 (s, 3 H), 2.69 - 2.89 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 4.04 (t, J = 6.6 Hz, 2 H), 6.47 (s, 1 H), 6.63 (dd, J = 3.4, 0.8 Hz, 1 H), 6.99 (d, J = 3.2 Hz, 1 H), 7.67 (s, 1 H).

Example 227 (2E)-N-(butylsulfonyl)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 203 and butane-1-

sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (t, J = 7.3 Hz, 3 H), 1.35 - 1.49 (m, 2 H), 1.67 - 1.79 (m, 2 H), 2.43 (s, 3 H), 3.34 - 3.42 (m, 2 H), 3.57 (s, 3 H), 5.64 (d, J = 15.8 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Example 228 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(propylamino)carbonyl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 181, propylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.3 Hz, 3 H), 1.38 - 1.52 (m, 2 H), 2.31 (s, 3 H), 2.68 - 2.91 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.20 (br s, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.97 (d, J = 0.9 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.4, 1.8 Hz, 1 H), 7.58 - 7.63 (m, 1 H).

Example 229 cyclopropylmethyl ({2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 181, cyclopropylmethanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.23 - 0.30 (m, 2 H), 0.53 - 0.61 (m, 2 H), 0.99 - 1.12 (m, 1 H), 2.32 (s, 3 H), 2.65 - 2.91 (m, 2 H), 3.34 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.89 (d, J = 7.3 Hz, 2 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.98 (s, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Example 230 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(2,2-dimethylpropyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference

Example 179, 2,2-dimethylpropan-1-amine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.85 (s, 9 H), 2.30 (s, 3 H), 2.69 - 2.86 (m, 2 H), 2.91 - 2.95 (m, 2 H), 2.98 - 3.12 (m, 2 H), 3.47 (s, 3 H), 6.29 (br s, 1 H), 6.70 (dd, J = 3.3, 0.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 231 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(piperidin-1-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and piperidine-1-sulfonamide obtained in Reference Example 177.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.21 - 1.27 (m, 1 H), 1.47 - 1.54 (m, 2 H), 1.57 - 1.65 (m, 3 H), 2.43 (s, 3 H), 3.23 - 3.30 (m, 4 H), 3.58 (s, 3 H), 5.60 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.22 (d, J = 3.6 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.1 Hz, 1 H).

Example 232 (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

A mixture of (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 206 (346 mg), 2-methyl-6-nitrobenzoic anhydride (483 mg), pentane-1-sulfonamide (185 mg), triethylamine (354 mg), 4-dimethylaminopyridine (142 mg) and acetonitrile (12 mL) was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and crystallized from diisopropyl ether-ethanol to give the title compound (448 mg, yield 89%) as colorless

crystals. melting point 211.1-212.9°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.25 - 1.44 (m, 4 H), 1.73 - 1.87 (m, 2 H), 2.30 (s, 3 H), 2.48 (s, 3 H), 3.38 - 3.47 (m, 2 H), 3.52 (s, 3 H), 5.53 (d, J = 15.6 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.11 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 15.8 Hz, 1 H), 7.81 (s, 1 H), 8.13 (d, J = 1.5 Hz, 1 H).

Example 233 3-methylbutyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 3-methylbutan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (d, J = 6.6 Hz, 6 H), 1.43 - 1.51 (m, 2 H), 1.58 - 1.70 (m, 1 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 4.08 (t, J = 6.9 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.9, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 234 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(6-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 181, cyclopropylmethylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.12 - 0.18 (m, 2 H), 0.42 - 0.51 (m, 2 H), 0.79 - 0.91 (m, 1 H), 2.30 (s, 3 H), 2.67 - 2.90 (m, 2 H), 2.98 (dd, J = 7.1, 5.6 Hz, 2 H), 3.03 - 3.19 (m, 2 H), 3.47 (s, 3 H), 6.27 (br s, 1 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 (d, J = 0.9 Hz, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 (d, J = 8.5 Hz, 1 H).

Example 235 cyclopropylmethyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title

compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184, cyclopropylmethanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.30 (t, J = 5.6 Hz, 2 H), 0.53 - 0.61 (m, 2 H), 1.02 - 1.15 (m, 1 H), 2.30 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.13 (br s, 1 H), 3.36 (s, 3 H), 3.71 - 3.82 (m, 1 H), 3.90 - 4.05 (m, 2 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.31 (d, J = 2.3 Hz, 1 H), 10.60 (br s, 1 H).

Example 236 4,4,4-trifluorobutyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 4,4,4-trifluorobutan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.79 - 1.92 (m, 2 H), 2.04 - 2.20 (m, 2 H), 2.31 (s, 3 H), 2.66 - 2.88 (m, 2 H), 3.28 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.08 (t, J = 6.4 Hz, 2 H), 6.70 (dd, J = 3.2, 0.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 237 isobutyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184, isobutanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (d, J = 6.8 Hz, 6 H), 1.82 - 1.97 (m, 1 H), 2.31 (s, 3 H), 2.79 - 2.88 (m, 2 H), 3.10 - 3.22 (m, 1 H), 3.34 (s, 3 H), 3.66 - 3.77 (m, 1 H), 3.85 - 4.10 (m, 2 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 10.52 (br s, 1 H).

Example 238 N-({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-

pyrazol-4-yl]ethyl}sulfonyl)piperidine-1-carboxamide

To a solution of butyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate obtained in Example 186 (347 mg) in toluene (8 mL) was added piperidine (196 mg), and the mixture was stirred at 90°C for 4 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 30:70, v/v) to give the title compound (118 mg, yield 33%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.45 - 1.65 (m, 6 H), 2.31 (s, 3 H), 2.61 - 2.86 (m, 2 H), 3.19 - 3.26 (m, 4 H), 3.41 - 3.53 (m, 5 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.15 - 7.21 (m, 2 H), 7.65 (d, J = 1.7 Hz, 1 H).

Example 239 propyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 184, propanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (t, J = 7.4 Hz, 3 H), 1.59 - 1.70 (m, 2 H), 2.31 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.10 - 3.21 (m, 1 H), 3.35 (s, 3 H), 3.86 - 4.11 (m, 3 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H), 10.60 (br s, 1 H).

Example 240 4,4,4-trifluorobutyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

obtained in Reference Example 184, 4,4,4-trifluorobutan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.84 - 1.96 (m, 2 H), 2.08 - 2.24 (m, 2 H), 2.30 (s, 3 H), 2.79 - 2.88 (m, 2 H), 3.18 (br s, 1 H), 3.34 (s, 3 H), 3.95 - 4.21 (m, 3 H), 6.71 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.05 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.1 Hz, 1 H), 10.88 (br s, 1 H).

Example 241 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(4,4,4-trifluorobutyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179, 4,4,4-trifluorobutan-1-amine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.66 - 1.79 (m, 2 H), 2.00 - 2.17 (m, 2 H), 2.30 (s, 3 H), 2.69 - 2.88 (m, 2 H), 2.94 - 3.09 (m, 2 H), 3.17 (q, J = 6.8 Hz, 2 H), 3.48 (s, 3 H), 6.21 (br s, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 242 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 206 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.3 Hz, 3 H), 1.27 - 1.41 (m, 2 H), 1.45 - 1.56 (m, 2 H), 2.30 (s, 3 H), 2.48 (s, 3 H), 3.03 (q, J = 6.7 Hz, 2 H), 3.51 (s, 3 H), 5.22 - 5.29 (m, 1 H), 5.45 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.8 Hz, 1 H), 7.33 (d, J = 15.8 Hz, 1 H), 7.81 (d, J = 1.1 Hz, 1 H), 8.12 (d, J = 1.3 Hz, 1 H).

Example 243 (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 215 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 (t, J = 7.2 Hz, 3 H), 1.30 - 1.48 (m, 4 H), 1.78 - 1.92 (m, 2 H), 2.13 (s, 3 H), 3.16 - 3.26 (m, 2 H), 3.45 - 3.54 (m, 2 H), 3.63 (s, 3 H), 3.76 - 3.94 (m, 2 H), 5.84 (d, J = 15.9 Hz, 1 H), 6.71 (dd, J = 7.2, 4.8 Hz, 1 H), 7.35 - 7.42 (m, 2 H), 7.88 (d, J = 4.8 Hz, 1 H), 10.63 (s, 1 H).

Example 244 (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 215 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.24 (s, 3 H), 2.37 (s, 3 H), 3.20 - 3.31 (m, 2 H), 3.52 (s, 3 H), 3.78 - 3.86 (m, 2 H), 6.17 (d, J = 15.8 Hz, 1 H), 6.67 (dd, J = 7.1, 5.2 Hz, 1 H), 7.18 (d, J = 15.8 Hz, 1 H), 7.40 (d, J = 8.1 Hz, 2 H), 7.50 (dd, J = 7.1, 1.2 Hz, 1 H), 7.71 - 7.75 (m, 1 H), 7.79 (d, J = 8.1 Hz, 2 H), 12.01 (s, 1 H).

Example 245 (2E)-N-[(butylamino)sulfonyl]-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 215 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.81 (t, J = 7.3 Hz, 3 H), 1.17 - 1.45 (m, 4 H), 2.28 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.22 - 3.38 (m, 2 H), 3.54 (s, 3 H), 3.81 - 3.89 (m, 2 H), 6.21 (d, J = 16.0 Hz, 1 H), 6.68 (dd, J = 7.2, 5.3 Hz, 1 H), 7.26 (d, J = 16.0 Hz, 1 H),

7.47 - 7.58 (m, 2 H), 7.74 - 7.78 (m, 1 H), 11.31 (s, 1 H).

Example 246 (2E)-N-[(butylamino)sulfonyl]-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 218 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.57 - 0.70 (m, 1 H), 0.75 - 0.98 (m, 6 H), 1.26 - 1.40 (m, 2 H), 1.42 - 1.56 (m, 2 H), 1.65 - 1.80 (m, 1 H), 2.96 - 3.03 (m, 2 H), 3.55 (s, 3 H), 5.11 - 5.18 (m, 1 H), 5.75 (d, J = 15.7 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.19 (d, J = 3.4 Hz, 1 H), 7.21 - 7.26 (m, 1 H), 7.38 (d, J = 15.7 Hz, 1 H), 8.06 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 - 8.35 (m, 1 H), 9.20 (br s, 1 H).

Example 247 (2E)-N-[(butylamino)sulfonyl]-3-[3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-cyclopropyl-5-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 221 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.45 - 0.58 (m, 1 H), 0.60 - 0.80 (m, 1 H), 0.82 - 0.88 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H), 1.32 - 1.46 (m, 2 H), 1.50 - 1.69 (m, 3 H), 3.08 - 3.18 (m, 2 H), 3.20 - 3.30 (m, 2 H), 3.64 (s, 3 H), 3.82 - 3.95 (m, 2 H), 5.25 - 5.32 (m, 1 H), 6.04 (d, J = 15.7 Hz, 1 H), 6.67 (dd, J = 7.3, 5.0 Hz, 1 H), 7.39 (d, J = 7.3 Hz, 1 H), 7.44 (d, J = 15.7 Hz, 1 H), 7.83 (d, J = 5.0 Hz, 1 H), 10.61 (br s, 1 H).

Example 248 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title

compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 13 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.14 - 0.20 (m, 2 H), 0.49 - 0.55 (m, 2 H), 0.88 - 1.02 (m, 1 H), 2.30 (s, 3 H), 2.86 - 2.91 (m, 2 H), 3.56 (s, 3 H), 5.32 (t, J = 5.9 Hz, 1 H), 5.47 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 8.0, 4.9 Hz, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 - 8.34 (m, 1 H), 8.77 (s, 1 H).

Example 249 (2E)-N-{[(cyclopropylmethyl)amino]sulfonyl}-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 60 and N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.10 - 0.17 (m, 2 H), 0.44 - 0.53 (m, 2 H), 0.83 - 0.92 (m, 1 H), 2.44 (s, 3 H), 2.80 (d, J = 6.5 Hz, 2 H), 3.55 (s, 3 H), 3.76 (s, 3 H), 5.14 - 5.20 (m, 2 H), 6.40 (d, J = 2.2 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.2 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.47 (d, J = 15.8 Hz, 1 H), 7.58 - 7.63 (m, 2 H).

Example 250 (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-3-(trifluoromethyl)-1H-pyrazol-4-yl]acrylic acid obtained in Example 230 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.71 - 1.84 (m, 2 H), 3.34 - 3.40 (m, 2 H), 3.70 (s, 3 H), 5.61 (d, J = 15.9 Hz, 1 H), 6.84 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.26 - 7.31 (m, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 8.06 - 8.10 (m, 1 H), 8.33 - 8.35 (m, 1 H), 8.40 (s, 1 H).

Example 251 (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 133 and 4-methylbenzenesulfonamide.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.36 (s, 3 H), 2.40 (s, 3 H), 3.55 (s, 3 H), 5.67 (d, J = 15.8 Hz, 1 H), 7.15 (s, 1 H), 7.23 - 7.34 (m, 4 H), 7.85 (d, J = 8.5 Hz, 2 H), 8.06 (dd, J = 7.9, 1.5 Hz, 1 H), 8.20 (br s, 1 H), 8.38 (dd, J = 4.7, 1.5 Hz, 1 H).

Example 252 (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 133 and pentane-1-sulfonamide:
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.1 Hz, 3 H), 1.25 - 1.46 (m, 4 H), 1.72 - 1.86 (m, 2 H), 2.36 (s, 3 H), 3.35 - 3.46 (m, 2 H), 3.54 (s, 3 H), 5.66 (d, J = 15.8 Hz, 1 H), 7.19 (s, 1 H), 7.29 - 7.40 (m, 2 H), 8.08 (dd, J = 7.9, 1.5 Hz, 1 H), 8.39 (dd, J = 4.8, 1.5 Hz, 1 H), 8.49 (s, 1 H).

Example 253 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[3,2-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 224 and pentane-1-sulfonamide.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 (t, J = 7.2 Hz, 3 H), 1.24 - 1.35 (m, 4 H), 1.65 - 1.75 (m, 2 H), 2.46 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.44 (s, 3 H), 5.54 (d, J = 16.1 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 6.1 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.68 (d, J = 16.1 Hz, 1 H), 8.06 (d, J = 6.1 Hz, 1 H), 8.24 (s, 1 H).

Example 254 (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-

yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 227 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.2 Hz, 3 H), 1.26 - 1.42 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.43 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.45 (s, 3 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.87 (d, J = 3.2 Hz, 1 H), 7.25 (d, J = 3.2 Hz, 1 H), 7.49 (d, J = 15.9 Hz, 1 H), 7.55 (d, J = 4.9 Hz, 1 H), 8.11 (d, J = 4.9 Hz, 1 H), 8.21 (s, 1 H).

Example 255 potassium {(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 254.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 - 0.83 (m, 3 H), 1.18 - 1.23 (m, 4 H), 1.37 - 1.46 (m, 2 H), 2.35 (s, 3 H), 2.81 - 2.88 (m, 2 H), 3.46 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 6.91 (d, J = 2.9 Hz, 1 H), 7.71 (dd, J = 5.4, 0.9 Hz, 1 H), 7.80 (d, J = 2.9 Hz, 1 H), 8.28 (d, J = 5.4 Hz, 1 H), 8.37 (s, 1 H).

Example 256 (2E)-N-[(butylamino)sulfonyl]-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-c]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 227 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.79 (t, J = 7.4 Hz, 3 H), 1.15 - 1.40 (m, 4 H), 2.40 (s, 3 H), 2.74 - 2.81 (m, 2 H), 3.51 (s, 3 H), 6.05 (d, J = 16.1 Hz, 1 H), 6.94 (d, J = 3.2 Hz, 1 H), 7.00 (d, J = 16.1 Hz, 1 H), 7.53 (t, J = 5.7 Hz, 1 H), 7.74 (d, J = 5.5

Hz, 1 H), 7.85 (d, J = 3.2 Hz, 1 H), 8.31 (d, J = 5.5 Hz, 1 H), 8.41 (s, 1 H), 11.31 (s, 1 H).

Example 257 sodium {(2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 28, the title compound was obtained from (2E)-3-[5-(6-methoxy-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 38.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 - 0.84 (m, 3 H), 1.18 - 1.24 (m, 4 H), 1.42 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.88 (m, 2 H), 3.42 (s, 3 H), 3.68 (s, 3 H), 5.61 (d, J = 15.9 Hz, 1 H), 6.43 (d, J = 1.9 Hz, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.75 - 6.84 (m, 2 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Example 258 (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(1-methyl-1H-imidazol-4-yl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(3-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 133 and 1-methyl-1H-imidazole-4-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.36 (s, 3 H), 3.48 (s, 3 H), 3.67 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.93 (d, J = 16.0 Hz, 1 H), 7.40 (dd, J = 7.9, 4.7 Hz, 1 H), 7.73 (d, J = 1.1 Hz, 1 H), 7.87 (d, J = 1.1 Hz, 1 H), 8.04 (s, 1 H), 8.16 (dd, J = 7.9, 1.5 Hz, 1 H), 8.36 (dd, J = 4.7, 1.5 Hz, 1 H), 11.87 (s, 1 H).

Example 259 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-methoxy-4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 21 and 2-methoxy-4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.35 (s, 3 H), 2.39 (s, 3 H), 3.48 (s, 3 H), 3.77 (s, 3 H), 5.59 (d, J = 15.8 Hz, 1 H), 6.70 (d, J = 3.4 Hz, 1 H), 6.74 (s, 1 H), 6.79 - 6.87 (m, 2 H), 6.90 - 7.00 (m, 1

H), 7.07 (d, J = 3.4 Hz, 1 H), 7.22 - 7.37 (m, 2 H), 7.76 (d, J = 8.1 Hz, 1 H), 8.26 (s, 1 H).

Example 260 (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-hydroxy-4-methylphenyl)sulfonyl]acrylamide

To a solution of (2E)-3-[5-(5-fluoro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-methoxy-4-methylphenyl)sulfonyl]acrylamide obtained in Example 259 (312 mg) in dichloromethane (30 mL) was added dropwise boron tribromide (1M dichloromethane solution, 1.3 mL) with stirring at -78°C, and the mixture was stirred at -78°C for 1 hr. The mixture was allowed to warm to room temperature, and stirred for 30 hr, and then heated under reflux for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 35:65, v/v), and crystallized from hexane-ethanol to give the title compound (220 mg, yield 72%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.32 (s, 3 H), 2.39 (s, 3 H), 3.50 (s, 3 H), 5.19 (d, J = 15.8 Hz, 1 H), 6.73 - 6.88 (m, 4 H), 6.94 - 7.02 (m, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.36 (dd, J = 9.0, 2.4 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.89 (s, 1 H), 8.71 (s, 1 H).

Example 261 (2E)-3-[3-(1-naphthyl)-2-thienyl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[3-(1-naphthyl)-2-thienyl]acrylic acid obtained in Reference Example 233 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.90 (m, 3 H), 1.25 - 1.41 (m, 4 H), 1.72 - 1.82 (m, 2 H), 3.35 - 3.42 (m, 2 H), 6.18 (d, J = 15.1 Hz, 1 H), 7.18 (d, J = 4.9 Hz, 1 H), 7.33 (d, J = 5.7 Hz, 1 H), 7.40 - 7.65 (m, 6 H), 7.73 (s, 1 H), 7.88 - 7.98 (m, 2 H).

Example 262 (2E)-N-[(butylamino)sulfonyl]-3-[3-(1-naphthyl)-2-thienyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[3-(1-naphthyl)-2-thienyl]acrylic acid obtained in Reference Example 233 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.86 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 2 H), 1.41 - 1.54 (m, 2 H), 2.91 - 3.00 (m, 2 H), 5.11 (t, J = 6.0 Hz, 1 H), 6.13 (d, J = 15.3 Hz, 1 H), 7.18 (d, J = 5.1 Hz, 1 H), 7.33 (dd, J = 7.0, 1.1 Hz, 1 H), 7.40 - 7.67 (m, 6 H), 7.84 (s, 1 H), 7.89 - 7.94 (m, 2 H).

Example 263 (2E)-N-[(butylamino)sulfonyl]-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (t, J = 7.3 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.44 - 1.52 (m, 2 H), 2.39 (s, 3 H), 2.96 - 3.03 (m, 2 H), 3.53 (s, 3 H), 5.20 (t, J = 6.1 Hz, 1 H), 5.44 (d, J = 15.6 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 15.6 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.23 (d, J = 2.3 Hz, 1 H), 8.42 (s, 1 H).

Example 264 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide

A mixture of (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 (380 mg), 2-methyl-6-nitrobenzoic anhydride (494 mg), N-(cyclopropylmethyl)sulfamide obtained in Reference Example 115 (186 mg), triethylamine (372 mg), 4-dimethylaminopyridine (151 mg) and acetonitrile (8 mL) was stirred at room temperature for 18 hr. The reaction mixture was

concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 35:65, v/v), and crystallized from hexane-ethanol to give the title compound (290 mg, yield 53%) as colorless crystals. melting point 209.3-210.0°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.13 - 0.19 (m, 2 H), 0.48 - 0.56 (m, 2 H), 0.89 - 1.03 (m, 1 H), 2.40 (s, 3 H), 2.86 (dd, J = 7.2, 6.0 Hz, 2 H), 3.55 (s, 3 H), 5.28 (t, J = 6.0 Hz, 1 H), 5.42 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 15.8 Hz, 1 H), 8.03 (d, J = 2.3 Hz, 1 H), 8.12 (s, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Example 265 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.1 Hz, 3 H), 1.25 - 1.45 (m, 4 H), 1.70 - 1.82 (m, 2 H), 2.40 (s, 3 H), 3.36 - 3.43 (m, 2 H), 3.54 (s, 3 H), 5.53 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 3.8 Hz, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.19 (s, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Example 266 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and 4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.36 (s, 3 H), 2.41 (s, 3 H), 3.54 (s, 3

H), 5.55 (d, J = 15.8 Hz, 1 H), 6.71 (d, J = 3.8 Hz, 1 H), 7.17 (d, J = 3.8 Hz, 1 H), 7.26 - 7.37 (m, 3 H), 7.79 - 7.86 (m, 2 H), 7.94 (d, J = 2.2 Hz, 1 H), 8.17 (s, 1 H), 8.24 (d, J = 2.2 Hz, 1 H).

Example 267 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-methoxy-4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and 2-methoxy-4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.35 (s, 3 H), 2.39 (s, 3 H), 3.53 (s, 3 H), 3.83 (s, 3 H), 5.83 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 6.76 (s, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 7.17 (d, J = 3.6 Hz, 1 H), 7.30 (d, J = 15.8 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.92 (d, J = 2.3 Hz, 1 H), 8.24 (d, J = 2.3 Hz, 1 H).

Example 268 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-hydroxy-4-methylphenyl)sulfonyl]acrylamide

To a solution of (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(2-methoxy-4-methylphenyl)sulfonyl]acrylamide obtained in Example 267 (396 mg) in dichloromethane (15 mL) was added dropwise boron tribromide (1M dichloromethane solution, 2.4 mL) with stirring at 0°C, and the mixture was stirred at 0°C for 4 hr. The reaction mixture was quenched with methanol, and concentrated under reduced pressure. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethanol to give the title compound (190 mg, yield 49%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.24 (s, 3 H), 2.35 (s, 3 H), 3.46 (s, 3 H), 6.11 (d, J = 16.1 Hz, 1 H), 6.69 - 6.74 (m, 2 H), 6.84 (d,

J = 3.8 Hz, 1 H), 6.89 (d, J = 16.1 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.77 (d, J = 3.8 Hz, 1 H), 8.25 - 8.30 (m, 2 H), 10.64 (s, 1 H), 11.80 (s, 1 H).

Example 269 (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(butylamino)sulfonyl]acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 238 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.3 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.44 - 1.55 (m, 2 H), 2.41 (s, 3 H), 2.95 - 3.03 (m, 2 H), 3.54 (s, 3 H), 5.14 (t, J = 6.2 Hz, 1 H), 5.43 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.10 (s, 1 H), 8.18 (d, J = 2.2 Hz, 1 H), 8.34 (d, J = 2.2 Hz, 1 H).

Example 270 (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(2-methoxy-4-methylphenyl)sulfonyl]acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 136 and 2-methoxy-4-methylbenzenesulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:2.33 (s, 3 H), 2.36 (s, 3 H), 2.37 (s, 3 H), 3.54 (s, 3 H), 3.82 (s, 3 H), 5.89 (d, J = 15.9 Hz, 1 H), 6.73 (s, 1 H) 6.78 (d, J = 8.3 Hz, 1 H), 6.90 (s, 1 H), 7.16 - 7.19 (m, 1 H), 7.31 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.93 - 7.96 (m, 1 H), 8.26 - 8.32 (m, 1 H), 8.40 (s, 1 H).

Example 271 3-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}imidazolidine-2,4-dione

To a solution of imidazolidine-2,4-dione (116 mg) in N,N-dimethylformamide (4 mL), which was cooled at 0°C in an ice bath, was added 60% sodium hydride (in oil, 49 mg) with stirring, and the mixture was stirred at 0°C for 20 min. 2-[5-(5-Chloro-1H-

indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate obtained in Reference Example 239 (329 mg) was added to this reaction mixture at 0°C, and the reaction mixture was stirred at 80°C for 18 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (ethyl acetate), and crystallized from hexane-ethanol to give the title compound (195 mg, yield 58%) as colorless crystals.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.18 (s, 3 H), 2.29 - 2.46 (m, 2 H), 3.26 (t, J = 7.0 Hz, 2 H), 3.33 (s, 3 H), 3.64 - 3.79 (m, 2 H), 6.75 (d, J = 3.0 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 2.0 Hz, 1 H), 7.53 (d, J = 3.0 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H), 7.92 (s, 1 H).

Example 272 3-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-5-propylimidazolidine-2,4-dione

By a method similar to that in Example 271, the title compound was obtained from 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl methanesulfonate obtained in Reference Example 239 and 5-propylimidazolidine-2,4-dione.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.4 Hz, 3 H), 1.24 - 1.43 (m, 2 H), 1.46 - 1.58 (m, 1 H), 1.68 - 1.84 (m, 1 H), 2.27 (s, 3 H), 2.38 - 2.51 (m, 1 H), 2.61 - 2.74 (m, 1 H), 3.35 - 3.47 (m, 5 H), 3.70 - 3.89 (m, 1 H), 5.27 - 5.29 (m, 1 H), 6.69 (d, J = 3.4 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.29 (dd, J = 5.7, 3.4 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Example 273 1-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}piperazin-2-one hydrochloride

To a solution of tert-butyl 4-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-3-oxopiperazine-1-carboxylate obtained in Reference Example 240 (223 mg) in ethyl acetate (4 mL) was added a 4M hydrogen chloride-ethyl acetate

solution (2 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative HPLC (tool and preparative conditions were the same as those in Reference Example 97). The obtained amorphous solid was neutralized with aqueous sodium hydrogencarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. A 4M hydrogen chloride-ethyl acetate solution (1 mL) was added to the obtained residue, and the mixture was concentrated under reduced pressure, and dried to give the title compound (132 mg, yield 68%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.24 (s, 3 H), 2.25 - 2.46 (m, 2 H), 3.15 - 3.34 (m, 6 H), 3.38 (s, 3 H), 3.52 - 3.60 (m, 2 H), 6.77 (d, J = 3.3 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.20 (dd, J = 8.7, 1.7 Hz, 1 H), 7.64 (d, J = 3.3 Hz, 1 H), 7.75 (d, J = 1.7 Hz, 1 H), 9.54 (s, 2 H).

Example 274 butyl {2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethoxy}carbamate

To a solution of 1-{4-[2-(aminooxy)ethyl]-1,3-dimethyl-1H-pyrazol-5-yl}-5-chloro-1H-indole obtained in Reference Example 242 (308 mg) in tetrahydrofuran (8 mL) was added triethylamine (330 mg), and then a solution of butyl chloroformate (172 mg) in tetrahydrofuran (6 mL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The residue was subjected to silica gel column chromatography (hexane-ethyl acetate 25:75, v/v) to give the title compound (146 mg, yield 35%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.49 - 1.62 (m, 2 H), 2.29 (s, 3 H), 2.45 - 2.68 (m, 2 H), 3.45 (s, 3 H), 3.71 (t, J = 6.6 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 2 H), 6.68 (d, J = 3.4 Hz, 1 H), 6.79 (s, 1 H), 6.95 (d, J =

8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 1.7 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Example 275 N-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethoxy}-N'-pentylurea

To a solution of 1-{4-[2-(aminooxy)ethyl]-1,3-dimethyl-1H-pyrazol-5-yl}-5-chloro-1H-indole obtained in Reference Example 242 (300 mg) in tetrahydrofuran (8 mL) was added pentyl isocyanate (175 mg), and the mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 25:75, v/v), and then purified by preparative HPLC (tool and preparative conditions were the same as those in Reference Example 97) to give the title compound (171 mg, yield 41%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$)δ: 0.89 (t, J = 7.0 Hz, 3 H), 1.18 - 1.47 (m, 6 H), 2.30 (s, 3 H), 2.45 - 2.66 (m, 2 H), 3.10 - 3.20 (m, 2 H), 3.46 (s, 3 H), 3.66 (t, J = 6.7 Hz, 2 H), 5.29 - 5.38 (m, 1 H), 6.66 - 6.71 (m, 2 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.9, 1.7 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Example 276 (4R)-5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-4-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide

(4R)-5-{2-[5-(5-Chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-4-isopropyl-2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide obtained in Reference Example 243 (205 mg) was dissolved in trifluoroacetic acid (4 mL), and the solution was stirred with heating at 65°C for 7 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried over anhydrous magnesium sulfate. The residue was subjected to silica gel column chromatography (ethyl acetate-methanol 95:5, v/v), and crystallized from hexane-ethanol to give the title compound (41 mg, yield 25%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.67 (dd, J = 14.0, 7.0 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 1.64 - 1.80 (m, 1 H), 2.32 (s, 3 H), 2.58 - 2.85 (m, 4 H), 3.06 - 3.30 (m, 1 H), 3.48 - 3.53 (m, 4 H), 6.70 (d, J = 2.9 Hz, 1 H), 6.93 (dd, J = 8.6, 4.8 Hz, 1 H), 7.11 (d, J = 2.9 Hz, 1 H), 7.20 - 7.24 (m, 1 H), 7.66 (s, 1 H).

Example 277 N-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethoxy}-4-methylbenzamide

By a method similar to that in Example 274, the title compound was obtained from 1-{4-[2-(aminooxy)ethyl]-1,3-dimethyl-1H-pyrazol-5-yl}-5-chloro-1H-indole obtained in Reference Example 242 and 4-methylbenzoyl chloride.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.31 (s, 3 H), 2.39 (s, 3 H), 2.64 (t, J = 6.2 Hz, 2 H), 3.48 (s, 3 H), 3.78 - 3.95 (m, 2 H), 6.66 (d, J = 3.4 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.14 - 7.27 (m, 6 H), 7.64 - 7.66 (m, 2 H).

Example 278 potassium {(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 9.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.77 - 0.84 (m, 3 H), 1.16 - 1.25 (m, 4 H), 1.40 - 1.48 (m, 2 H), 2.33 (s, 3 H), 2.82 - 2.90 (m, 2 H), 3.43 (s, 3 H), 5.59 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz, 1 H), 6.84 (d, J = 3.6 Hz, 1 H), 7.25 (dd, J = 8.0, 4.7 Hz, 1 H), 7.64 (d, J = 3.6 Hz, 1 H), 8.14 (dd, J = 8.0, 1.5 Hz, 1 H), 8.24 - 8.28 (m, 1 H).

Example 279 N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide

To a solution of butylamine (110 mg) in N,N-dimethylformamide (8 mL) was added N,N'-carbonyldiimidazole (265 mg), and the mixture was stirred at 60°C for 1 hr. 2-[5-(5-Chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-

pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 246 (350 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (259 mg) and 4-dimethylaminopyridine (209 mg) were added to the reaction mixture, and the mixture was stirred at 60°C for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 60:40, v/v), and crystallized from hexane-ethyl acetate to give the title compound (200 mg, yield 45%) as colorless crystals.
melting point 166.8-167.6°C.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.90 - 0.96 (m, 7 H), 1.23 - 1.52 (m, 4 H), 1.76 - 1.84 (m, 1 H), 2.75 - 3.02 (m, 2 H), 3.08 - 3.20 (m, 2 H), 3.21 - 3.34 (m, 1 H), 3.39 (s, 3 H), 3.75 - 3.90 (m, 1 H), 5.77 (s, 1 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.26 (d, J = 2.3 Hz, 1 H), 8.68 (s, 1 H).

Example 280 butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 246, butanol and N,N'-carbonyldiimidazole.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.78 - 1.00 (m, 7 H), 1.30 - 1.41 (m, 2 H), 1.53 - 1.65 (m, 2 H), 1.76 - 1.86 (m, 1 H), 2.80 - 3.03 (m, 2 H), 3.18 - 3.30 (m, 1 H), 3.33 (s, 3 H), 3.94 - 4.18 (m, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.03 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 10.37 (s, 1 H).

Example 281 5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}-1,2,5-thiadiazolidin-3-one 1,1-dioxide

By a method similar to that in Example 276, the title compound was obtained from 5-{2-[5-(5-chloro-1H-indol-1-yl)-1,3-

dimethyl-1H-pyrazol-4-yl]ethyl}-2-(4-methoxybenzyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide obtained in Reference Example 247.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:2.22 (s, 3 H), 2.30 - 2.47 (m, 2 H), 2.90 (t, J = 7.1 Hz, 2 H), 3.37 (s, 3 H), 3.43 - 3.70 (m, 2 H), 6.76 (d, J = 3.4 Hz, 1 H), 7.03 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 2.0 Hz, 1 H), 7.56 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H).

Example 282 (2E)-3-[1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1-benzyl-3-methyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 251 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.90 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.70 - 1.82 (m, 2 H), 2.39 (s, 3 H), 3.35 - 3.40 (m, 2 H), 4.91 (d, J = 15.6 Hz, 1 H), 5.16 (d, J = 15.6 Hz, 1 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.65 (d, J = 3.8 Hz, 1 H), 6.81 - 6.91 (m, 3 H), 7.12 - 7.25 (m, 4 H), 7.38 (d, J = 15.9 Hz, 1 H), 8.02 (dd, J = 7.9, 1.5 Hz, 1 H), 8.06 - 8.17 (m, 1 H), 8.32 (dd, J = 4.7, 1.5 Hz, 1 H).

Example 283 (2E)-N-(butylsulfonyl)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

A mixture of (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 (414 mg), 2-methyl-6-nitrobenzoic anhydride (547 mg), butane-1-sulfonamide (188 mg), triethylamine (412 mg), 4-dimethylaminopyridine (165 mg) and acetonitrile (12 mL) was stirred at room temperature for 20 hr. The reaction mixture was concentrated under reduced pressure, a saturated aqueous ammonium chloride solution (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was

concentrated, and the residue was subjected to silica gel chromatography (hexane-ethyl acetate 30:70, v/v), and crystallized from hexane-ethanol to give the title compound (505 mg, yield 88%) as colorless crystals. melting point 245.3-248.1°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.4 Hz, 3 H), 1.35 - 1.50 (m, 2 H), 1.70 - 1.81 (m, 2 H), 2.39 (s, 3 H), 3.37 - 3.43 (m, 2 H), 3.53 (s, 3 H), 5.53 (d, J = 15.7 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 7.20 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.7 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.24 (d, J = 2.3 Hz, 1 H), 8.35 (s, 1 H).

Example 284 (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(propylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 235 and propane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.04 (t, J = 7.4 Hz, 3 H), 1.75 - 1.90 (m, 2 H), 2.40 (s, 3 H), 3.35 - 3.41 (m, 2 H), 3.54 (s, 3 H), 5.53 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.21 (d, J = 3.6 Hz, 1 H), 7.39 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.14 (s, 1 H), 8.26 (d, J = 2.3 Hz, 1 H).

Example 285 potassium {(2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]prop-2-enoyl}(pentylsulfonyl)azanide

By a method similar to that in Example 7, the title compound was obtained from (2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 265.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.83 (m, 3 H), 1.17 - 1.24 (m, 4 H), 1.38 - 1.50 (m, 2 H), 2.32 (s, 3 H), 2.80 - 2.89 (m, 2 H), 3.43 (s, 3 H), 5.56 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 6.84 (d, J = 3.8 Hz, 1 H), 7.77 (d, J = 3.8 Hz, 1 H), 8.26 - 8.29 (m, 2 H).

Example 286 (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-

1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 238 and pentane-1-sulfonamide.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.30 - 1.45 (m, 4 H), 1.72 - 1.85 (m, 2 H), 2.41 (s, 3 H), 3.34 - 3.45 (m, 2 H), 3.54 (s, 3 H), 5.52 (d, J = 15.6 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 8.15 (br s, 1 H), 8.18 (d, J = 2.1 Hz, 1 H), 8.34 (d, J = 2.1 Hz, 1 H).

Example 287 (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(butylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 238 and butane-1-sulfonamide.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.3 Hz, 3 H), 1.36 - 1.49 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.41 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.54 (s, 3 H), 5.52 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.39 (d, J = 15.8 Hz, 1 H), 8.03 (br s, 1 H), 8.18 (d, J = 2.1 Hz, 1 H), 8.34 (d, J = 2.1 Hz, 1 H).

Example 288 (2E)-N-[(butylamino)sulfonyl]-3-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide

To a mixture of (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(butylamino)sulfonyl]acrylamide obtained in Example 269 (395 mg), cyclopropylboronic acid (408 mg), a 2.0M aqueous sodium carbonate solution (1.6 mL) and 1,2-dimethoxyethane (10 mL) was added tetrakis(triphenylphosphine)palladium(0) (92 mg), and the reaction mixture was heated under reflux under nitrogen atmosphere for 40 hr. After the reaction mixture was allowed to cool to room temperature, water was added, and the mixture was

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 45:55, v/v), and crystallized from hexane-ethyl acetate to give the title compound (125 mg, yield 34%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.74 - 0.80 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H), 1.05 - 1.10 (m, 2 H), 1.24 - 1.41 (m, 2 H), 1.44 - 1.55 (m, 2 H), 1.99 - 2.10 (m, 1 H), 2.32 (s, 3 H), 2.98 - 3.05 (m, 2 H), 3.53 (s, 3 H), 5.09 - 5.25 (m, 1 H), 5.44 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 15.8 Hz, 1 H), 7.66 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H), 8.73 (br s, 1 H).

Example 289 (2E)-3-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 288, the title compound was obtained from (2E)-3-[5-(5-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 286 and cyclopropylboronic acid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.74 - 0.80 (m, 2 H), 0.88 (t, J = 7.1 Hz, 3 H), 1.07 (dd, J = 8.3, 1.3 Hz, 2 H), 1.26 - 1.47 (m, 4 H), 1.72 - 1.86 (m, 2 H), 2.00 - 2.12 (m, 1 H), 2.30 (s, 3 H), 3.39 - 3.45 (m, 2 H), 3.52 (s, 3 H), 5.51 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.8 Hz, 1 H), 7.10 (d, J = 3.8 Hz, 1 H), 7.35 (d, J = 15.8 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H), 8.16 (d, J = 1.9 Hz, 1 H), 8.81 (s, 1 H).

Example 290 tert-butyl 5-methyl-4-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-1-carboxylate

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1-(tert-butoxycarbonyl)-5-methyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 255 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.24 - 1.42 (m, 4 H), 1.65 (s, 9 H), 1.66 - 1.76 (m, 2 H), 2.72 (s, 3 H), 3.28 - 3.33 (m, 2 H), 5.18 (d, J = 15.7 Hz, 1 H), 6.69 (d, J = 3.8 Hz, 1 H), 7.16 (dd, J = 8.0, 4.7 Hz, 1 H), 7.31 - 7.37 (m, 1 H), 7.39 (d, J = 3.8 Hz, 1 H), 7.64 (d, J = 15.7 Hz, 1 H), 7.99 (dd, J = 8.0, 1.5 Hz, 1 H), 8.31 (dd, J = 4.7, 1.5 Hz, 1 H).

Example 291 (2E)-3-[5-methyl-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

To tert-butyl 5-methyl-4-{(1E)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}-3-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazole-1-carboxylate obtained in Example 290 (321 mg) was added trifluoroacetic acid (6 mL), and the mixture was stirred at 0°C for 90 min. The reaction mixture was concentrated under reduced pressure, an aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 15:85, v/v), and crystallized from hexane-ethanol to give the title compound (146 mg, yield 57%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.88 (t, J = 7.0 Hz, 3 H), 1.25 - 1.45 (m, 4 H), 1.71 - 1.89 (m, 2 H), 2.12 (s, 3 H), 3.35 - 3.42 (m, 2 H), 5.51 (d, J = 15.8 Hz, 1 H), 6.59 (d, J = 3.6 Hz, 1 H), 7.10 - 7.41 (m, 3 H), 7.98 (d, J = 7.8 Hz, 1 H), 8.23 (d, J = 3.6 Hz, 1 H), 10.23 (s, 1 H), 11.99 (s, 1 H).

Example 292 trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)cyclopropanecarboxamide

To a solution of trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxylic acid obtained in Reference Example 148 (312 mg) in acetonitrile (5 mL) were added 1-pentanesulfonamide (144 mg), 4-dimethylaminopyridine (231 mg) and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (363 mg) with stirring at room temperature, and the mixture was

stirred at room temperature for 15 hr. 1N Hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 90:10 - 80:20, v/v) to give the title compound (210 mg, yield 48%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.70 - 0.84 (m, 2 H), 0.86 - 0.95 (m, 3 H), 1.14 - 1.52 (m, 4 H), 1.60 - 1.84 (m, 3 H), 1.95 - 2.21 (m, 1 H), 2.31 (s, 1.5 H), 2.32 (s, 1.5 H), 2.86 - 3.01 (m, 0.5 H), 3.10 - 3.24 (m, 0.5 H), 3.26 - 3.37 (m, 1 H), 3.54 (s, 1.5 H), 3.58 (s, 1.5 H), 6.74 - 6.84 (m, 1 H), 6.86 - 7.05 (m, 1 H), 7.14 (t, J = 3.5 Hz, 1 H), 7.21 - 7.26 (m, 1 H), 7.75 (d, J = 1.9 Hz, 1 H).

Example 293 trans-N-[(butylamino)sulfonyl]-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxamide

By a method similar to that in Example 62, the title compound was obtained from trans-2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]cyclopropanecarboxylic acid obtained in Reference Example 148 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.31 - 0.60 (m, 1 H), 0.73 - 0.90 (m, 3 H), 0.83 - 1.00 (m, 1 H), 1.14 - 1.49 (m, 3 H), 1.60 - 1.75 (m, 1 H), 1.81 - 2.04 (m, 2 H), 2.19 - 2.25 (m, 3 H), 2.57 - 2.93 (m, 2 H), 3.34 - 3.43 (m, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.94 - 7.12 (m, 1 H), 7.13 - 7.27 (m, 1 H), 7.44 - 7.57 (m, 1 H), 7.58 (dd, J = 3.2, 1.7 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 11.24 - 11.66 (m, 1 H).

Example 294 N-[(butylamino)carbonyl]-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide

To a solution of butylamine (90.6 mg) in N,N-dimethylformamide (10 mL) was added N,N'-carbonyldiimidazole

(218 mg), and the mixture was stirred at 60°C for 1 hr. 2-{1,3-Dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208 (400 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (220 mg) and 4-dimethylaminopyridine (176 mg) were added to the reaction mixture, and the mixture was stirred at 60°C for 18 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (323 g, yield 64 %) as colorless crystals.
melting point 162.7-164.0°C.
^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.96 (m, 3 H), 1.26 - 1.40 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.32 (s, 3 H), 2.78 - 2.92 (m, 2 H), 3.07 - 3.24 (m, 3 H), 3.43 (s, 3 H), 3.64 - 3.80 (m, 1 H), 5.59 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.6 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.3 Hz, 1 H).

Example 295 butyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

To a solution of butanol (91.8 mg) in N,N-dimethylformamide (10 mL) was added N,N'-carbonyldiimidazole (217 mg), and the mixture was stirred at 60°C for 1 hr. 2-{1,3-Dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208 (400 mg), 1,8-diazabicyclo[5.4.0]undec-7-ene (220 mg) and 4-dimethylaminopyridine (176 mg) were added to this reaction mixture, and the mixture was stirred at 60°C for 18 hr. A saturated aqueous ammonium chloride solution (10 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The

filtrate was concentrated, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 40:60, v/v), and crystallized from hexane-ethyl acetate to give the title compound (214 mg, yield 43%) as colorless crystals.

melting point 122.3-123.2°C.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.3 Hz, 3 H), 1.30 - 1.44 (m, 2 H), 1.54 - 1.66 (m, 2 H), 2.32 (s, 3 H), 2.74 - 2.90 (m, 2 H), 3.11 - 3.23 (m, 1 H), 3.37 (s, 3 H), 3.91 - 4.18 (m, 3 H), 6.85 (d, J = 3.6 Hz, 1 H), 7.25 - 7.27 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.61 (d, J = 1.3 Hz, 1 H), 10.41 (br s, 1 H).

Example 296 ethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

To a solution of 2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 179 (520 mg) in pyridine (20 mL) was added ethyl chlorocarbonate (10 mL), and the mixture was heated under reflux for 2 hr. 1N Hydrochloric acid (20 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The filtrate was concentrated, and the residue was crystallized from hexane-ethyl acetate to give the title compound (426 mg, yield 68%) as colorless crystals.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.23 (t, J = 7.2 Hz, 3 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 4.11 (q, J = 7.2 Hz, 2 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Example 297 butyl ({2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 210, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.42 (m, 2 H), 1.52 - 1.64 (m, 2 H), 2.31 (s, 3 H), 2.47 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.07 - 3.18 (m, 1 H), 3.31 (s, 3 H), 3.85 - 3.96 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.65 (d, J = 3.8 Hz, 1 H), 7.05 (d, J = 3.6 Hz, 1 H), 7.85 (d, J = 1.1 Hz, 1 H), 8.14 (d, J = 1.9 Hz, 1 H), 11.91 (br s, 1 H).

Example 298 N-[(butylamino)carbonyl]-2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 210, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 - 0.96 (m, 3 H), 1.25 - 1.37 (m, 2 H), 1.38 - 1.51 (m, 2 H), 2.32 (s, 3 H), 2.48 (s, 3 H), 2.80 - 2.89 (m, 2 H), 3.00 (br s, 1 H), 3.10 - 3.26 (m, 2 H), 3.35 (s, 3 H), 3.95 (br s, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.6 Hz, 1 H), 7.89 (d, J = 1.1 Hz, 1 H), 8.13 (d, J = 1.9 Hz, 1 H).

Example 299 (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}-N-(propylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 203 and propane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.02 (t, J = 7.6 Hz, 3 H), 1.72 - 1.86 (m, 2 H), 2.42 (s, 3 H), 3.33 - 3.39 (m, 2 H), 3.57 (s, 3 H), 5.65 (d, J = 15.5 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.9 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H).

Example 300 (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}-N-

(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 203 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.91 (m, 3 H), 1.24 - 1.43 (m, 4 H), 1.69 - 1.82 (m, 2 H), 2.42 (s, 3 H), 3.33 - 3.42 (m, 2 H), 3.57 (s, 3 H), 5.63 (d, J = 15.8 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Example 301 (2E)-N-[(butylamino)sulfonyl]-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylamide

By a method similar to that in Example 62, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 203 and N-butylsulfamide obtained in Reference Example 111.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.83 - 0.90 (m, 3 H), 1.25 - 1.38 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.43 (s, 3 H), 2.95 (q, J = 6.8 Hz, 2 H), 3.58 (s, 3 H), 5.17 (t, J = 5.9 Hz, 1 H), 5.52 (d, J = 15.9 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.31 - 7.39 (m, 2 H), 8.32 (d, J = 1.9 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Example 302 (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}-N-(piperidin-1-ylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}acrylic acid obtained in Reference Example 203 and piperidine-1-sulfonamide obtained in Reference Example 177.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.46 - 1.65 (m, 6 H), 2.45 (s, 3 H), 3.22 - 3.29 (m, 4 H), 3.59 (s, 3 H), 5.65 (d, J = 15.9 Hz, 1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.31 - 7.40 (m, 2 H), 7.91 (br s, 1

H), 8.32 (d, J = 1.9 Hz, 1 H), 8.61 (d, J = 1.9 Hz, 1 H).

Example 303 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propyl [(butylamino)sulfonyl]carbamate

By a method similar to that in Example 71, the title compound was obtained from 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propan-1-ol obtained in Reference Example 212, chlorosulfonyl isocyanate and butylamine.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.3 Hz, 3 H), 1.33 - 1.47 (m, 2 H), 1.51 - 1.62 (m, 3 H), 1.78 - 1.91 (m, 1 H), 2.29 (s, 3 H), 2.35 - 2.57 (m, 2 H), 3.11 (q, J = 6.7 Hz, 2 H), 3.53 (s, 3 H), 3.67 - 3.78 (m, 1 H), 4.16 - 4.26 (m, 1 H), 5.13 (t, J = 6.0 Hz, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 3.6 Hz, 1 H), 8.33 (d, J = 1.5 Hz, 1 H), 8.64 (d, J = 1.3 Hz, 1 H), 9.27 (s, 1 H).

Example 304 (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]acrylic acid obtained in Reference Example 258 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.80 - 0.94 (m, 6 H), 1.23 - 1.30 (m, 4 H), 1.33 - 1.48 (m, 2 H), 1.55 - 1.65 (m, 2 H), 1.68 - 1.83 (m, 2 H), 2.73 - 2.80 (m, 2 H), 3.11 - 3.18 (m, 2 H), 5.33 (s, 2 H), 5.39 (d, J = 15.5 Hz, 1 H), 7.09 (d, J = 7.2 Hz, 2 H), 7.30 - 7.57 (m, 9 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.87 - 7.96 (m, 2 H).

Example 305 3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]-N-(pentylsulfonyl)propanamide

By a method similar to that in Example 2, the title compound was obtained from (2E)-3-[1-benzyl-2-butyl-4-(1-naphthyl)-1H-imidazol-5-yl]-N-(pentylsulfonyl)acrylamide obtained in Example 304.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.84 - 0.89 (m, 6 H), 1.24 - 1.42 (m, 6 H), 1.55 - 1.75 (m, 4 H), 1.95 (t, J = 7.6 Hz, 2 H), 2.63 - 2.76

(m, 4 H), 3.04 - 3.12 (m, 2 H), 5.18 (s, 2 H), 7.04 (d, J = 7.2 Hz, 2 H), 7.28 - 7.53 (m, 7 H), 7.82 - 7.89 (m, 3 H).

Example 306 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propyl ethylcarbamate

To a solution of 3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 66 (374 mg) in pyridine (4 mL) was added ethyl isocyanate (525 mg), and the mixture was stirred at room temperature for 14 hr, and then stirred with heating at 50°C for 5 hr. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to silica gel column chromatography (hexane-ethyl acetate 30:70, v/v) to give the title compound (398 mg, yield 86%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.08 (t, J = 7.0 Hz, 3 H), 1.53 - 1.63 (m, 2 H), 2.19 - 2.38 (m, 5 H), 2.90 - 3.20 (m, 2 H), 3.45 (s, 3 H), 3.70 - 3.92 (m, 2 H), 4.28 (s, 1 H), 6.67 (d, J = 3.4 Hz, 1 H), 6.94 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.9, 2.0 Hz, 1 H), 7.65 (d, J = 2.0 Hz, 1 H).

Example 307 (2E)-3-(2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-3-yl)-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-(2,5-dimethyl-4-(1-naphthyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrol-3-yl)acrylic acid obtained in Reference Example 277 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.00 (s, 9 H), 0.79 - 0.87 (m, 3 H), 0.90 - 0.97 (m, 2 H), 1.20 - 1.29 (m, 4 H), 1.54 - 1.65 (m, 2 H), 1.96 (s, 3 H), 2.45 - 2.48 (m, 3 H), 3.11 - 3.20 (m, 2 H), 3.53 - 3.60 (m, 2 H), 4.83 (d, J = 15.3 Hz, 1 H), 5.18 - 5.28 (m, 2 H), 7.29 - 7.38 (m, 2 H), 7.42 - 7.57 (m, 3 H), 7.70 - 7.76 (m, 1 H), 7.84 - 7.90 (m, 2 H).

Example 308 cyclopropylmethyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title

compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, cyclopropylmethanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.31 (t, J = 5.8 Hz, 2 H), 0.55 - 0.61 (m, 2 H), 1.03 - 1.16 (m, 1 H), 2.31 (s, 3 H), 2.75 - 2.88 (m, 2 H), 3.12 - 3.21 (m, 1 H), 3.39 (s, 3 H), 3.74 - 3.82 (m, 1 H), 3.91 - 4.08 (m, 2 H), 6.85 (d, J = 3.6 Hz, 1 H), 7.25 - 7.27 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.64 (d, J = 1.5 Hz, 1 H), 10.46 (br s, 1 H).

Example 309 N-{[(cyclopropylmethyl)amino]carbonyl}-2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, cyclopropylmethylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.16 - 0.23 (m, 2 H), 0.47 - 0.54 (m, 2 H), 0.86 - 1.00 (m, 1 H), 2.32 (s, 3 H), 2.76 - 2.89 (m, 2 H), 2.99 (br s, 2 H), 3.19 (br s, 1 H), 3.43 (s, 3 H), 3.68 - 3.87 (m, 1 H), 5.61 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.35 (d, J = 1.5 Hz, 1 H), 8.61 (d, J = 1.5 Hz, 1 H).

Example 310 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

By a method similar to that in Example 71, the title compound was obtained from 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propan-1-ol obtained in Reference Example 212, chlorosulfonyl isocyanate and 2-aminoethylisopropyl ether.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.15 (d, J = 6.0 Hz, 6 H), 1.56 (dd, J = 12.6, 6.4 Hz, 1 H), 1.74 - 1.88 (m, 1 H), 2.30 (s, 3 H), 2.35 - 2.55 (m, 2 H), 3.21 - 3.30 (m, 2 H), 3.50 - 3.64 (m, 6 H), 3.71

- 3.81 (m, 1 H), 4.13 - 4.25 (m, 1 H), 5.52 (t, J = 5.9 Hz, 1 H), 6.86 (d, J = 3.8 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.63 (d, J = 1.3 Hz, 1 H), 9.19 (s, 1 H).

Example 311 butyl ({2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 282, butanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.73 - 0.80 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H), 1.00 - 1.08 (m, 2 H), 1.28 - 1.42 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.31 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.09 - 3.18 (m, 1 H), 3.31 (s, 3 H), 3.86 - 3.96 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.64 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 3.6 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H), 8.16 (d, J = 2.1 Hz, 1 H), 11.93 (br s, 1 H).

Example 312 N-[(butylamino)carbonyl]-2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-[5-(5-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethanesulfonamide obtained in Reference Example 282, butylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.73 - 0.81 (m, 2 H), 0.89 - 0.96 (m, 3 H), 1.02 - 1.09 (m, 2 H), 1.24 - 1.52 (m, 4 H), 1.99 - 2.11 (m, 1 H), 2.32 (s, 3 H), 2.80 - 2.88 (m, 2 H), 3.00 (br s, 1 H), 3.09 - 3.24 (m, 2 H), 3.35 (s, 3 H), 3.94 (br s, 1 H), 5.43 (br s, 1 H), 6.66 (d, J = 3.6 Hz, 1 H), 7.09 (d, J = 3.8 Hz, 1 H), 7.72 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 1.9 Hz, 1 H).

Example 313 3-methylbutyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, 3-methylbutan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (d, J = 6.4 Hz, 6 H), 1.46 - 1.55 (m, 2 H), 1.62 - 1.73 (m, 1 H), 2.32 (s, 3 H), 2.78 - 2.91 (m, 2 H), 3.11 - 3.21 (m, 1 H), 3.37 (s, 3 H), 3.93 - 4.08 (m, 2 H), 4.10 - 4.22 (m, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H), 10.46 (br s, 1 H).

Example 314 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}-N-{[(3-methylbutyl)amino]carbonyl}ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, 3-methylbutan-1-amine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.91 (d, J = 6.6 Hz, 6 H), 1.32 - 1.41 (m, 2 H), 1.51 - 1.66 (m, 1 H), 2.32 (s, 3 H), 2.75 - 2.88 (m, 2 H), 3.09 - 3.25 (m, 3 H), 3.44 (s, 3 H), 3.64 - 3.80 (m, 1 H), 5.58 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.59 (d, J = 1.3 Hz, 1 H).

Example 315 2-cyclopropylethyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, 2-cyclopropylethanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.05 - 0.11 (m, 2 H), 0.43 - 0.50 (m, 2 H), 0.62 - 0.76 (m, 1 H), 1.46 - 1.55 (m, 2 H), 2.32 (s, 3 H), 2.77 - 2.90 (m, 2 H), 3.12 - 3.23 (m, 1 H), 3.37 (s, 3 H), 3.96

- 4.09 (m, 2 H), 4.14 - 4.26 (m, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.3 Hz, 1 H), 10.50 (br s, 1 H).

Example 316 (2E)-3-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide

By a method similar to that in Example 1, the title compound was obtained from (2E)-3-[5-(5-fluoro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylic acid obtained in Reference Example 285 and pentane-1-sulfonamide.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:0.78 - 0.85 (m, 3 H), 1.22 - 1.36 (m, 4 H), 1.52 - 1.66 (m, 2 H), 2.39 (s, 3 H), 3.28 - 3.35 (m, 2 H), 3.50 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.90 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.0 Hz, 1 H), 7.83 (d, J = 3.8 Hz, 1 H), 8.10 (dd, J = 9.2, 2.8 Hz, 1 H), 8.26 - 8.30 (m, 1 H), 11.65 (br s, 1 H).

Example 317 potassium 1-[(3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propoxy)carbonyl]-3-(2-isopropoxyethyl)diazathian-1-ide 2,2-dioxide

To a solution of 3-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate obtained in Example 310 (352 mg) in methanol (10 mL) was added an aqueous solution (2 mL) of potassium hydrogencarbonate (64 mg), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and gave the title compound (343 mg, yield 91%) as a colorless amorphous solid.

^{1}H-NMR (300 MHz, DMSO-d_6)δ:1.03 (d, J = 6.0 Hz, 6 H), 1.33 - 1.45 (m, 2 H), 2.07 - 2.30 (m, 5 H), 2.71 - 2.79 (m, 2 H), 3.35 - 3.51 (m, 5 H), 3.53 - 3.60 (m, 2 H), 5.22 (t, J = 6.6 Hz, 1 H), 6.95 (d, J = 3.6 Hz, 1 H), 7.88 (d, J = 3.6 Hz, 1 H), 8.57 (d, J = 1.5 Hz, 1 H), 8.62 (s, 1 H).

Example 318 isobutyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, 2-methylpropan-1-ol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.93 (d, J = 6.8 Hz, 6 H), 1.83 - 1.98 (m, 1 H), 2.32 (s, 3 H), 2.78 - 2.90 (m, 2 H), 3.11 - 3.22 (m, 1 H), 3.36 (s, 3 H), 3.69 - 3.79 (m, 1 H), 3.89 - 4.14 (m, 2 H), 6.86 (d, J = 3.8 Hz, 1 H), 7.27 (s, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H), 10.35 (s, 1 H).

Example 319 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}-N-[(isobutylamino)carbonyl]ethanesulfonamide

By a method similar to that in Example 208, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, isobutylamine and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.89 (d, J = 6.6 Hz, 6 H), 1.67 - 1.81 (m, 1 H), 2.32 (s, 3 H), 2.76 - 3.05 (m, 4 H), 3.20 (br s, 1 H), 3.43 (s, 3 H), 3.67 (br s, 1 H), 5.74 (br s, 1 H), 6.87 (d, J = 3.8 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.59 (d, J = 1.3 Hz, 1 H).

Example 320 propyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate

By a method similar to that in Example 186, the title compound was obtained from 2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide obtained in Reference Example 208, propanol and N,N'-carbonyldiimidazole.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:0.94 (t, J = 7.4 Hz, 3 H), 1.60 - 1.71 (m, 2 H), 2.32 (s, 3 H), 2.77 - 2.89 (m, 2 H), 3.11 - 3.21 (m, 1 H), 3.37 (s, 3 H), 3.89 - 4.13 (m, 3 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.24 - 7.27 (m, 1 H), 8.34 (d, J = 1.7 Hz, 1 H), 8.61 (d, J

= 1.5 Hz, 1 H), 10.46 (s, 1 H).

Example 321 3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propyl {[(2-isopropoxyethyl)amino]sulfonyl}carbamate

By a method similar to that in Example 71, the title compound was obtained from 3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]propan-1-ol obtained in Reference Example 289, chlorosulfonyl isocyanate and 2-aminoethylisopropyl ether.

^{1}H-NMR (300 MHz, $CDCl_3$)δ:1.16 (d, J = 2.4 Hz, 3 H), 1.18 (d, J = 2.4 Hz, 3 H), 1.40 - 1.54 (m, 1 H), 1.83 - 1.96 (m, 1 H), 2.28 (s, 3 H), 2.41 - 2.64 (m, 5 H), 3.23 - 3.31 (m, 2 H), 3.51 (s, 3 H), 3.55 - 3.66 (m, 4 H), 4.25 - 4.35 (m, 1 H), 5.54 (t, J = 5.8 Hz, 1 H), 6.65 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 7.84 - 7.86 (m, 1 H), 8.22 (d, J = 1.9 Hz, 1 H), 10.85 (br s, 1 H).

Experimental Example 1 (PPARγ-RXRα heterodimer ligand activity)

The PPARγ:RXRα:4ERPP/CHO-K1 cells described in WO03/099793 were cultured in a Ham F12 medium [manufactured by Life Technologies, Inc., US] containing 10% calf fetal serum [manufactured by Life Technologies, Inc., US], sown in a 96-well white plate [manufactured by Corning Coster Corporation, US] at 1×10^4 cells/well, and incubated overnight in a carbon dioxide gas incubator at 37°C.

Then, the medium was removed from the 96 well white plate, 45 µl of Ham F12 medium containing 0.1% fatty acid-free bovine serum albumin (BSA) and a test compound (5 µl) were added, and the cells were incubated for one day in a carbon dioxide gas incubator at 37°C. The medium was removed, 20 µl of PicaGene 7.5 (manufactured by Wako Pure Chemical Industries, Ltd.) 2-fold diluted with HBSS (HANKS' BALANCED SALT SOLUTION) [manufactured by BIO WHITTAKER, US] was added. After stirring, the luciferase activity was determined using the 1420 ARVO Multilabel Counter [manufactured by PerkinElmer, US].

The induction rate was calculated from the luciferase activity of each test compound based on the luciferase activity of the test compound non-administration group as 1. The test compound concentration and the induction rate were analyzed by PRISM [manufactured by GraphPad Software, Inc., US] to calculate EC_{50} value (compound concentration showing 50% of the maximum value of induction rate) of the test compound. The results are shown in Table 1.

Table 1

Test compound (Example No.)	EC_{50} (nM)
6	19
7	39
9	64
24	54
27	6.1
31	5.5
33	88
40	12
55	44
62	37
66	22
82	67
84	220
99	24
189	54
197	86
232	15
264	26
279	60
283	14
294	32
295	22

As shown above, the compound of the present invention has been shown to have a superior PPARγ-RXRα heterodimer ligand activity.

Formulation Example 1 (production of capsule)

1) compound of Example 1	30 mg
2) finely divided powder cellulose	10 mg
3) lactose	19 mg

4) magnesium stearate	1 mg
total	60 mg

1), 2), 3) and 4) are mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

1) compound of Example 1	30 g
2) lactose	50 g
3) cornstarch	15 g
4) calcium carboxymethylcellulose	44 g
5) magnesium stearate	1 g
1000 tablets total	140 g

The total amount of 1), 2), 3) and 30 g of 4) are kneaded with water, vacuum dried and sized. The sized powder is mixed with 14 g of 4) and 1 g of 5) and the mixture is punched out with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

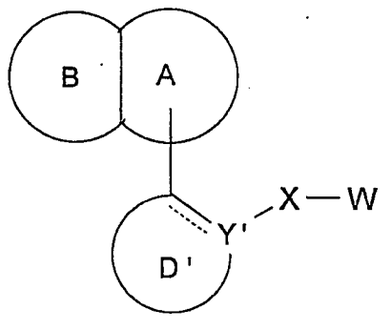
Industrial Applicability

The compound of the present invention is useful for an agent for the prophylaxis or treatment of diabetes, which has a superior hypoglycemic action, and is associated with a fewer side effects such as body weight gain and the like.

This application is based on patent application No. 31221/2007 filed in Japan, the contents of which are hereby incorporated by reference.

CLAIMS

1. A compound represented by the formula (I'):



(I')

wherein

ring A and ring B are the same or different and each is an optionally substituted 5- to 7-membered monocycle;

ring D' is an optionally substituted 5-membered monocyclic aromatic heterocycle wherein Y' is N or C;

X is a spacer having 1 to 4 atoms in the main chain; and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} and R^{1b} are the same or different and each is a hydrogen atom or a C_{1-6} alkyl group;

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

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

m and n are the same or different and each is an integer of 1 or 2, or

a 5- or 6-membered heterocyclic group containing NH, which is optionally substituted,

provided that

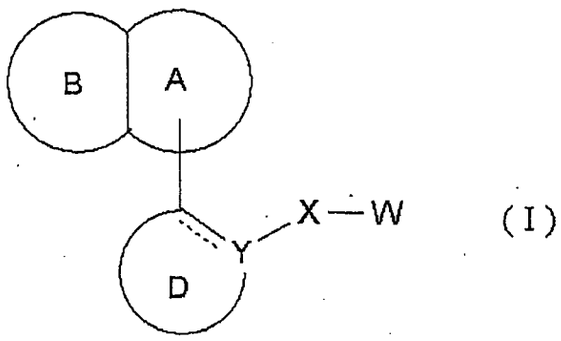
1) when ring D' is a substituted imidazole, then W should not be 2-amino-1H-imidazol-5-yl, 1H-imidazol-2-yl, 3,5-dimethyl-1H-pyrazol-4-yl and piperazin-1-yl;

2) when ring D' is a substituted pyrazole, and X is -CH=, then W should not be 4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene, 5-oxo-2-thioxoimidazolidin-4-ylidene optionally substituted by phenyl group(s), 3-methyl-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene, 2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene and 4,6-dioxo-2-thioxotetrahydropyrimidin-5(2H)-ylidene; and

3) 5-(6-methoxy-2-naphthyl)-1-(pyrrolidin-2-ylmethyl)-1H-1,2,3-triazole is excluded,

or a salt thereof.

2. A compound represented by the formula (I):



(I)

wherein

ring A and ring B are the same or different and each is an optionally substituted 5- to 7-membered monocycle;

ring D is an optionally substituted 5-membered monocycle wherein Y is N, C or CH;

X is a spacer having 1 to 4 atoms in the main chain; and

W is a group represented by

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, or

$-ONR^{1a}CONR^{1c}R^2$

wherein

R^{1a} and R^{1b} are the same or different and each is a hydrogen atom or a C_{1-6} alkyl group;

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

R^2 is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group; and

m and n are the same or different and each is an integer of 1 or 2, or

a 5- or 6-membered heterocyclic group containing NH, which is optionally substituted,

provided that

1) when ring D is a substituted imidazole, then W should not be an aminoimidazole; and

2) when ring D is a substituted pyrazole, and X is -CH=, then W should not be an oxothioxothiazolidinyl and an oxothioxoimidazolidinyl,

or a salt thereof.

3. The compound of claim 1, wherein ring D' is an optionally substituted pyrazole.

4. The compound of claim 2, wherein ring D is an optionally substituted pyrazole.

5. The compound of claim 1 or 2, wherein X is a C_{1-4} alkylene group or a C_{2-4} alkenylene group.

6. The compound of claim 1 or 2, wherein W is a group represented by $-CONR^{1a}S(O)_mR^2$ wherein each symbol is as defined in claim 1.

7. (2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 9),
(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 27),
(2E)-3-[1,3-dimethyl-5-(1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-[(4-methylphenyl)sulfonyl]acrylamide (Example 33),
(2E)-3-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-[(pentylamino)sulfonyl]acrylamide (Example 62),
cyclopropylmethyl ({2-[5-(5-chloro-1H-indol-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 189),
butyl ({2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]ethyl}sulfonyl)carbamate (Example 197),
(2E)-3-[1,3-dimethyl-5-(5-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-pyrazol-4-yl]-N-(pentylsulfonyl)acrylamide (Example 232),
(2E)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]-N-{[(cyclopropylmethyl)amino]sulfonyl}acrylamide (Example 264),
N-[(butylamino)carbonyl]-2-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-3-cyclopropyl-1-methyl-1H-pyrazol-4-yl]ethanesulfonamide (Example 279),
(2E)-N-(butylsulfonyl)-3-[5-(5-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,3-dimethyl-1H-pyrazol-4-yl]acrylamide (Example 283),
N-[(butylamino)carbonyl]-2-{1,3-dimethyl-5-[5-

(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethanesulfonamide (Example 294), or

butyl [(2-{1,3-dimethyl-5-[5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-1-yl]-1H-pyrazol-4-yl}ethyl)sulfonyl]carbamate (Example 295),

or a salt thereof.

8. A prodrug of a compound of claim 1.

9. A pharmaceutical agent comprising a compound of claim 1 or a prodrug thereof.

10. The pharmaceutical agent of claim 9, which is an insulin sensitizer.

11. The pharmaceutical agent of claim 9, which is an agent for the prophylaxis or treatment of diabetes.

12. A method of improving insulin resistance in a mammal, which comprises administering a compound of claim 1 or a prodrug thereof to the mammal.

13. A method for the prophylaxis or treatment of diabetes in a mammal, which comprises administering a compound of claim 1 or a prodrug thereof to the mammal.

14. Use of a compound of claim 1 or a prodrug thereof for the production of an insulin sensitizer.

15. Use of a compound of claim 1 or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetes.

COMPUESTOS ANULARES FUSIONADOS COMO AGONISTAS PARCIALES DE PPAR-GAMMA

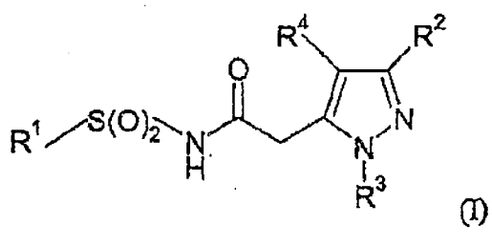
Campo de la invención

La presente invención se refiere a un compuesto anular fusionado como un agente para la prevención o el tratamiento de diabetes.

Antecedentes de la invención

Como un compuesto anular fusionado, se conocen los compuestos descritos en las siguientes bibliografías.

(1) Como un compuesto que tiene una acción inhibidora de la enzima convertidora de la endotelina, el documento WO2006/075955 describe un compuesto representado por la fórmula:



(I)

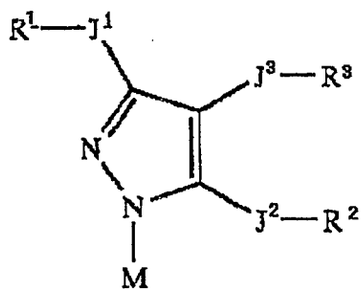
en donde

R^1 es un grupo arilo opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido;

R^2 y R^4 son, de modo independiente, un átomo de hidrógeno, un átomo de halógeno, un grupo alquilo de C_{1-6} y similares; y

R^3 es un grupo arilo opcionalmente sustituido, un grupo heteroarilo opcionalmente sustituido o un grupo cicloalquilo de C_{3-7}.

(2) Como un compuesto que tiene una acción inhibidora de la 15-lipoxigenasa, el documento US2005/0070589 describe un compuesto representado por la fórmula:



en donde

J^1 es un enlace, -C(O)-, -OC(O)-, -C(O)O-, $-NR^4-$, $-NR^4$-CO- o $-CONR^4-$;

J^2 es un enlace, -CO-, -OC(O)-, -C(O)O-, $-NR^{4a}-$, $-NR^{4a}$-C(O)- o $-C(O)NR^{4a}-$;

J^3 es un grupo alquileno, un grupo alquenileno, un grupo alquinileno y similares, cada uno de los cuales está opcionalmente sustituido con un grupo alquilo y similares;

R^1 y R^2 son, de modo independiente, un átomo de hidrógeno, un grupo cicloalquilo, un grupo heterocíclico, un grupo arilo, un grupo heteroarilo y similares, cada uno de los cuales está opcionalmente sustituido con un grupo alquilo y similares;

R^3 es $-NR^{3a}SO_2Z$, $-NR^{3a}C(O)OZ$, $-NR^{3a}C(O)Z$, $-NR^{3a}C(O)NR^{3b}Z$ y similares;

R^{3a}, R^{3b}, R^4 y R^{4a} son, de modo independiente, un átomo de hidrógeno, un grupo alquilo y similares;

Z es $-NR^5R^6$, $-C(O)R^7$, $-C(O)OR^7$ y similares;

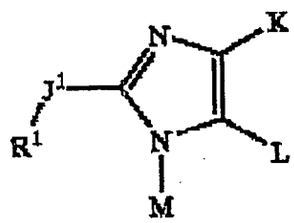
R^5 y R^6 son, de modo independiente, un átomo de hidrógeno, un grupo alquilo y similares;

R^7 es un átomo de hidrógeno, un grupo alquilo y similares; y

M es un átomo de hidrógeno, un grupo alquilo y similares,

con la condición de que se excluya un compuesto en donde R^1-J^1- y R^2-J^2- son ambos átomos de hidrógeno.

(3) Como un compuesto que tiene una acción inhibidora de la 15-lipoxigenasa, el documento US2005/0070588 describe un compuesto representado por la fórmula:



en donde

uno de K y L es $-J^2-R^2$ y el otro es $-J^3-R^3$;

J^1 es un enlace, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-NR^4-$, $-NR^4-CO-$ o $-CONR^4-$;

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J^2 es un enlace, -CO-, -OC(O)-, -C(O)O-, $-NR^{4a}-$, $-NR^{4a}$-C(O)- o $-C(O)NR^{4a}-$;

J^3 es un grupo alquileno, un grupo alquenileno, un grupo alquinileno y similares, cada uno de los cuales está opcionalmente sustituido con un grupo alquilo y similares;

R^1 y R^2 son, de modo independiente, un átomo de hidrógeno, un grupo cicloalquilo, un grupo heterocíclico, un grupo arilo, un grupo heteroarilo y similares, cada uno de los cuales está opcionalmente sustituido con un grupo alquilo y similares;

R^3 es $-NR^{3a}SO_2Z$, $-NR^{3a}C(O)OZ$, $-NR^{3a}C(O)Z$, $-NR^{3a}C(O)NR^{3b}Z$ y similares;

R^{3a}, R^{3b}, R^4 y R^{4a} son, de modo independiente, un átomo de hidrógeno, un grupo alquilo y similares;

Z es $-NR^5R^6$, $-C(O)R^7$, $-C(O)OR^7$ y similares;

R^5 y R^6 son, de modo independiente, un átomo de hidrógeno, un grupo alquilo y similares;

R^7 es un átomo de hidrógeno, un grupo alquilo y similares; y

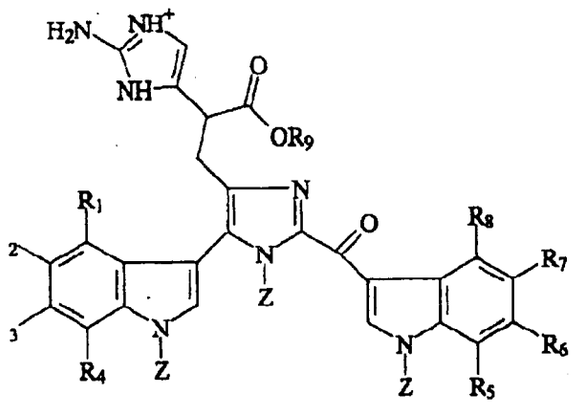
M es un átomo de hidrógeno, un grupo alquilo y similares,

con la condición de que se excluya un compuesto en donde R^1-J^1- y R^2-J^2- son ambos átomos de hidrógeno.

(4) Como un agente terapéutico para neuritis, el documento WO99/42092 describe un compuesto representado por

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la fórmula:



(III)

en donde

R^1 a R^8 son, de modo independiente, un átomo de hidrógeno, un grupo hidroxi, un átomo de halógeno, -R, -OR, -OCOR, -OA o NZZ;

R^9 es un grupo alquilo de C_{1-8} o un grupo arilo;

Z es un átomo de hidrógeno, -R, un grupo hidroxi o -COR;

R es un grupo alquilo de C_{1-3}, un grupo alcoxi C_{1-8}, un grupo mesilo o un grupo tosilo; y

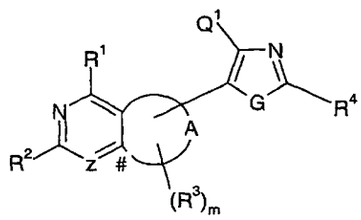
A es -R-fenilo.

El receptor gamma activado por el proliferador de peroxisoma (PPARγ), que es un miembro de la superfamilia de los receptores de la hormona nuclear representado por receptores de hormonas esteroides y receptores de la hormona de la glándula tiroidea, muestra una expresión inducida al comienzo de la diferenciación de adipocitos y desempeña un

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papel importante como un regulador maestro en la diferenciación de adipocitos. El PPARγ se une con un ligando para formar un dímero con el receptor de retinoide X (RXR), y el dímero se une con un elemento de respuesta de un gen objetivo en el núcleo para controlar (activar) directamente la eficacia de la transcripción.

(5) Como un inhibidor de la tirosina cinasa del receptor Tie2, el documento WO2004/013141 describe un compuesto representado por la fórmula:



en donde

A es un heterociclo aromático de 5 miembros;

G es O, S o NR^5;

Z es N o CR^6;

Q^1 es un grupo arilo o un grupo heteroarilo, cada uno de los cuales está opcionalmente sustituido;

R^2 es H, un amino y similares;

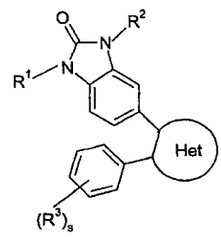
R^3, R^4, R^5 y R^6 son, de modo independiente, H, OH, un átomo de halógeno, Q^4-X^5- y similares;

Q^4 es un grupo arilo, un grupo aril-alquilo de C_{1-6}, un grupo heteroarilo, un grupo heteroaril-alquilo de C_{1-6}, un grupo heterociclilo o un grupo heterociclil-alquilo de C_{1-6}; y

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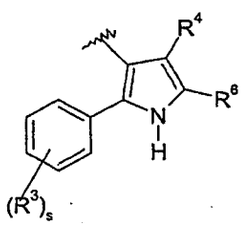
m es 0, 1 ó 2.

(6) Como un inhibidor de ERK/MAP, el documento WO2002/072576 describe un compuesto representado por la fórmula:

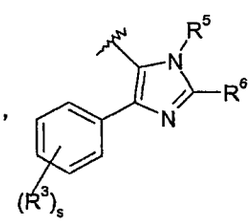


en donde

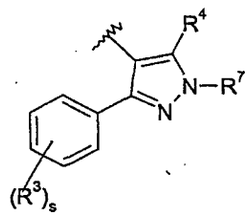
Het es cualquiera de



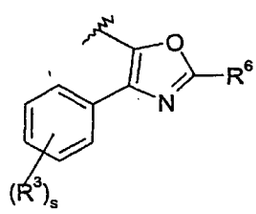
(a)



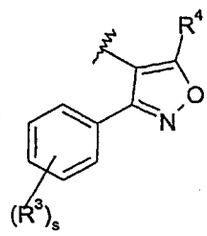
(b)



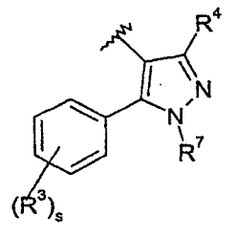
(c)



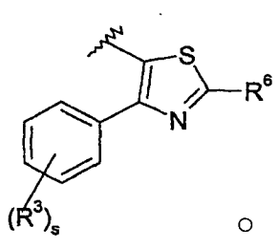
(d)



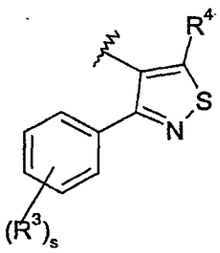
(e)



(f)



(g) o



(h) ;

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R^1 y R^2 son, de modo independiente, H, un alquilo de C_{1-6} y similares;

R^3 es un átomo de halógeno, un alquilo de C_{1-6} y similares;

R^4 y R^6 son, de modo independiente, H, un átomo de halógeno o $-(CH_2)_n-B-R^9$;

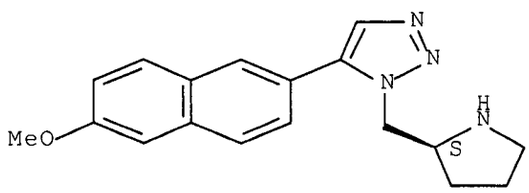
B es un enlace, -O-, -S-, -CO- y similares;

R^5 y R^7 son, de modo independiente, H, un fenilo opcionalmente sustituido, un heteroarilo de C_{1-10} opcionalmente sustituido, un heterociclilo de C_{1-10} opcionalmente sustituido y similares;

R^9 es H, un fenilo opcionalmente sustituido, un heteroarilo de C_{1-10} opcionalmente sustituido, un heterociclilo de C_{1-10} opcionalmente sustituido y similares; y

s es un número entero de 0 a 5.

(7) Como un catalizador, Journal of Organic Chemistry, 2006, 71(24), pp. 9244-9247, describe el siguiente compuesto:



Breve descripción de la invención

Hay una demanda de desarrollo de un agente para la prevención o el tratamiento de diabetes que tenga una acción

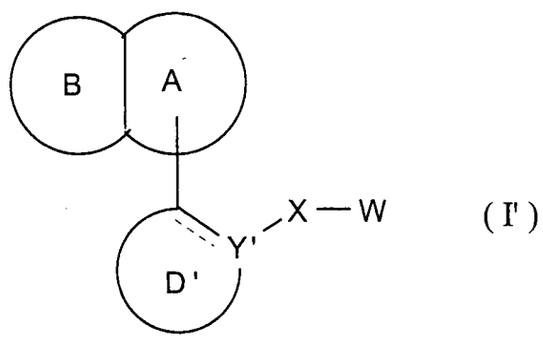
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hipoglucémica superior y que se asocie con menos efectos secundarios, por ejemplo aumento de peso corporal, y similares.

Los presentes inventores hallaron que un compuesto representado por las siguientes fórmulas (I') y un compuesto representado por las siguientes fórmulas (I) tienen una acción hipoglucémica superior, y son de utilidad para la prevención o el tratamiento de diabetes, lo que dio resultado en la terminación de la presente invención.

Conforme a ello, la presente invención se refiere a

[1] un compuesto representado por la fórmula (I'):



(I')

en donde

el anillo A y el anillo B son iguales o diferentes y cada uno es un monociclo de 5 a 7 miembros opcionalmente sustituido;

el anillo D' es un heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido en donde Y' es N o C;

X es un espaciador que tiene 1 a 4 átomos en la

cadena principal; y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} y R^{1b} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-6};

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} o un grupo alcoxi de C_{1-6};

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; y

m y n son iguales o diferentes y cada uno es un número entero de 1 ó 2, o

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un grupo heterocíclico de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido,

con la condición de que

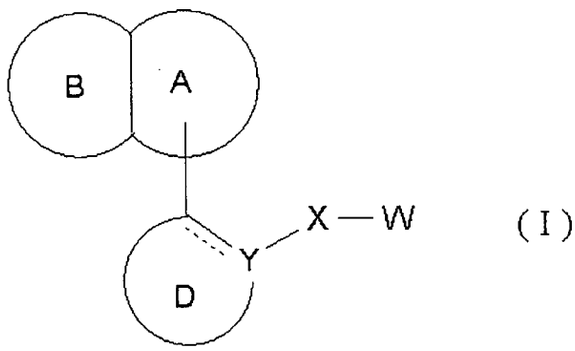
1) cuando el anillo D' es un imidazol sustituido, entonces W no sea 2-amino-1H-imidazol-5-ilo, 1H-imidazol-2-ilo, 3.5-dimetil-1H-pirazol-4-ilo y piperazin-1-ilo;

2) cuando el anillo D' es un pirazol sustituido, y X es -CH=, entonces W no sea 4-oxo-2-tioxo-1,3-tiazolidin-5-ilideno, 5-oxo-2-tioxoimidazolidin-4-ilideno opcionalmente sustituido con grupo(s) fenilo, 3-metil-5-oxo-1.5-dihidro-4H-pirazol-4-ilideno, 2,4,6-trioxotetrahidropirimidin-5(2H)-ilideno y 4,6-dioxo-2-tioxotetrahidropirimidin-5(2H)-ilideno; y

3) se excluya 5-(6-metoxi-2-naftil)-1-(pirrolidin-2-ilmetil)-1H-1,2,3-triazol,

o una de sus sales (de ahora en adelante, abreviado como compuesto (I'));

[2] un compuesto representado por la fórmula (I):



(I)

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en donde

el anillo A y el anillo B son iguales o diferentes y cada uno es un monociclo de 5 a 7 miembros opcionalmente sustituidos;

el anillo D es un monociclo de 5 miembros opcionalmente sustituido en donde Y es N, C o CH;

X es un espaciador que tiene 1 a 4 átomos en la cadena principal; y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} y R^{1b} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-6};

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} o un grupo alcoxi de C_{1-6};

R^2 es un átomo de hidrógeno, un grupo hidrocarburo

opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; y

m y n son iguales o diferentes y cada uno es un número entero de 1 ó 2, o

un grupo heterocíclico de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido,

con la condición de que

1) cuando el anillo D es un imidazol sustituido, entonces W no sea un aminoimidazol; y

2) cuando el anillo D es un pirazol sustituido, y X es -CH=, entonces W no sea un oxotioxotiazolidinilo y un oxotioxoimidazolidinilo,

o una de sus sales (de ahora en adelante, abreviado como compuesto (I));

[3] el compuesto del punto [1] antes mencionado, en donde el anillo D' es un pirazol opcionalmente sustituido;

[4] el compuesto del punto [2] antes mencionado, en donde el anillo D es un pirazol opcionalmente sustituido;

[5] el compuesto del punto [1] o [2] antes mencionado, en donde X es un grupo alquileno de C_{1-4} o un grupo alquenileno de C_{2-4};

[6] el compuesto del punto [1] o [2] antes mencionado, en donde W es un grupo representado por $-CONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió en el punto [1] antes mencionado;

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[7] (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 9),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 27),

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida (Ejemplo 33),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida (Ejemplo 62),

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo (Ejemplo 189),

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo (Ejemplo 197),

(2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 232),

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida (Ejemplo 264),

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-

4-il]etansulfonamida (Ejemplo 279),

(2E)-N-(butilsulfonil)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida (Ejemplo 283),

N-[(butilamino)carbonil]-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida (Ejemplo 294), o

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de butilo (Ejemplo 295),

o una de sus sales;

[8] un profármaco del compuesto (I');

[9] un agente farmacéutico que comprende el compuesto (I') o uno de sus profármacos;

[10] el agente farmacéutico del punto [9] antes mencionado, que es un sensibilizador de insulina;

[11] el agente farmacéutico del punto [9] antes mencionado, que es un agente para la prevención o el tratamiento de diabetes;

[12] un método para mejorar la resistencia a la insulina en un mamífero, que comprende la administración del compuesto (I') o uno de sus profármacos al mamífero;

[13] un método para la prevención o el tratamiento de diabetes en un mamífero, que comprende la administración del compuesto (I') o uno de sus profármacos al mamífero;

[14] uso del compuesto (I') o uno de sus profármacos para la producción de un sensibilizador de insulina;

[15] uso del compuesto (I') o uno de sus profármacos para la producción de un agente para la prevención o el tratamiento de diabetes;

y similares.

De acuerdo con la presente invención, se puede proveer un agente para la prevención o el tratamiento de diabetes que tiene una acción hipoglucémica superior y que está asociado con menor cantidad de efectos secundarios tales como aumento de peso corporal, y similares.

Descripción detallada de la invención

La presente invención se explica en detalle a continuación.

Salvo que se especifique otra cosa, el "átomo de halógeno" en la presente especificación significa átomo de flúor, átomo de cloro, átomo de bromo o átomo de yodo.

Salvo que se especifique otra cosa, el "grupo alquilenodioxi de C_{1-3}" en la presente especificación significa metilenodioxi, etilenodioxi, trimetilenodioxi o similares.

Salvo que se especifique otra cosa, el "grupo alquilo de C_{1-6}" en la presente especificación significa

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metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1.1-dimetilbutilo, 2.2-dimetilbutilo, 3.3-dimetilbutilo, 2-etilbutilo o similares.

Salvo que se especifique otra cosa, el "grupo alcoxi de C_{1-6}" en la presente especificación significa metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, sec-butoxi, ter-butoxi o similares.

Salvo que se especifique otra cosa, el "grupo alcoxi de C_{1-6}-carbonilo" en la presente especificación significa metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, ter-butoxicarbonilo o similares.

Salvo que se especifique otra cosa, el "grupo alquil de C_{1-6}-carbonilo" en la presente especificación significa acetilo, propanoílo, butanoílo, isobutanoílo, pentanoílo, isopentanoílo, hexanoílo o similares.

La definición de cada símbolo en las fórmulas (I') y (I) se describe en detalle a continuación.

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} y R^{1b} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-6};

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} o un grupo alcoxi de C_{1-6};

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; y

m y n son iguales o diferentes y cada uno es un número entero de 1 ó 2, o

un grupo heterocíclico de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido.

Como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2, por ejemplo, se pueden mencionar un grupo alquilo de C_{1-10}, un grupo alquenilo de C_{2-10}, un grupo alquinilo de C_{2-10}, un grupo cicloalquilo de C_{3-10}, un grupo cicloalquenilo de C_{3-10}, un grupo cicloalcadienilo de C_{4-10}, un grupo arilo de C_{6-14}, un

grupo aralquilo de C_{7-13}, un grupo arilalquenilo de C_{8-13} y similares.

Como el grupo alquilo de C_{1-10}, se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec-butilo, ter-butilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, hexilo, isohexilo, 1.1-dimetilbutilo, 2.2-dimetilbutilo, 3.3-dimetilbutilo, 2-etilbutilo, heptilo, octilo, nonilo, decilo y similares. De ellos, se prefiere un grupo alquilo de C_{1-6}.

Como el grupo alquenilo de C_{2-10}, se pueden mencionar, por ejemplo, etenilo, 1-propenilo, 2-propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo, 3-butenilo, 3-metil-2-butenilo, 1-pentenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 4-metil-3-pentenilo, 1-hexenilo, 3-hexenilo, 5-hexenilo, 1-heptenilo, 1-octenilo y similares. De ellos, se prefiere un grupo alquenilo de C_{2-6}.

Como el grupo alquinilo de C_{2-10}, se pueden mencionar, por ejemplo, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, 3-butinilo, 1-pentinilo, 2-pentinilo, 3-pentinilo, 4-pentinilo, 1-hexinilo, 2-hexinilo, 3-hexinilo, 4-hexinilo, 5-hexinilo, 1-heptinilo, 1-octinilo y similares. De ellos, se prefiere un grupo alquinilo de C_{2-6}.

Como el grupo cicloalquilo de C_{3-10}, se pueden mencionar, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y

similares. De ellos, se prefiere un grupo cicloalquilo de C_{3-6}.

Como el grupo cicloalquenilo de C_{3-10}, se pueden mencionar, por ejemplo, 2-ciclopenten-1-ilo, 3-ciclopenten-1-ilo, 2-ciclohexen-1-ilo, 3-ciclohexen-1-ilo y similares. De ellos, se prefiere un grupo cicloalquenilo de C_{3-6}.

Como el grupo cicloalcadienilo de C_{4-10}, se pueden mencionar, por ejemplo, 2,4-ciclopentadien-1-ilo, 2,4-ciclohexadien-1-ilo, 2.5-ciclohexadien-1-ilo y similares. De ellos, se prefiere un grupo cicloalcadienilo de C_{4-6}.

El grupo cicloalquilo de C_{3-10} antes mencionado, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} están cada uno opcionalmente condensados con un anillo benceno para formar un grupo cíclico fusionado, y como el grupo cíclico fusionado se pueden mencionar, por ejemplo, indanilo, dihidronaftilo, tetrahidronaftilo, fluorenilo y similares.

Además, el grupo cicloalquilo de C_{3-10}, el grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} antes mencionados pueden ser cada uno un grupo hidrocarburo de C_{7-10} con enlaces cruzados. Como el grupo hidrocarburo de C_{7-10} con enlaces cruzados se pueden mencionar biciclo[2.2,1]heptilo (norbornilo), biciclo[2.2,2]octilo, biciclo[3.2,1]octilo, biciclo[3.2,2]nonilo, biciclo[3.3,1]nonilo, biciclo[4.2,1]nonilo, biciclo[4.3,1]decilo, adamantilo y

similares.

Más aún, el grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} antes mencionados pueden formar opcionalmente, junto con un cicloalcano de C_{3-10}, un cicloalqueno de C_{3-10} o un cicloalcadieno de C_{4-10}, un grupo espiroanillo. Como el cicloalcano de C_{3-10}, cicloalqueno de C_{3-10} y cicloalcadieno de C_{4-10}, se pueden mencionar los anillos correspondientes al grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} antes mencionados. Como los grupos espiroanillos, se pueden mencionar espiro[4.5]decan-8-ilo y similares.

Como el grupo arilo de C_{6-14}, se pueden mencionar, por ejemplo, fenilo, naftilo, antrilo, fenantrilo, acenaftilenilo, bifenililo y similares. De ellos, se prefiere un grupo arilo de C_{6-12}.

Como el grupo aralquilo de C_{7-13}, se pueden mencionar, por ejemplo, bencilo, fenetilo, naftilmetilo, bifenililmetilo y similares.

Como el grupo arilalquenilo de C_{8-13}, se pueden mencionar, por ejemplo, estirilo y similares.

El grupo alquilo de C_{1-10}, grupo alquenilo de C_{2-10} y grupo alquinilo de C_{2-10} ejemplificados como el "grupo hidrocarburo" antes mencionado tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles.

Como tales sustituyentes, se pueden mencionar, por ejemplo,

(1) un grupo cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo, ciclohexilo);

(2) un grupo arilo de C_{6-14} (por ejemplo, fenilo, naftilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) un grupo hidroxi,

(c) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, y

(d) un átomo de halógeno;

(3) un grupo heterocíclico aromático (por ejemplo, tienilo, furilo, piridilo, pirazolilo, imidazolilo, tetrazolilo, oxazolilo, tiazolilo, oxadiazolilo, tiadiazolilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) un grupo hidroxi,

(c) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, y

(d) un átomo de halógeno;

(4) un grupo heterocíclico no aromático (por

ejemplo, tetrahidrofurilo, morfolinilo, tiomorfolinilo, piperidinilo, pirrolidinilo, piperazinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) un grupo hidroxi,

(c) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno, y

(d) un átomo de halógeno;

(5) un grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de

(a) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno y un grupo cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo),

(b) un grupo alquil C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno, y

(c) un grupo alcoxi de C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(6) un grupo alquil C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 átomos de halógeno;

(7) un grupo alcoxi de C_{1-6}-carbonilo opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) un grupo alcoxi de C_{1-6};

(8) un grupo alquil de C_{1-6}-sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo, isopropilsulfonilo) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(9) un grupo carbamoílo opcionalmente mono- o disustituido con grupos alquilo de C_{1-6} opcionalmente sustituidos con 1 a 3 átomos de halógeno;

(10) un grupo tiocarbamoílo opcionalmente mono- o disustituido con grupos alquilo de $C_{1-6carba}$ opcionalmente sustituidos con 1 a 3 átomos de halógeno;

(11) un grupo sulfamoílo opcionalmente mono- o disustituido con grupos alquilo de C_{1-6} opcionalmente sustituidos con 1 a 3 átomos de halógeno;

(12) un grupo carboxi;

(13) un grupo hidroxi;

(14) un grupo alcoxi de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) un grupo carboxi,

(c) un grupo alcoxi de C_{1-6},

(d) un grupo alquil C_{1-6}-carbonilo,

(e) un grupo alcoxi de C_{1-6}-carbonilo,

(f) un grupo amino opcionalmente mono- o disustituido con sustituyentes seleccionados de un grupo alquilo de C_{1-6} y un grupo alcoxi de C_{1-6}-carbonilo,

(g) un grupo arilo de C_{6-14} (por ejemplo, fenilo), y

(h) un grupo cicloalquilo de C_{3-10} (por ejemplo, ciclopropilo);

(15) un grupo alquenil de C_{2-6}-oxi (por ejemplo, eteniloxi) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(16) un grupo aril de C_{6-14}-oxi (por ejemplo, feniloxi, naftiloxi);

(17) un grupo alquil de C_{1-6}-carboniloxi (por ejemplo, acetiloxi, ter-butilcarboniloxi);

(18) un grupo aril de C_{6-14}-carbonilo (por ejemplo, benzoílo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno;

(19) un grupo heterociclilcarbonilo no aromático (por ejemplo, pirrolidinilcarbonilo, morfolinilcarbonilo, 1,1-dióxidotiomorfolinilcarbonilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno;

(20) un grupo mercapto;

(21) un grupo alquil de C_{1-6}-tio (por ejemplo, metiltio, etiltio) opcionalmente sustituido con 1 a 3 átomos de halógeno;

(22) un grupo aralquil de C_{7-13}-tio (por ejemplo,

benciltio);

(23) un grupo aril de C_{6-14}-tio (por ejemplo, feniltio, naftiltio);

(24) un grupo ciano;

(25) un grupo nitro;

(26) un átomo de halógeno;

(27) un grupo alquilen de C_{1-3}-dioxi;

(28) un grupo heterociclilcarbonilo aromático (por ejemplo, pirazolilcarbonilo, pirazinilcarbonilo, isoxazolilcarbonilo, piridilcarbonilo, tiazolilcarbonilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno;

(29) un grupo hidroxiimino opcionalmente sustituido con un grupo alquilo de C_{1-6} (por ejemplo, metilo) opcionalmente sustituido con 1 a 3 grupos arilo de C_{6-14} (por ejemplo, fenilo);

(30) un grupo alquil de C_{1-6}-sulfoniloxi (por ejemplo, metilsulfoniloxi)

y similares. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

El grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10}, grupo cicloalcadienilo de C_{4-10}, grupo arilo de C_{6-14}, grupo aralquilo de C_{7-13} y grupo arilalquenilo de C_{8-13} ejemplificado como el "grupo hidrocarburo" antes mencionado

tienen opcionalmente 1 a 3 sustituyentes en posiciones sustituibles.

Como el sustituyente, se pueden mencionar, por ejemplo,

(1) los grupos ejemplificados como los sustituyentes para el grupo alquilo de C_{1-10} antes mencionado, y similares;

(2) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) un grupo carboxi,

(c) un grupo hidroxi,

(d) un grupo alcoxi de C_{1-6}-carbonilo,

(e) un grupo alcoxi de C_{1-6} opcionalmente sustituido con sililo grupos opcionalmente sustituidos con 1 a 3 grupos alquilo de C_{1-6} (por ejemplo, trimetilsililo),

(f) un grupo amino opcionalmente mono- o disustituido con grupos alquilo de C_{1-6}, y

(g) un grupo arilo de C_{6-14} (por ejemplo, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6};

(3) un grupo alquenilo de C_{2-6} (por ejemplo, etenilo, 1-propenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) un grupo carboxi,

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(c) un grupo hidroxi,

(d) un grupo alcoxi de C_{1-6}-carbonilo,

(e) un grupo alcoxi de C_{1-6}, y

(f) un grupo amino opcionalmente mono- o disustituido con grupos alquilo de C_{1-6};

(4) un grupo aralquilo de C_{7-13} (por ejemplo, bencilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo alquilo de C_{1-6} opcionalmente sustituido con 1 a 3 átomos de halógeno,

(b) un grupo hidroxi,

(c) un grupo alcoxi de C_{1-6}, y

(d) un átomo de halógeno;

y similares. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2, se pueden mencionar un grupo heterocíclico aromático y un grupo heterocíclico no aromático.

Como el grupo heterocíclico aromático, se pueden mencionar, por ejemplo, un grupo heterocíclico aromático monocíclico de 5 a 7 miembros que contiene, como un átomo constitutivo del anillo además de átomos de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo

de azufre y un átomo de nitrógeno, y un grupo heterocíclico aromático fusionado. Como el grupo heterocíclico aromático fusionado, se pueden mencionar, por ejemplo, un grupo derivado de un anillo fusionado, en donde un anillo correspondiente al grupo heterocíclico aromático monocíclico de 5 a 7 miembros y 1 ó 2 anillos seleccionados de un heterociclo aromático de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno (por ejemplo, pirrol, imidazol, pirazol, pirazina, piridina, pirimidina), un heterociclo aromático de 5 miembros que contiene un átomo de azufre (por ejemplo, tiofeno) y un anillo benceno están fusionados, y similares.

Como ejemplos preferidos del grupo heterocíclico aromático, se pueden mencionar:

grupos heterocíclicos aromáticos monocíclicos tales como furilo (por ejemplo, 2-furilo, 3-furilo), tienilo (por ejemplo, 2-tienilo, 3-tienilo), piridilo (por ejemplo, 2-piridilo, 3-piridilo, 4-piridilo), pirimidinilo (por ejemplo, 2-pirimidinilo, 4-pirimidinilo, 5-pirimidinilo), piridazinilo (por ejemplo, 3-piridazinilo, 4-piridazinilo), pirazinilo (por ejemplo, 2-pirazinilo), pirrolilo (por ejemplo, 1-pirrolilo, 2-pirrolilo, 3-pirrolilo), imidazolilo (por ejemplo, 1-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo), pirazolilo (por ejemplo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo), tiazolilo (por ejemplo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo), isotiazolilo (por

ejemplo, 4-isotiazolilo), oxazolilo (por ejemplo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo), isoxazolilo, oxadiazolilo (por ejemplo, 1,2,4-oxadiazol-5-ilo, 1.3,4-oxadiazol-2-ilo), tiadiazolilo (por ejemplo, 1.3,4-tiadiazol-2-ilo), triazolilo (por ejemplo, 1,2,4-triazol-1-ilo, 1,2,4-triazol-3-ilo, 1,2,3-triazol-1-ilo, 1,2,3-triazol-2-ilo, 1,2,3-triazol-4-ilo), tetrazolilo (por ejemplo, tetrazol-1-ilo, tetrazol-5-ilo), triazinilo (por ejemplo, 1,2,4-triazin-1-ilo, 1,2,4-triazin-3-ilo, 1.3,5-triazin-1-ilo) y similares;

grupos heterocíclicos aromáticos fusionados tales como quinolilo (por ejemplo, 2-quinolilo, 3-quinolilo, 4-quinolilo, 6-quinolilo), isoquinolilo (por ejemplo, 3-isoquinolilo), quinazolilo (por ejemplo, 2-quinazolilo, 4-quinazolilo), quinoxalilo (por ejemplo, 2-quinoxalilo, 6-quinoxalilo), benzofuranilo (por ejemplo, 2-benzofuranilo, 3-benzofuranilo), benzotiofenilo (por ejemplo, 2-benzotiofenilo, 3-benzotiofenilo), benzoxazolilo (por ejemplo, 2-benzoxazolilo), benzisoxazolilo (por ejemplo, 7-benzisoxazolilo), benzotiazolilo (por ejemplo, 2-benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol-1-ilo, bencimidazol-2-ilo, bencimidazol-5-ilo), benzotriazolilo (por ejemplo, 1H-1,2,3-benzotriazol-5-ilo), indolilo (por ejemplo, indol-1-ilo, indol-2-ilo, indol-3-ilo, indol-5-ilo), indazolilo (por ejemplo, 1H-indazol-3-ilo), pirrolopirazinilo (por ejemplo, 1H-pirrolo[2,3-b]pirazin-2-

ilo, 1H-pirrolo[2,3-b]pirazin-6-ilo), pirrolopiridilo (por ejemplo, 1H-pirrolo[2,3-b]piridin-1-ilo), imidazopiridinilo (por ejemplo, 1H-imidazo[4.5-b]piridin-2-ilo, 1H-imidazo[4.5-c]piridin-2-ilo, 2H-imidazo[1.2-a]piridin-3-ilo), imidazopirazinilo (por ejemplo, 1H-imidazo[4.5-b]pirazin-2-ilo), pirazolopiridinilo (por ejemplo, 1H-pirazolo[4.3-c]piridin-3-ilo), pirazolotienilo (por ejemplo, 2H-pirazolo[3,4-b]tiofen-2-ilo), pirazolotriazinilo (por ejemplo, pirazolo[5.1-c][1,2,4]triazin-3-ilo) y similares;

y similares.

Como el grupo heterocíclico no aromático, se pueden mencionar, por ejemplo, un grupo heterocíclico no aromático monocíclico de 5 a 7 miembros que contiene, como un átomo constitutivo del anillo además de átomos de carbono, 1 a 4 heteroátomos seleccionados de un átomo de oxígeno, un átomo de azufre (el átomo de azufre está opcionalmente oxidado) y un átomo de nitrógeno, y un grupo heterocíclico no aromático fusionado. Como el grupo heterocíclico no aromático fusionado, se pueden mencionar, por ejemplo, un grupo derivado de un anillo fusionado en donde un anillo correspondiente al grupo heterocíclico no aromático monocíclico de 5 a 7 miembros y 1 ó 2 anillos seleccionados de un heterociclo aromático de 5 ó 6 miembros que contiene 1 ó 2 átomos de nitrógeno (por ejemplo, pirrol, imidazol, pirazol, pirazina, piridina, pirimidina), un heterociclo

aromático de 5 miembros que contiene un átomo de azufre (por ejemplo, tiofeno) y un anillo benceno están fusionados, un grupo en donde el grupo antes mencionado está parcialmente saturado, y similares. Además, como el grupo heterocíclico no aromático, se puede mencionar un grupo en donde cualquiera de los átomos de carbono que constituyen el anillo en el anillo del grupo heterocíclico no aromático antes mencionado está sustituido con 1 a 3 grupos oxo y/o grupos tioxo.

Como ejemplos preferidos del grupo heterocíclico no aromático, se pueden mencionar:

grupos heterocíclicos no aromáticos monocíclicos tales como tetrahidrofurilo (por ejemplo, 2-tetrahidrofurilo), dihidropirrolilo (por ejemplo, 2,3-dihidro-1H-pirrol-1-ilo), pirrolidinilo (por ejemplo, 1-pirrolidinilo), 1,1-dióxidotetrahidrotienilo (por ejemplo, 1,1-dióxidotetrahidro-3-tienilo), piperidinilo (por ejemplo, piperidino), morfolinilo (por ejemplo, morfolino), tiomorfolinilo (por ejemplo, tiomorfolino), 1,1-dióxidotiomorfolinilo (por ejemplo, 1,1-dióxidotiomorfolino), piperazinilo (por ejemplo, 1-piperazinilo), hexametileniminilo (por ejemplo, hexametilenimin-1-ilo), oxazolinilo (por ejemplo, 2.5-dihidrooxazol-3-ilo, 3,4-dihidrooxazol-3-ilo), tiazolinilo (por ejemplo, 2.5-dihidrotiazol-3-ilo, 3,4-dihidrotiazol-3-ilo), imidazolinilo (por ejemplo, 2-imidazolin-3-ilo), oxazolidinilo (por

ejemplo, oxazolidin-3-ilo), tiazolidinilo (por ejemplo, tiazolidin-3-ilo), imidazolidinilo (por ejemplo, imidazolidin-3-ilo), dioxolilo (por ejemplo, 1,3-dioxol-4-ilo), dioxolanilo (por ejemplo, 1,3-dioxolan-4-ilo), dihidrooxadiazolilo (por ejemplo, 4.5-dihidro-1,2,4-oxadiazol-3-ilo), tioxooxazolidinilo (por ejemplo, 2-tioxo-1,3-oxazolidin-5-ilo), tetrahidropiranilo (por ejemplo, 4-tetrahidropiranilo), tetrahidrotiopiranilo (por ejemplo, 4-tetrahidrotiopiranilo), 1,1-dióxidotetrahidrotiopiranilo (por ejemplo, 1,1-dióxidotetrahidrotiopiran-4-ilo), pirazolinilo (por ejemplo, pirazolin-3-ilo), pirazolidinilo (por ejemplo, pirazolidin-1-ilo), oxotetrahidropiridazinilo (por ejemplo, 3-oxo-2.3,4.5-tetrahidropiridazin-4-ilo) y similares;

grupos heterocíclicos no aromáticos fusionados tales como dihidroisoindolilo (por ejemplo, 1,3-dihidro-2H-isoindol-2-ilo), dihidrobenzofuranilo (por ejemplo, 2,3-dihidro-1-benzofuran-5-ilo), dihidrobenzodioxinilo (por ejemplo, 2,3-dihidro-1.4-benzodioxin-2-ilo), dihidrobenzodioxepinilo (por ejemplo, 3,4-dihidro-2H-1.5-benzodioxepin-2-ilo), tetrahidrobenzofuranilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzofuran-3-ilo), tetrahidrobenzotiazolilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzotiazol-2-ilo), tetrahidrobenzoxazolilo (por ejemplo, 4,5,6,7-tetrahidro-1-benzoxazol-2-ilo); cromenilo (por ejemplo, 4H-cromen-2-ilo, 2H-cromen-3-ilo),

dihidroquinolinilo (por ejemplo, 1.2-dihidroquinolin-2-ilo), tetrahidroquinolinilo (por ejemplo, 1,2,3,4-tetrahidroquinolin-2-ilo), dihidroisoquinolinilo (por ejemplo, 1.2-dihidroisoquinolin-2-ilo), tetrahidroisoquinolinilo (por ejemplo, 1,2,3,4-tetrahidroisoquinolin-4-ilo, 1,2,3,4-tetrahidroisoquinolin-2-ilo), dihidroftalazinilo (por ejemplo, 1.4-dihidroftalazin-4-ilo), tetrahidroindazolilo (por ejemplo, 4,5,6,7-tetrahidro-2H-indazol-2-ilo), tetrahidroquinazolinilo (por ejemplo, 5,6,7,8-tetrahidroquinazolin-6-ilo), tetrahidrotiazolopiridinilo (por ejemplo, 4,5,6,7-tetrahidrotiazolo[5.4-c]piridin-6-ilo), tetrahidroimidazopiridinilo (por ejemplo, 1,2,3,4-tetrahidroimidazo[4.5-c]piridin-2-ilo), tetrahidropirazolopiridinilo (por ejemplo, 1,2,3,4-tetrahidropirazolo[3,4-c]piridin-2-ilo), tetrahidrotriazolopirazinilo (por ejemplo, 1,2,3,4-tetrahidrotriazolo[4.3-a]pirazin-2-ilo), tetrahidroimidazopirazinilo (por ejemplo, 1,2,3,4-tetrahidroimidazo[1.2-a]pirazin-2-ilo, 1,2,3,4-tetrahidroimidazo[3,4-a]pirazin-2-ilo), tetrahidropiridopirimidinilo (por ejemplo, 5,6,7,8-tetrahidropirido[5.4-c]pirimidin-6-ilo) y similares.

El "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2 tiene opcionalmente 1 a 3

sustituyentes en posiciones sustituibles. Como el sustituyentes, se pueden mencionar aquellos similares a los sustituyentes que tiene el grupo cicloalquilo de C_{3-10} y similares ejemplificados como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

R^{1a} es preferentemente un átomo de hidrógeno.

R^{1b} es preferentemente un átomo de hidrógeno.

R^{1c} es preferentemente un átomo de hidrógeno o un grupo alquilo de C_{1-6} (preferentemente metilo), con mayor preferencia, un átomo de hidrógeno.

R^2 es preferentemente

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con

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preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo)

opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi).

m es preferentemente 2.

El "grupo heterocíclico que contiene NH de 5 ó 6 miembros" del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W es un grupo heterocíclico de 5 ó 6 miembros que contiene, como miembro constitutivo del anillo, al menos un NH no sustituido (es decir, -NH-), y que además contiene, como átomo constitutivo del anillo, 4 ó 5 átomos seleccionados de un átomo de carbono (el átomo de carbono está opcionalmente sustituido con un grupo oxo o un grupo tioxo), un átomo de oxígeno, un átomo de azufre (el átomo de azufre está opcionalmente oxidado) y un átomo de nitrógeno. Por ejemplo, un grupo heterocíclico aromático de 5 ó 6 miembros y un grupo heterocíclico no aromático de 5 ó 6 miembros, cada uno de los cuales contiene NH.

Como ejemplos preferidos específicos del "grupo heterocíclico aromático de 5 ó 6 miembros que contiene NH",

se pueden mencionar pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo y similares.

Como ejemplos preferidos específicos del "grupo heterocíclico no aromático que contiene NH de 5 ó 6 miembros", se pueden mencionar pirrolinilo, 2.5-dioxopirrolinilo, pirrolidinilo, 2-oxopirrolidinilo, 2.5-dioxopirrolidinilo, pirazolinilo, pirazolidinilo, imidazolinilo, imidazolidinilo, 2-oxoimidazolidinilo, 2,4-dioxoimidazolidinilo, triazolinilo, triazolidinilo, tetrazolinilo, tetrazolidinilo, piperidinilo, 2.6-dioxopiperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, 2-oxopiperazinilo, hexametileniminilo, oxazolinilo, oxooxazolinilo, oxazolidinilo, 2,4-dioxooxazolidinilo, tiazolinilo, tiazolidinilo, 2,4-dioxotiazolidinilo, isoxazolinilo, isoxazolidinilo, isotiazolinilo, isotiazolidinilo, 1,1-dióxidoisotiazolidinilo, 1,1-dióxido-3-oxoisotiazolidinilo, oxadiazolinilo, oxadiazolidinilo, oxooxadiazolinilo, oxooxadiazolidinilo, tiadiazolinilo, tiadiazolidinilo, 1,1-dióxido-3-oxotiadiazolidinilo, dihidropiridilo, tetrahidropiridilo, dihidropirimidinilo, tetrahidropirimidinilo, 2,6-dioxohexahidropirimidinilo, dihidropiridazinilo, tetrahidropiridazinilo, dihidropirazinilo, tetrahidropirazinilo, 1,1-dióxido-1,2-tiazinanilo, 1,1-dióxido-3-oxo-1,2-tiazinanilo y similares.

El "grupo heterocíclico que contiene NH de 5 ó 6

miembros" del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como el sustituyentes, se pueden mencionar aquellos similares a los sustituyentes que tiene opcionalmente el grupo cicloalquilo de C_{3-10} y similares ejemplificados como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como sustituyentes preferidos para el "grupo heterocíclico que contiene NH de 5 ó 6 miembros", se pueden mencionar un grupo alquilo de C_{1-6} (con preferencia, propilo, isopropilo) y similares.

El "grupo heterocíclico que contiene NH de 5 ó 6 miembros" del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W es preferentemente un grupo heterocíclico no aromático de 5 ó 6 miembros que contiene NH, con mayor preferencia, oxooxadiazolinilo (con preferencia, 5(4H)-oxo-1,2,4-oxadiazol-3-ilo), 2,4-dioxotiazolidinilo (con preferencia, 2,4-dioxotiazolidin-5-ilo), 2,4-dioxoimidazolidinilo (con preferencia, 2,4-dioxoimidazolidin-3-ilo), 2-oxopiperazinilo (con preferencia, 2-oxopiperazin-1-ilo) o 1,1-dióxido-3-oxotiadiazolidinilo (con preferencia, 1,1-dióxido-3-oxo-1,2,5-tiadiazolidin-5-ilo).

W es preferentemente un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde cada símbolo es como se definió con anterioridad, o

un grupo heterocíclico no aromático de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido. De ellos, es preferentemente un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, o

$-S(O)_mNR^{1a}CONR^{1c}R^2$

en donde cada símbolo es como se definió con anterioridad,

con preferencia particular, un grupo representado

por $-CONR^{1a}S(O)_mR^2$, en donde cada símbolo es como se definió con anterioridad.

Como ejemplos preferidos específicos de W, se pueden mencionar

(A) un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1b} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (con preferencia, metilo) o un grupo alcoxi de C_{1-6} (con preferencia, propoxi);

R^2 es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi);

m es 2; y

n es 1 ó 2, y

(B) un grupo heterocíclico no aromático de 5 ó 6 miembros que contiene NH [con preferencia, oxooxadiazolinilo (con preferencia, 5(4H)-oxo-1,2,4-oxadiazol-3-ilo), 2,4-dioxotiazolidinilo (con preferencia, 2,4-dioxotiazolidin-5-

ilo), 2,4-dioxoimidazolidinilo (con preferencia, 2,4-dioxoimidazolidin-3-ilo), 2-oxopiperazinilo (con preferencia, 2-oxopiperazin-1-ilo), 1,1-dióxido-3-oxotiadiazolidinilo (con preferencia, 1,1-dióxido-3-oxo-1,2,5-tiadiazolidin-5-il)] opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, propilo, isopropilo).

Como ejemplos específicos de mayor preferencia de W, se puede mencionar un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, o

$-S(O)_mNR^{1a}CONR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (con preferencia, metilo) o un grupo alcoxi de C_{1-6} (con preferencia, propoxi);

R^2 es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia,

fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente

sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi);

m es 2; y

n es 1 ó 2.

Como ejemplos específicos de particular preferencia de W, se puede mencionar un grupo representado por

$-CONR^{1a}S(O)_mR^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^2 es

(1) un grupo alquilo de C_{1-10} (con preferencia, metilo, propilo, butilo, pentilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia,

fenilo), y

(b) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(2) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(4) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(5) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi); y

m es 2.

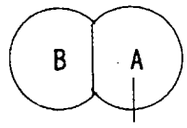
El anillo A y el anillo B son iguales o diferentes y cada uno es un monociclo de 5 a 7 miembros opcionalmente sustituido. Como el "monociclo de 5 a 7 miembros" del "monociclo de 5 a 7 miembros opcionalmente sustituido" para el anillo A o el anillo B, se pueden mencionar "un anillo aromático monocíclico de 5 a 7 miembros" y un "un anillo no aromático monocíclico de 5 a 7 miembros".

Como el "anillo aromático monocíclico de 5 a 7 miembros", se pueden mencionar benceno, un anillo de 5 a 7 miembros (por ejemplo, pirrol, pirazol, imidazol, tiofeno, piridina), de entre el heterociclo aromático monocíclico correspondiente al grupo heterocíclico aromático monocíclico ejemplificado como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2.

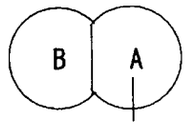
Como "el anillo no aromático monocíclico de 5 a 7 miembros", se pueden mencionar un anillo de 5 a 7 miembros (es decir, un cicloalcano de C_{5-7}, un cicloalqueno de C_{5-7} y un cicloalcadieno de C_{5-7}), de entre un cicloalcano de C_{3-10}, un cicloalqueno de C_{3-10} y un cicloalcadieno de C_{4-10}

correspondiente al grupo cicloalquilo de C_{3-10}, grupo cicloalquenilo de C_{3-10} y grupo cicloalcadienilo de C_{4-10} ejemplificado como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2, y un anillo de 5 a 7 miembros (por ejemplo, pirrolina), de entre un heterociclo no aromático monocíclico correspondiente al grupo heterocíclico no aromático monocíclico ejemplificado como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2.

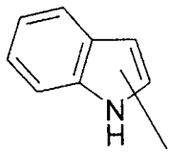
En la presente especificación, el resto representado por



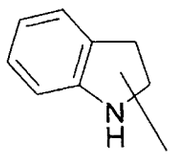
de la fórmula (I') y la fórmula (I) es un grupo derivado de un biciclo, formado por el anillo A y el anillo B que tienen un enlace común (es decir, están condensados). La multiplicidad de enlaces para el anillo A y aquella para el anillo B, implicadas en la formación del biciclo, son iguales. Por ejemplo, cuando el resto representado por



de la fórmula (I') y la fórmula (I) es un grupo representado por (A)



entonces el anillo A deberá ser "pirrol", y el anillo B deberá ser "benceno". Cuando el resto es

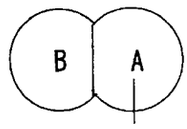


entonces el anillo A deberá ser "pirrolina", y el anillo B deberá ser "benceno".

Como ejemplos preferidos específicos del "monociclo de 5 a 7 miembros" del "monociclo de 5 a 7 miembros opcionalmente sustituido" para el anillo A, se pueden mencionar benceno, un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, pirrol, pirazol, imidazol, tiofeno), un heterociclo no aromático monocíclico de 5 a 7 miembros (con preferencia, pirrolina) y similares.

Como ejemplos preferidos específicos del "monociclo de 5 a 7 miembros" del "monociclo de 5 a 7 miembros opcionalmente sustituido" para el anillo B, se pueden mencionar benceno, un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, piridina) y similares.

Como ejemplos preferidos específicos del resto representado por



se pueden mencionar 1H-indol-1-ilo, 1H-indol-2-ilo, 1H-indol-3-ilo, 1H-indazol-1-ilo, 1H-indazol-3-ilo, 2H-indazol-2-ilo, 1H-bencimidazol-1-ilo, 1H-bencimidazol-2-ilo, 1-benzotiofen-2-ilo, 1-benzotiofen-3-ilo, 2-benzotiofen-1-ilo, 1-benzofuran-2-ilo, 1-benzofuran-3-ilo, 2-benzofuran-1-ilo, 1H-pirrolo[2,3-b]piridin-1-ilo, 1H-pirrolo[2,3-b]piridin-2-ilo, 1H-pirrolo[2,3-b]piridin-3-ilo, 2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-ilo, 2,3-dihidro-1H-pirrolo[2,3-b]piridin-2-ilo, 2,3-dihidro-1H-pirrolo[2,3-b]piridin-3-ilo, 1H-pirrolo[3,2-c]piridin-1-ilo, 1H-pirrolo[3,2-c]piridin-2-ilo, 1H-pirrolo[3,2-c]piridin-3-ilo, 1H-pirrolo[2,3-c]piridin-1-ilo, 1H-pirrolo[2,3-c]piridin-2-ilo, 1H-pirrolo[2,3-c]piridin-3-ilo, 1-naftilo, 2-naftilo, quinolin-5-ilo, quinolin-6-ilo, quinolin-7-ilo, quinolin-8-ilo, isoquinolin-5-ilo, isoquinolin-6-ilo, isoquinolin-7-ilo, isoquinolin-8-ilo y similares.

El "monociclo de 5 a 7 miembros" del "monociclo de 5 a 7 miembros opcionalmente sustituido" para el anillo A o el anillo B tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como el sustituyentes, se pueden mencionar aquellos similares a los sustituyentes que tiene

opcionalmente el grupo cicloalquilo de C_{3-10} y similares ejemplificado como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como sustituyentes preferidos para el anillo A y el anillo B, se pueden mencionar

(1) un átomo de halógeno (con preferencia, átomo de cloro, átomo de flúor, átomo de bromo),

(2) un grupo hidroxi,

(3) un grupo ciano,

(4) un grupo alquilo de C_{1-6} (con preferencia, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(5) un grupo alcoxi de C_{1-6} (con preferencia, metoxi, etoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi),

(c) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo), y

(d) un grupo alquil C_{1-6}-carbonilo (con preferencia, acetilo),

(6) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo),

(7) un grupo alquil C_{1-6}-sulfoniloxi (con preferencia, metilsulfoniloxi),

(8) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(9) un grupo heterocíclico aromático (con preferencia, furilo, tienilo),

(10) un grupo heterocíclico no aromático (con preferencia, pirrolidinilo),

(11) un grupo amino opcionalmente mono- o disustituido con grupos alquilo de C_{1-6} (con preferencia, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos cicloalquilo de C_{3-10} (con preferencia, ciclopropilo)

y similares.

El anillo A es preferentemente benceno opcionalmente sustituido, un heterociclo aromático monocíclico opcionalmente sustituido de 5 a 7 miembros (con preferencia, pirrol, pirazol, imidazol, tiofeno) o un heterociclo no aromático monocíclico opcionalmente sustituido de 5 a 7 miembros (con preferencia, pirrolina).

Como ejemplos preferidos específicos del anillo A, se pueden mencionar benceno, un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, pirrol, pirazol, imidazol, tiofeno) y un heterociclo no aromático

monocíclico de 5 a 7 miembros (con preferencia, pirrolina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno (con preferencia, átomo de cloro) y un grupo alquilo de C_{1-6} (con preferencia, metilo).

El anillo B es preferentemente un benceno opcionalmente sustituido o un heterociclo aromático monocíclico opcionalmente sustituido de 5 a 7 miembros (con preferencia, piridina).

Como ejemplos preferidos específicos del anillo B, se pueden mencionar benceno y un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, piridina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno (con preferencia, átomo de cloro, átomo de flúor, átomo de bromo),

(2) un grupo hidroxi,

(3) un grupo ciano,

(4) un grupo alquilo de C_{1-6} (con preferencia, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(5) un grupo alcoxi de C_{1-6} (con preferencia, metoxi, etoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia,

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fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi),

(c) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo), y

(d) un grupo alquil C_{1-6}-carbonilo (con preferencia, acetilo),

(6) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo),

(7) un grupo alquil C_{1-6}-sulfoniloxi (con preferencia, metilsulfoniloxi),

(8) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(9) un grupo heterocíclico aromático (con preferencia, furilo, tienilo),

(10) un grupo heterocíclico no aromático (con preferencia, pirrolidinilo), y

(11) un grupo amino opcionalmente mono- o disustituido con grupos alquilo de C_{1-6} (con preferencia, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos cicloalquilo de C_{3-10} (con preferencia, ciclopropilo).

El anillo D es un monociclo de 5 miembros opcionalmente sustituido, en donde Y es N, C o CH, que es un átomo constitutivo del anillo D en la fórmula (I). Como el "monociclo de 5 miembros" del "monociclo de 5 miembros

opcionalmente sustituido" para el anillo D, se pueden mencionar un "anillo aromático monocíclico de 5 miembros" y un "anillo no aromático monocíclico de 5 miembros".

Como el "anillo aromático monocíclico de 5 miembros", se pueden mencionar un anillo de 5 miembros (por ejemplo, pirazol), de entre los cuales se pueden mencionar un heterociclo aromático monocíclico correspondiente al grupo heterocíclico aromático monocíclico ejemplificado como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2.

Como el "anillo no aromático monocíclico de 5 miembros", se pueden mencionar ciclopentano, ciclopenteno, ciclopentadieno, y un anillo de 5 miembros (por ejemplo, pirazolidina, pirazolina, imidazolina, imidazolidina), de entre los cuales se puede mencionar un heterociclo no aromático monocíclico correspondiente al grupo heterocíclico no aromático monocíclico ejemplificado como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2.

En el anillo D, Y (un átomo constituyente del anillo D) y el átomo de carbono en el anillo D (unido al anillo A) son adyacentes a través de un enlace simple o un enlace doble.

El "monociclo de 5 miembros" del "monociclo de 5 miembros opcionalmente sustituido" para el anillo D es

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preferentemente un heterociclo aromático monocíclico de 5 miembros (con preferencia, pirazol) y similares.

El "monociclo de 5 miembros" del "monociclo de 5 miembros opcionalmente sustituido" para el anillo D tiene opcionalmente 1 a 3 sustituyentes en posiciones sustituibles. Como el sustituyentes, se pueden mencionar aquellos similares a los sustituyentes que opcionalmente tiene el grupo cicloalquilo de C_{3-10} y similares ejemplificado como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como sustituyentes preferidos para el anillo D, se pueden mencionar

(1) un grupo alquilo de C_{1-6} (con preferencia, metilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno (con preferencia, átomo de flúor) y un grupo alcoxi de C_{1-6} (con preferencia, metoxi)

y similares.

El anillo D es preferentemente un heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido, con mayor preferencia, un pirazol opcionalmente sustituido.

Como ejemplos preferidos específicos del anillo D, se puede mencionar pirazol opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un grupo alquilo de C_{1-6} (con preferencia,

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metilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno (con preferencia, átomo de flúor) y un grupo alcoxi de C_{1-6} (con preferencia, metoxi).

El anillo D' es un heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido, en donde Y' es N o C, que es un átomo constitutivo del anillo D' en la fórmula (I'). Como el "heterociclo aromático monocíclico de 5 miembros" del "heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido" para el anillo D', se puede mencionar un anillo de 5 miembros (por ejemplo, pirazol, imidazol, pirrol, triazol, tetrazol, tiofeno, furano, oxazol, tiazol, isoxazol, isotiazol, oxadiazol, tiadiazol), de entre los cuales se puede mencionar un heterociclo aromático monocíclico correspondiente al grupo heterocíclico aromático monocíclico ejemplificado como el "grupo heterocíclico" del "grupo heterocíclico opcionalmente sustituido" para R^2. De ellos, es preferentemente pirazol, tiofeno, imidazol o pirrol, con particular preferencia, pirazol (está unido (i) con el anillo A en la posición 5 y está unido con X en la posición 4, (ii) está unido con el anillo A en la posición 3 y unido con X en la posición 4, o (iii) está unido con el anillo A en la posición 5 y unido con X en la posición 1, con preferencia, (i) está unido con el anillo A en la posición 5 y unido con X en la posición 4).

En el anillo D', Y' (un átomo constitutivo del

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anillo D') y el átomo de carbono en el anillo D' (unido con el anillo A) son adyacentes a través de un enlace simple o un enlace doble.

El "heterociclo aromático monocíclico de 5 miembros" del "heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido" para el anillo D' tiene 1 a 3 sustituyentes en posiciones sustituibles. Como el sustituyentes, se pueden mencionar aquellos similares a los sustituyentes que opcionalmente tiene el grupo cicloalquilo de C_{3-10} y similares ejemplificado como el "grupo hidrocarburo" del "grupo hidrocarburo opcionalmente sustituido" para R^2. Cuando se usan dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como sustituyentes preferidos para el anillo D', se pueden mencionar

(1) un grupo alquilo de C_{1-6} (con preferencia, metilo, etilo, butilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de flúor),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(c) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

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(2) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, t-butoxicarbonilo),

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropil)

y similares.

El anillo D' es preferentemente pirazol, tiofeno, imidazol o pirrol, cada uno de los cuales está opcionalmente sustituido, con mayor preferencia, un pirazol opcionalmente sustituido ((i) está unido con el anillo A en la posición 5 y unido con X en la posición 4, (ii) unido con el anillo A en la posición 3 y unido con X en la posición 4, o (iii) unido con el anillo A en la posición 5 y unido con X en la posición 1, con preferencia, (i) unido con el anillo A en la posición 5 y unido con X en la posición 4).

Como ejemplos preferidos específicos del anillo D', se puede mencionar un heterociclo aromático monocíclico de 5 miembros (con preferencia, pirazol, tiofeno, imidazol, pirrol, con mayor preferencia, pirazol ((i) está unido con el anillo A en la posición 5 y unido con X en la posición 4, (ii) unido con el anillo A en la posición 3 y unido con X en la posición 4, o (iii) unido con el anillo A en la posición 5 y unido con X en la posición 1, con preferencia, (i) unido con el anillo A en la posición 5 y unido con X en la posición 4)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(1) un grupo alquilo de C_{1-6} (con preferencia, metilo, etilo, butilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de flúor),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(c) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(2) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, t-butoxicarbonilo), y

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo).

X es un espaciador que tiene 1 a 4 átomos en la cadena principal.

La "cadena principal" del "espaciador que tiene 1 a 4 átomos en la cadena principal" para X es una cadena lineal que conecta Y' (un átomo constitutivo del anillo D') o Y (un átomo constitutivo del anillo D) y el grupo W, y el número atómico de la cadena principal se cuenta de modo tal que la cantidad de átomos en la cadena principal sea mínima. El número atómico total en el espaciador no está particularmente limitado, siempre que la cadena principal consista en 1 a 4 átomos, y el espaciador tiene opcionalmente 4 o más átomos.

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La "cadena principal" consiste en 1 a 4 átomos seleccionados de un átomo de carbono (el átomo de carbono está opcionalmente sustituido con grupos oxo) y un heteroátomo (por ejemplo, O, S, N), y puede estar saturado o insaturado. Además, cuando el grupo W es un "grupo heterocíclico no aromático que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido", y el grupo heterocíclico no aromático está unido con X en el átomo de carbono saturado constitutivo del anillo, el terminal lateral del grupo W del "espaciador que tiene 1 a 4 átomos en la cadena principal" para X puede ser un enlace doble (por ejemplo, -CH=).

Como el "espaciador que tiene 1 a 4 átomos en la cadena principal", se pueden mencionar, por ejemplo, un grupo alquileno de C_{1-4}, un grupo alquenileno de C_{2-4}, un grupo alquinileno C_{2-4}, un grupo cicloalquileno de C3-6, $-X^{1a}-Z-X^{2a}-$, en donde Z es NH, O o S, X^{1a} y X^{2a} son iguales o diferentes y cada uno es un grupo alquileno de C_{1-3} de cadena lineal, y la cantidad total de carbonos de X^{1a} y X^{2a} es 3 o menos, $-X^{3a}-CH=$, en donde X^{3a} es un enlace o un grupo alquileno de C_{1-3} de cadena lineal, y similares.

Como ejemplos específicos del "espaciador que tiene 1 a 4 átomos en la cadena principal", se pueden mencionar

(1) un grupo alquileno de C_{1-4} (por ejemplo, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)-$, $-CH(C_2H_5)-$, $-CH(C_3H_7)-$, $-CH(i-C_3H_7)-$, $-CH(CH_3)-CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)(CH_2)_2-$, -

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$(CH_2)_2CH(CH_3)-$, $-CH_2-CH(CH_3)-CH_2-$, $-C(CH_3)_2-$, $-(CH(CH_3))_2-$, $-CH(CH_3)-CH(CH_3)-$, $-CH_2-C(CH_3)_2-$);

(2) un grupo alquenileno de C_{2-4} (por ejemplo, $-CH=CH-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-C(CH_3)=CH-$, $-CH=C(CH_3)-$, $-CH=C(C_2H_5)-$);

(3) un grupo alquinileno C_{2-4} (por ejemplo, $-C\equiv C-$, $-CH_2-C\equiv C-$, $-CH_2-C\equiv C-CH_2-$);

(4) un grupo cicloalquileno de C3-6 (por ejemplo, 1.2-ciclopropileno, 1.2-ciclobutileno, 1,3-ciclobutileno, 1.2-ciclopentileno, 1,3-ciclopentileno, 1.2-ciclohexileno, 1,3-ciclohexileno, 1.4-ciclohexileno);

(5) $-X^{1a}-Z-X^{2a}-$, en donde Z es NH, O o S, X^{1a} y X^{2a} son iguales o diferentes y cada uno un grupo alquileno de C_{1-3} de cadena lineal, y la cantidad total de carbonos de X^{1a} y X^{2a} es 3 o menos (por ejemplo, $-CH_2-NH-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-S-CH_2-$);

(6) $-X^{3a}-CH=$, en donde X^{3a} es un enlace o un grupo alquileno de C_{1-3} de cadena lineal (por ejemplo, $-CH=$, $-CH_2-CH_2-CH=$, $-CH_2-CH_2-CH_2-CH=$);

y similares.

X es con preferencia, un grupo alquileno de C_{1-4}, un grupo alquenileno de C_{2-4}, un grupo cicloalquileno de C3-6, $-X^{1a}-Z-X^{2a}-$ o $-X^{3a}-CH=$, en donde cada símbolo es como se definió con anterioridad, con mayor preferencia, un grupo

alquileno de C_{1-4} o un grupo alquenileno de C_{2-4}.

Como ejemplos preferidos específicos de X, se pueden mencionar

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$;

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) un grupo cicloalquileno de C_{3-6} (con preferencia, 1.2-ciclopropileno);

(4) $-X^{1a}-Z-X^{2a}-$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH_2-O-CH_2-$); y

(5) $-X^{3a}-CH=$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH=$, $-CH_2-CH_2-CH=$);

con mayor preferencia,

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$; y

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$).

En el compuesto (I),

1) cuando el anillo D es un imidazol sustituido, entonces W no es un aminoimidazol; y

2) cuando el anillo D es un pirazol sustituido, y X es $-CH=$, entonces W no es un oxotioxotiazolidinilo y un oxotioxoimidazolidinilo.

En el compuesto (I'),

1) cuando el anillo D' es un imidazol sustituido, entonces W no es 2-amino-1H-imidazol-5-ilo, 1H-imidazol-2-ilo, 3.5-dimetil-1H-pirazol-4-ilo y piperazin-1-ilo;

2) cuando el anillo D' es un pirazol sustituido, y X es -CH=, entonces W no es 4-oxo-2-tioxo-1,3-tiazolidin-5-ilideno, 5-oxo-2-tioxoimidazolidin-4-ilideno opcionalmente sustituido con grupo(s) fenilo, 3-metil-5-oxo-1.5-dihidro-4H-pirazol-4-ilideno, 2,4,6-trioxotetrahidropirimidin-5(2H)-ilideno y 4,6-dioxo-2-tioxotetrahidropirimidin-5(2H)-ilideno; y

3) se excluye 5-(6-metoxi-2-naftil)-1-(pirrolidin-2-ilmetil)-1H-1,2,3-triazol.

Como ejemplos preferidos del compuesto (I), se pueden mencionar los siguientes compuestos.

[Compuesto A]

Compuesto (I) en donde

el anillo D es un pirazol opcionalmente sustituido;

X es un grupo alquileno de C_{1-4} o un grupo alquenileno de C_{2-4}; y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$

en donde cada símbolo es como se definió con anterioridad.

[Compuesto B]

Compuesto (I), en donde

el anillo A es benceno, un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, pirrol, pirazol, imidazol, tiofeno) o un heterociclo no aromático monocíclico de 5 a 7 miembros (con preferencia, pirrolina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de cloro);

el anillo B es benceno o un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, piridina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno (con preferencia, átomo de cloro, átomo de flúor),

(2) un grupo hidroxi,

(3) un grupo ciano,

(4) un grupo alquilo de C_{1-6} (con preferencia, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor), y

(5) un grupo alcoxi de C_{1-6} (con preferencia, metoxi) opcionalmente sustituido con 1 a 3 grupos arilo de C_{6-14} (con preferencia, fenilo);

el anillo D es pirazol opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un grupo alquilo de C_{1-6} (con preferencia,

metilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno (con preferencia, átomo de flúor) y un grupo alcoxi de C_{1-6} (con preferencia, metoxi);

X es

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$);

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) $-X^{1a}-Z-X^{2a}-$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH_2-O-CH_2-$); o

(4) $-X^{3a}-CH=$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH=$, $-CH_2-CH_2-CH=$); y

W es

(A) un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mR^2$, o

$-OCONR^{1a}S(O)_mNR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1b} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno o un grupo alquilo de C_{1-6} (con preferencia, metilo);

R^2 es

(1) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, butilo, pentilo, 1-etilpropilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo), y

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(2) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor), y

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi);

(3) un grupo cicloalquilo de C_{3-10} (con preferencia,

ciclopropilo, ciclohexilo);

(4) un grupo heterocíclico aromático (con preferencia, furilo, tienilo); o

(5) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo); y

m es 2, o

(B) oxooxadiazolinilo (con preferencia, 5(4H)-oxo-1,2,4-oxadiazol-3-il) o 2,4-dioxotiazolidinilo (con preferencia, 2,4-dioxotiazolidin-5-ilo).

[Compuesto C]

Compuesto B, en donde

X es

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$); o

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$); y

W es un grupo representado por $-CONR^{1a}S(O)_mR^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^2 es

(1) un grupo alquilo de C_{1-10} (con preferencia, metilo, pentilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo), y

(b) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(2) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor), y

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi);

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(4) un grupo heterocíclico aromático (con preferencia, furilo, tienilo); o

(5) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo); y

m es 2.

Como ejemplos preferidos de compuesto (I'), se pueden mencionar los siguientes compuestos.

[Compuesto BB-1]

Compuesto (I'), en donde

el anillo A es benceno, un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, pirrol,

pirazol, imidazol, tiofeno) o un heterociclo no aromático monocíclico de 5 a 7 miembros (con preferencia, pirrolina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de un átomo de halógeno (con preferencia, átomo de cloro) y un grupo alquilo de C_{1-6} (con preferencia, metilo);

el anillo B es benceno o un heterociclo aromático monocíclico de 5 a 7 miembros (con preferencia, piridina), cada uno de los cuales está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un átomo de halógeno (con preferencia, átomo de cloro, átomo de flúor, átomo de bromo),

(2) un grupo hidroxi,

(3) un grupo ciano,

(4) un grupo alquilo de C_{1-6} (con preferencia, metilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(5) un grupo alcoxi de C_{1-6} (con preferencia, metoxi, etoxi, isopropoxi) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi),

(c) un grupo cicloalquilo de C_{3-10} (con preferencia,

ciclopropilo), y

(d) un grupo alquil C_{1-6}-carbonilo (con preferencia, acetilo),

(6) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo),

(7) un grupo alquil C_{1-6}-sulfoniloxi (con preferencia, metilsulfoniloxi),

(8) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(9) un grupo heterocíclico aromático (con preferencia, furilo, tienilo),

(10) un grupo heterocíclico no aromático (con preferencia, pirrolidinilo), y

(11) un grupo amino opcionalmente mono- o disustituido con grupos alquilo de C_{1-6} (con preferencia, metilo, etilo) opcionalmente sustituido con 1 a 3 grupos cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

el anillo D' es un heterociclo aromático monocíclico de 5 miembros (con preferencia, pirazol, tiofeno, imidazol, pirrol, con mayor preferencia, pirazol ((i) está unido con el anillo A en la posición 5 y unido con X en la posición 4, (ii) unido con el anillo A en la posición 3 y unido con X en la posición 4, o (iii) unido con el anillo A en la posición 5 y unido con X en la posición 1, con preferencia, (i) unido con el anillo A en la posición 5 y

unido con X en la posición 4)) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(1) un grupo alquilo de C_{1-6} (con preferencia, metilo, etilo, butilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de flúor),

(b) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(c) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(2) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, t-butoxicarbonilo), y

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

X es

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$;

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$);

(3) un grupo cicloalquileno de C3-6 (con preferencia, 1.2-ciclopropileno);

(4) $-X^{1a}-Z-X^{2a}-$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH_2-O-CH_2-$); o

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(5) $-X^{3a}-CH=$, en donde cada símbolo es como se definió con anterioridad (con preferencia, $-CH=$, $-CH_2-CH_2-CH=$); y

W es

(A) un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1b} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (con preferencia, metilo) o un grupo alcoxi de C_{1-6} (con preferencia, propoxi);

R^2 es

(1) un átomo de hidrógeno,

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(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-etilpropilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 grupos alcoxi de C_{1-6} (con preferencia, metoxi),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi);

m es 2; y

n es 1 ó 2, o

(B) un grupo heterocíclico no aromático de 5 ó 6 miembros que contiene NH [con preferencia, oxooxadiazolinilo (con preferencia, 5(4H)-oxo-1,2,4-oxadiazol-3-ilo), 2,4-dioxotiazolidinilo (con preferencia, 2,4-dioxotiazolidin-5-

ilo), 2,4-dioxoimidazolidinilo (con preferencia, 2,4-dioxoimidazolidin-3-ilo), 2-oxopiperazinilo (con preferencia, 2-oxopiperazin-1-ilo), 1,1-dióxido-3-oxotiadiazolidinilo (con preferencia, 1,1-dióxido-3-oxo-1,2,5-tiadiazolidin-5-il)] opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, propilo, isopropilo).

[Compuesto BB-2]

Compuesto BB-1, en donde

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, o

$-S(O)_mNR^{1a}CONR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (con preferencia, metilo) o un grupo alcoxi de C_{1-6} (con preferencia, propoxi);

R^2 es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

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(a) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con

preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi);

m es 2; y

n es 1 ó 2.

[Compuesto BB-3]

Compuesto BB-1, en donde

X es

(1) un grupo alquileno de C_{1-4} (con preferencia, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-; o

(2) un grupo alquenileno de C_{2-4} (con preferencia, -CH=CH-, -CH=C(CH_3)-, -CH_2-CH=CH-); y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-S(O)_mNR^{1a}CO_nR^2$, o

$-S(O)_mNR^{1a}CONR^{1c}R^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} (con preferencia, metilo) o un grupo alcoxi de C_{1-6} (con preferencia, propoxi);

R^2 es

(1) un átomo de hidrógeno,

(2) un grupo alquilo de C_{1-10} (con preferencia, metilo, etilo, propilo, butilo, isobutilo, pentilo, isopentilo, neopentilo, 1-propilbutilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo),

(b) un grupo alcoxi de C_{1-6} (con preferencia, isopropoxi),

(c) un grupo alcoxi de C_{1-6}-carbonilo (con preferencia, etoxicarbonilo),

(d) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo),

(e) un grupo hidroxi, y

(f) un átomo de halógeno (con preferencia, átomo de flúor);

(3) un grupo arilo de C_{6-14} (con preferencia, fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(4) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo, ciclohexilo);

(5) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(6) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con preferencia, etilenodioxi);

m es 2; y

n es 1 ó 2.

[Compuesto CC]

Compuesto BB-1, en donde

X es

(1) un grupo alquileno de C_{1-4} (con preferencia, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$; o

(2) un grupo alquenileno de C_{2-4} (con preferencia, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH_2-CH=CH-$); y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$

en donde

R^{1a} es un átomo de hidrógeno;

R^2 es

(1) un grupo alquilo de C_{1-10} (con preferencia, metilo, propilo, butilo, pentilo, 4-metilpentilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo arilo de C_{6-14} (con preferencia, fenilo), y

(b) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(2) un grupo arilo de C_{6-14} (con preferencia,

fenilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno (con preferencia, átomo de cloro),

(b) un grupo alquilo de C_{1-6} (con preferencia, metilo, butilo) opcionalmente sustituido con 1 a 3 átomos de halógeno (con preferencia, átomo de flúor),

(c) un grupo alcoxi de C_{1-6} (con preferencia, metoxi), y

(d) un grupo hidroxi;

(3) un grupo cicloalquilo de C_{3-10} (con preferencia, ciclopropilo);

(4) un grupo heterocíclico aromático (con preferencia, furilo, tienilo, imidazolilo) opcionalmente sustituido con 1 a 3 grupos alquilo de C_{1-6} (con preferencia, metilo); o

(5) un grupo heterocíclico no aromático (con preferencia, dihidrobenzofuranilo, morfolinilo, piperidinilo) opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de

(a) un grupo oxo,

(b) un grupo hidroxi,

(c) un grupo alquilo de C_{1-6} (con preferencia, metilo), y

(d) un grupo alquilen de C_{1-3}-dioxi (con

preferencia, etilenodioxi); y

m es 2.

[Compuesto D]

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 9),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 27),

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida (Ejemplo 33),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida (Ejemplo 62),

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo (Ejemplo 189),

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo (Ejemplo 197),

(2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 232),

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-

{[(ciclopropilmetil)amino]sulfonil}acrilamida (Ejemplo 264),

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida (Ejemplo 279),

(2E)-N-(butilsulfonil)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida (Ejemplo 283),

N-[(butilamino)carbonil]-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida (Ejemplo 294), o

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de butilo (Ejemplo 295),

o una de sus sales.

Las sales de un compuesto representado por la fórmula (I') y un compuesto representado por la fórmula (I) son, con preferencia, sales farmacológicamente aceptables y, por ejemplo, se pueden mencionar sales con bases inorgánicas, sales con bases orgánicas, sales con ácidos inorgánicos, sales con ácidos orgánicos, sales con aminoácidos básicos o ácidos y similares.

Los ejemplos preferidos de las sales con base inorgánica incluyen sales de metales alcalinos tales como sal de sodio, sal de potasio y similares; sales de metales alcalinotérreos tales como sal de calcio, sal de magnesio y

similares; sal de aluminio, sal de amonio y similares.

Los ejemplos preferidos de la sal con base orgánica incluyen una sal con trimetilamina, trietilamina, piridina, picolina, etanolamina, dietanolamina, trietanolamina, trometamina [tris(hidroximetil)metilamina], ter-butilamina, ciclohexilamina, bencilamina, diciclohexilamina, N,N'-dibenciletilenodiamina, y similares.

Los ejemplos preferidos de la sal con ácido inorgánico incluyen una sal con ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, y similares.

Los ejemplos preferidos de la sal con ácido orgánico incluyen una sal con ácido fórmico, ácido acético, ácido trifluoroacético, ácido ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido málico, ácido metansulfónico, ácido bencensulfónico, ácido p-toluensulfónico, y similares.

Los ejemplos preferidos de la sal con aminoácido básico incluyen una sal con arginina, lisina, ornitina y similares.

Los ejemplos preferidos de la sal con aminoácido ácido incluyen una sal con ácido aspártico, ácido glutámico, y similares.

El profármaco de los compuestos (I') y (I) (de ahora en más, mencionado como compuesto (I)) es un compuesto

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que se convierte en el compuesto (I) con una reacción debida a una enzima, ácido gástrico, etc. en la afección fisiológica en el organismo vivo, es decir, un compuesto que se convierte en el compuesto (I) por oxidación enzimática, reducción, hidrólisis, etc.; un compuesto que se convierte en el compuesto (I) por hidrólisis, etc. debido a un ácido gástrico, y similares. Un profármaco del compuesto (I) puede ser un compuesto obtenido al someter un grupo amino en el compuesto (I) a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido al someter un grupo amino en el compuesto (I) a una eicosanoilación, alanilación, pentilaminocarbonilación, (5-metil-2-oxo-1,3-dioxolen-4-il)metoxicarbonilación, tetrahidrofuranilación, tetrahidropiranilación, pirrolidilmetilación, pivaloiloximetilación o ter-butilación); un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) a una acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) a una acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumarilación, alanilación, dimetilaminometilcarbonilación, o tetrahidropiranilación); un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) a una esterificación o amidación (por ejemplo, un compuesto obtenido al someter un grupo carboxilo en el compuesto (I) a una etilesterificación,

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fenilesterificación, carboximetilesterificación, dimetilaminometilesterificación, pivaloiloximetilesterificación, etoxicarboniloxietilesterificación, ftalidilesterificación, (5-metil-2-oxo-1,3-dioxolen-4-il)metilesterificación, ciclohexiloxicarboniletilesterificación o metilamidación) y similares. Cualquiera de estos compuestos se puede producir a partir del compuesto (I) por medio de un método conocido *per se*.

Un profármaco del compuesto (I) puede ser un compuesto que se convierte en el compuesto (I) en condiciones fisiológicas, tal como se describen en Development of Pharmaceutical Products, vol. 7, Molecule Design, 163-198, Hirokawa Shoten (1990).

El compuesto (I) puede tener forma de un cristal, y la forma cristalina del cristal puede ser única o múltiple. El cristal se puede producir mediante un método de cristalización conocido *per se*. En la presente especificación, el punto de fusión significa aquel que se midió con, por ejemplo, un aparato de punto de microfusión (Yanaco, MP-500D o Buchi, B-545) o un dispositivo DSC (calorimetría diferencial de barrido) (SEIKO, EXSTAR6000) [velocidad de calentamiento: 5°C/min], y similares.

En general, los puntos de fusión varían según los aparatos de medición, las condiciones de medición, y

similares. El cristal en la presente especificación puede mostrar diferentes valores del punto de fusión descrito en la presente especificación, siempre que estén dentro de un rango de error general.

El cristal del compuesto (I) es superior en propiedades fisicoquímicas (punto de fusión, solubilidad, estabilidad, etc.) y propiedades biológicas (farmacocinéticas (absorción, distribución, metabolismo, excreción), expresión de la eficacia, etc.) y, así, es extremadamente útil como medicamento.

El compuesto (I) puede ser un solvato (por ejemplo, hidrato) o un no solvato, los cuales están incluidos en el compuesto (I).

El compuesto (I) puede ser rotulado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S, ^{125}I) y similares. También está incluido en el compuesto (I).

El compuesto convertido en deuterio, en donde ^{1}H se convirtió en $^{2}H(D)$, también está incluido en el compuesto (I).

El compuesto (I) o uno de sus profármacos (de ahora en más, a veces simplemente abreviado como compuesto de la presente invención) muestra una baja toxicidad (por ejemplo, toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, cardiotoxicidad, interacción farmacológica, carcinogenicidad), y se puede usar como está o

como composición farmacéutica en mezcla con un portador farmacéuticamente aceptable comúnmente conocido, etc., como un agente para la prevención o el tratamiento de las distintas enfermedades mencionadas más abajo, un sensibilizador de insulina y similares, en mamíferos (por ejemplo, humanos, ratones, ratas, conejos, perros, gatos, bovinos, caballos, cerdos, monos).

Aquí, como portador farmacológicamente aceptable se pueden usar varias sustancias portadoras orgánicas o inorgánicas utilizadas como material de preparación. Se incorporan como excipiente, lubricante, aglutinante y disgregante para preparaciones sólidas; solvente, auxiliares de disolución, agente de suspensión, agente de isotonicidad, regulador de pH y agente suavizante para preparaciones líquidas y similares. De ser necesario, se pueden usar aditivos de preparación tales como conservantes, antioxidantes, colorantes, endulzantes, similares.

Como ejemplos preferidos de excipientes se pueden mencionar lactosa, sacarosa, D-manitol, D-sorbitol, almidón, α-almidón, dextrina, celulosa cristalina, hidroxipropilcelulosa de baja sustitución, carboximetilcelulosa sódica, goma arábiga, pululano, ácido silícico anhidro ligero, silicato de aluminio sintético, metasilicato de aluminio y magnesio, y similares.

Como ejemplos preferidos del lubricante se pueden

mencionar estearato de magnesio, estearato de calcio, talco, sílice coloidal, y similares.

Como ejemplos preferidos del aglutinante se pueden mencionar α-almidón, sacarosa, gelatina, goma arábiga, metilcelulosa, carboximetilcelulosa, carboximetilcelulosa sódica, celulosa cristalina, sacarosa, D-manitol, trehalosa, dextrina, pululano, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona y similares.

Como ejemplos preferidos del disgregante se pueden mencionar lactosa, sacarosa, almidón, carboximetilcelulosa, carboximetilcelulosa cálcica, croscarmelosa sódica, carboximetilalmidón sódico, ácido silícico anhidro liviano, hidroxipropilcelulosa de baja sustitución y similares.

Como ejemplos preferidos del solvente se pueden mencionar agua para inyección, suero fisiológico, solución de Ringer, alcohol, propilenglicol, polietilenglicol, aceite de sésamo, aceite de maíz, aceite de oliva, aceite de semillas de algodón, y similares.

Como ejemplos preferidos de los auxiliares de disolución se pueden mencionar polietilenglicol, propilenglicol, D-manitol, trehalosa, benzoato de bencilo, etanol, trisaminometano, colesterol, trietanolamina, carbonato de sodio, citrato de sodio, salicilato de sodio, acetato de sodio, y similares.

Como ejemplos preferidos del agente de suspensión

se pueden mencionar tensioactivos tales como estearíltrietanolamina, laurilsulfato sódico, ácido laurilaminopropiónico, lecitina, cloruro de benzalconio, cloruro de bencetonio, monoestearato de glicerol, y similares; polímeros hidrofílicos tales como alcohol polivinílico, polivinilpirrolidona, carboximetilcelulosa sódica, metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa y similares; polisorbatos, aceite de ricino hidrogenado con polioxietileno, y similares.

Como ejemplos preferidos del agente de isotonicidad se pueden mencionar cloruro de sodio, glicerina, D-manitol, D-sorbitol, glucosa y similares.

Como ejemplos preferidos de regulador de pH se pueden mencionar regulador de pH tales como fosfato, acetato, carbonato, citrato y similares, y otros.

Como ejemplos preferidos de agente suavizante se pueden mencionar alcohol bencílico y similares.

Como ejemplos preferidos de conservante se pueden mencionar, p-oxibenzoatos, clorobutanol, alcohol bencílico, alcohol fenetílico, ácido deshidroacético, ácido sórbico y similares.

Como ejemplos preferidos de antioxidante se puede mencionar sulfito, ascorbato y similares.

Como ejemplos preferidos de agente colorante se

pueden mencionar colorantes de alquitrán alimenticios hidrosolubles (por ejemplo, colorantes alimenticios tales como Rojo alimenticio No. 2 y 3, Amarillo alimenticio No. 4 y 5, Azul alimenticio No. 1 y 2 y similares), tinturas de laca insolubles en agua (por ejemplo, sales de aluminio de los antes mencionados colores de alquitrán alimenticios hidrosolubles), tinturas naturales (por ejemplo, β-caroteno, clorofila, óxido de hierro rojo) y similares.

Como ejemplos preferidos de agente edulcorante, se pueden mencionar sacarina sódica, glicirricinato dipotásico, aspartame, stevia y similares.

La forma de dosificación de la composición farmacéutica antes mencionada es, por ejemplo, un agente oral tales como comprimidos (incluso comprimidos recubiertos de azúcar, comprimidos entéricos, comprimidos sublinguales y comprimidos orales de desintegración), cápsulas (incluso cápsulas blandas y microcápsulas), gránulos, polvos, sobres, jarabes, emulsiones, suspensiones, películas (por ejemplo, película de desintegración oral) y similares; un agente parenteral tales como inyecciones (por ejemplo, inyecciones subcutáneas, inyecciones intravenosas, inyecciones intramusculares, inyecciones intraperitoneales, infusiones por goteo), agentes externos (por ejemplo, preparaciones transdérmicas, ungüentos), supositorios (por ejemplo, supositorios rectales, supositorios vaginales), gránulos,

preparaciones nasales, preparaciones pulmonares (inhalaciones), preparaciones oftálmicas y similares, y otros. Se pueden administrar con seguridad por vía oral o parenteral (por ejemplo, administraciones tópica, rectal, intravenosa, etc.).

Estas preparaciones pueden ser preparaciones de liberación controlada (por ejemplo, microcápsulas de liberación sostenida) tales como preparaciones de liberación inmediata, preparaciones de liberación sostenida, y similares.

La composición farmacéutica se puede producir por un método de uso convencional en el campo técnico de preparación, tal como un método descrito en la Farmacopea Japonesa y similares.

Si bien el contenido del compuesto de la presente invención en la composición farmacéutica varía según la forma de dosificación, la dosis del compuesto de la presente invención y similares, es decir, por ejemplo, aproximadamente 0.1 a 100% en peso.

El compuesto de la presente invención tiene una acción hipoglucémica, una acción hipolipidémica, una acción sensibilizante a insulina, una acción mejoradora de la sensibilidad a la insulina y una acción agonista (activación) del receptor de respuesta al crecimiento de peroxisoma (PPAR)γ (acceso a GenBank N°. L40904). Aquí, el PPARγ puede

formar un receptor heterodimérico con cualquiera de los receptores del retinoide X (RXR)α (acceso a GenBank N°. X52773), RXRβ (acceso a GenBank N°. M84820) y RXRγ (acceso a GenBank N°. U38480).

El compuesto de la presente invención tiene particularmente una acción selectiva agonista parcial (agonista parcial) sobre PPARγ.

Se informó que un agonista selectivo parcial para PPARγ no estaba acompañado de efectos secundarios tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardíaca y similares, en comparación con un agonista total para PPARγ (por ejemplo, compuesto de tiazolidindiona) (Molecular Endocrinology, vol. 17, No. 4, página 662, 2003). En consecuencia, el compuesto de la presente invención es de utilidad como agente hipoglucémico no acompañado de efectos secundarios tales como aumento de peso corporal, acumulación de adipocitos, hipertrofia cardíaca y similares, en comparación con un agonista total para PPARγ.

El compuesto de la presente invención se puede usar, por ejemplo, como un agente para la prevención o el tratamiento de diabetes (por ejemplo, diabetes de tipo 1, diabetes de tipo 2, diabetes gestacional, diabetes por obesidad); un agente para la prevención o el tratamiento de hiperlipidemia (por ejemplo, hipertrigliceridemia,

hipercolesterolemia, hipo-HDL-emia, hiperlipidemia posprandial); sensibilizador de insulina; un agente para mejorar la sensibilidad a la insulina; un agente para la prevención o el tratamiento de tolerancia alterada a la glucosa [IGT, por sus siglas en inglés (Tolerancia a Glucosa alterada)]; y un agente para prevenir el avance de la tolerancia alterada a la glucosa en diabetes.

Para los criterios diagnósticos de diabetes, la Sociedad de Diabetes de Japón informó nuevos criterios de diagnóstico. De acuerdo con el presente informe, la diabetes es una afección que muestra cualquiera de un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 126 mg/dl, una prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl, y un nivel de glucosa sanguínea no en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl. Una afección que no cae bajo la antes mencionada diabetes y diferente de "una afección que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) inferior a 110 mg/dl o una prueba de tolerancia a 75 g de glucosa oral (75 g OGTT) a las 2 h (concentración de glucosa plasmática intravenosa) inferior a 140 mg/dl" (tipo normal) se denomina "tipo casi inaceptable".

Además, ADA (Asociación Americana de Diabetes) y

OMS informaron nuevos criterios diagnósticos de diabetes.

De acuerdo con estos informes, la diabetes es una afección que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 126 mg/dl y una prueba de tolerancia a 75 g de glucosa oral a las 2 h (concentración de glucosa plasmática intravenosa) no inferior a 200 mg/dl.

De acuerdo con los informes antes mencionados de ADA y OMS, la alteración de tolerancia de glucosa es una afección que muestra un nivel de prueba de tolerancia a 75 g de glucosa oral a las 2 h (concentración de glucosa plasmática intravenosa) no inferior de 140 mg/dl e inferior a 200 mg/dl. De acuerdo con el informe de ADA, una afección que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 100 mg/dl e inferior a 126 mg/dl se denomina IFG (deterioro de glucosa en ayunas). Por otra parte, OMS define IFG (deterioro de glucosa en ayunas) como una afección que muestra un nivel de glucosa sanguínea en ayunas (concentración de glucosa plasmática intravenosa) no inferior a 110 mg/dl e inferior a 126 mg/dl, y la denomina IFG (alteración de glucosa en ayunas).

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento de diabetes, tipo casi inaceptable, alteración de tolerancia de

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glucosa, IFG (alteración de glucosa en ayunas) y IFG (alteración de glucosa en ayunas), tal como se determina de acuerdo con los nuevos criterios diagnósticos antes mencionados. Además, el compuesto de la presente invención puede prevenir el progreso del tipo casi inaceptable, la alteración de la tolerancia de glucosa, IFG (alteración de glucosa en ayunas) o IFG (alteración de glucemia en ayunas) a diabetes.

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento, por ejemplo, de complicaciones diabéticas [por ejemplo, neuropatía, nefropatía, retinopatía, cataratas, macroangiopatía, osteopenia, coma diabético hiperosmolar, enfermedad infecciosa (por ejemplo, infección respiratoria, infección de las vías urinarias, infección gastrointestinal, infecciones de los tejidos blandos dérmicos, infección de los miembros inferiores), gangrena diabética, xerostomia, hipoacusia, trastornos cerebrovasculares, trastornos de la circulación sanguínea periférica], obesidad, osteoporosis, caquexia (por ejemplo, caquexia cancerosa, caquexia tuberculosa, caquexia diabética, caquexia de enfermedad sanguínea, caquexia de enfermedad endocrina, caquexia de enfermedad infecciosa o caquexia debida a síndrome de inmunodeficiencia adquirida), hígado graso, hipertensión, síndrome de ovario poliquístico, enfermedad renal (por

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ejemplo, neuropatía diabética, nefritis glomerular, glomeruloesclerosis, síndrome nefrótico, nefroesclerosis hipertensiva, enfermedad renal de estadio terminal), distrofia muscular, infarto de miocardio, angina de pecho, accidente cerebrovascular (por ejemplo, infarto cerebral, apoplejía cerebral), síndrome de resistencia a insulina, Síndrome X, síndrome metabólico (patología con tres o más seleccionados de hipertrigliceridemia (TG), hipo-HDL-colesterolemia (HDL-C), hipertensión, sobrepeso abdominal y deterioro de la tolerancia a glucosa), hiperinsulinemia, trastorno sensitivo inducido por hiperinsulinemia, tumor (por ejemplo, leucemia, cáncer de mama, cáncer de próstata, cáncer de piel), síndrome de intestino irritable, diarrea aguda o crónica, enfermedades inflamatorias (por ejemplo, arterioesclerosis (por ejemplo, aterosclerosis), artritis reumatoide crónica, espondilitis deformante, osteoartritis, lumbago, gota, inflamación después de cirugía o traumática, tumefacción, neuralgia, faringolaringitis, cistitis, hepatitis (inclusive esteatohepatitis no alcohólica), neumonía, pancreatitis, enfermedad inflamatoria intestinal, colitis ulcerativa, enfermedad pulmonar obstructiva crónica (EPOC), síndrome de obesidad visceral, úlcera de pierna, asepsia, psoriasis y similares.

Además, el compuesto de la presente invención también se puede usar para aliviar condiciones tales como

dolor abdominal, náuseas, vómitos, molestias del abdomen superior y similares, asociados con úlcera péptica, gastritis aguda o crónica, disquinesia biliar, colecistitis y similares, y otros.

El compuesto de la presente invención también se puede usar como agente para la prevención o tratamiento de una enfermedad inflamatoria que incluye TNF-α. Aquí, la enfermedad inflamatoria que incluye TNF-α es una enfermedad inflamatoria desarrollada por la presencia de TNF-α, que se puede tratar con un efecto inhibitorio de TNF-α. Como tal enfermedad inflamatoria, por ejemplo, se pueden mencionar complicaciones diabéticas (por ejemplo, retinopatía, nefropatía, neuropatía, macroangiopatía), artritis reumatoide crónica, espondilitis deformante, osteoartritis, lumbago, gota, inflamación después de cirugía o traumática, tumefacción, neuralgia, faringolaringitis, cistitis, hepatitis, neumonía, lesión de membrana mucosa del estómago (incluso lesión de membrana mucosa estomacal causada por aspirina) y similares.

El compuesto de la presente invención tiene acción inhibitoria de apoptosis y también se puede usar como agente para la prevención o tratamiento de enfermedades que incluyen promoción de apoptosis. Como enfermedad que incluye la promoción de apoptosis, por ejemplo, se pueden mencionar enfermedades virales (por ejemplo, sida, hepatitis

fulminante), enfermedades neurodegenerativas (por ejemplo, enfermedad de Alzheimer, enfermedad de Parkinson, esclerosis lateral amiotrófica, pigmentosa, degeneración cerebelar), mielodisplasia (por ejemplo, anemia aplásica), enfermedades isquémicas (por ejemplo, infarto de miocardio, apoplejía cerebral), enfermedades hepáticas (por ejemplo, hepatitis alcohólica, hepatitis B, hepatitis C), enfermedades articulares (por ejemplo, osteoartritis), aterosclerosis y similares.

El compuesto de la presente invención también se pueden usar para la reducción de grasa visceral, inhibición de la acumulación de grasa visceral, mejoramiento del metabolismo glúcido, mejoramiento del metabolismo lipídico, mejoramiento de la resistencia a insulina, inhibición de la producción de LDL oxidado, mejoramiento de metabolismo lipoproteíco, mejoramiento del metabolismo coronario, prevención o tratamiento de complicaciones cardiovasculares, prevención o tratamiento de complicaciones de insuficiencia cardiaca, reducción de flujo sanguíneo, prevención o tratamiento de anovulación, prevención o tratamiento de hirsutismo, prevención o tratamiento de hiperandrogenemia y similares.

El compuesto de la presente invención también se puede usar como prevención secundaria y supresión de la progresión de las diversas enfermedades antes mencionadas

(por ejemplo, eventos cardiovasculares tales como infarto de miocardio y similares).

Si bien la dosis del compuesto de la presente invención varía según el sujeto de la administración, la vía de administración, la enfermedad objetivo, la afección y similares, por ejemplo, generalmente es de aproximadamente 0.005 a 50 mg/kg de peso corporal, de preferencia 0.01 a 2 mg/kg de peso corporal, con mayor preferencia 0.025 a 0.5 mg/kg de peso corporal, para la administración oral a pacientes diabéticos adultos, que de preferencia se administran en una a tres porciones por día.

El compuesto de la presente invención se puede usar en combinación con agentes farmacéuticos (en adelante abreviado como fármaco de combinación) tales como agentes terapéuticos para diabetes, agentes terapéuticos para complicaciones diabéticas, agentes terapéuticos para hiperlipidemia, agentes antihipertensivos, agentes antiobesidad, diuréticos, agentes quimioterapéuticos, agentes inmunoterapéuticos, agentes antitrombóticos, agentes terapéuticos para osteoporosis, agentes antidemencia, agentes para aliviar la disfunción eréctil, agentes terapéuticos para incontinencia urinaria o polaquiuria, agentes terapéuticos para disuria y similares. Estos fármacos de combinación pueden ser compuestos de bajo peso molecular, proteínas de alto peso molecular, polipéptidos, anticuerpos o ácidos

nucleicos (incluso ácido nucleico antisentido, ARNsi, ARNsh), vacunas y similares.

El tiempo de administración del compuesto de la presente invención y el fármaco de combinación no está restringido, y se pueden administrar a un sujeto de administración simultáneamente, o se pueden administrar en tiempos escalonados.

Como modo de administración del compuesto de la presente invención y el fármaco de combinación, se pueden mencionar los siguientes métodos: (1) El compuesto de la presente invención y el fármaco de combinación se formulan simultáneamente para dar una única preparación que se administra. (2) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos tipos de preparaciones que se administran simultáneamente por la misma vía de administración. (3) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones que se administran por la misma vía de administración a tiempos escalonados. (4) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones que se administran simultáneamente por las diferentes vías de administración. (5) El compuesto de la presente invención y el fármaco de combinación se formulan por separado para dar dos clases de preparaciones

que se administran por e diferentes vías de administración a tiempos escalonados (por ejemplo, el compuesto de la presente invención y el fármaco de combinación se administran en este orden, o en orden inverso), y similares.

La dosis del fármaco de combinación se puede determinar adecuadamente en base a la dosis empleada clínicamente. La proporción de mezclado del compuesto de la presente invención y un fármaco de combinación se pueden determinar adecuadamente según el sujeto de administración, la vía de administración, la enfermedad objetivo, los síntomas, la combinación y similares. Si el sujeto de administración es humano, por ejemplo, se puede usar un fármaco de combinación en 0.01 a 100 partes en peso respecto de 1 parte en peso del compuesto de la presente invención.

Como agentes terapéuticos para diabetes se pueden mencionar preparaciones de insulina (por ejemplo, preparaciones de insulina animal extraídos de páncreas bovino y cerdo; preparaciones de insulina humana sintetizados genéticamente con *Escherichia coli*, levaduras; insulina cinc; insulina protamina cinc; fragmento o derivado de insulina (por ejemplo, INS-1), preparación oral de insulina), sensibilizadores de insulina (por ejemplo, pioglitazona o su sal (de preferencia clorhidrato), rosiglitazona o una de sus sales (de preferencia maleato), Tesaglitazar, Ragaglitazar, Muraglitazar, Edaglitazone, Metaglidasen, Naveglitazar, AMG-

131, THR-0921), inhibidores de α-glucosidasa (por ejemplo, voglibosa, acarbosa, miglitol, emiglitato, etc.), biguanidas (por ejemplo, fenformina, metformina, buformina o una de sus sales (por ejemplo, clorhidrato, fumarato, succinato)), secretagogos de insulina [sulfonilurea (por ejemplo, tolbutamida, glibenclamida, gliclazida, clorpropamida, tolazamida, acetohexamida, gliclopiramida, glimepirida, glipizida, glibuzol), nateglinida, mitiglinida o su sal de calcio hidratado], inhibidores de dipeptidilpeptidasa IV (por ejemplo, Alogliptina o su sal (con preferencia, benzoato), Vildagliptina, Sitagliptina, Saxagliptina, T-6666, TS-021), agonistas β3 (por ejemplo, AJ-9677), agonistas de GPR40, agonistas del receptor GLP-1 [por ejemplo, GLP-1, agente GLP-1MR, NN-2211, AC-2993 (exendina-4), BIM-51077, Aib(8.35)hGLP-1(7.37)NH_2, CJC-1131], agonistas de amilina (por ejemplo, pramlintida), inhibidores de fosfatasa de fosfotirosina (por ejemplo, vanadato de sodio), inhibidores de gluconeogénesis (por ejemplo, inhibidores de glucógeno fosforilasa, inhibidores de glucosa-6-fosfatasa, antagonistas de glucagón), SGLUT (cotransportadores de glucosa-sodio) (por ejemplo, T-1095), inhibidores de 11β-hidroxiesteroide deshidrogenasa (por ejemplo, BVT-3498), adiponectina o sus agonistas, inhibidores de IKK (por ejemplo, AS-2868), fármacos mejoradores de resistencia de leptina, agonistas de receptor de somatostatina, activadores de glucocinasa (por

ejemplo, Ro-28-1675), GIP (péptido insulinotrópico dependiente de glucosa) y similares.

Los ejemplos de los agentes terapéuticos para complicaciones diabéticas incluyen inhibidores de aldosareductasa (por ejemplo, Tolrestat, Epalrestat, Zenarestat, Zopolrestat, Minalrestat, Fidarestat, CT-112, ranirestat (AS-3201)), factores neurotróficos y sus fármacos incrementadores (por ejemplo, NGF, NT-3, BDNF, promotores de producción-secreción de neurotrofinas (por ejemplo, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-oxazolpropanol, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-oxazolbutanol, 4-(4-clorofenil)-5-[3-(1-imidazolil)propil]-2-(2-metil-1-imidazolil)oxazol, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-oxazolpentanol, 4-(4-clorofenil)-5-[4-(1-imidazolil)butil]-2-(2-metil-1-imidazolil)oxazol, 3-[3-[4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-oxazolil]propil]-1-metil-2, 4-imidazolidindiona, 4-(4-clorofenil)-5-[3-(2-metoxifenoxi)propil]-2-(2-metil-1-imidazolil)oxazol, 4-(4-clorofenil)-5-[3-(3-metoxifenoxi)propil]-2-(2-metil-1-imidazolil)oxazol,4-(4-clorofenil)-5-[3-(4-metoxifenoxi)propil]-2-(2-metil-1-imidazolil)oxazol, 4-(4-clorofenil)-2-(2-metil-1-imidazolil)-5-[3-(2-metilfenoxi)propil]oxazol, [4-({(2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]prop-2-enoil}amino)bencil]fosfonato de dietilo, (2E)-N-{4-[(2,4-dioxo-1,3-tiazolidin-5-

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il)metil]fenil}-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]acrilamida, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-[4-(1H-imidazol-1-ilmetil)fenil]acrilamida, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-[4-(1H-pirazol-1-ilmetil)fenil]acrilamida, [4-({(2E)-3-[1-metil-5-(2-tienil)-1H-pirazol-4-il]prop-2-enoil}amino)bencil]fosfonato de dietilo, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-{4-[(3-metil-2,4-dioxo-1,3-tiazolidin-5-il)metil]fenil}acrilamida, (2E)-N-[4-(1H-bencimidazol-1-ilmetil)fenil]-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]acrilamida, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-{4-[(metilsulfonil)metil]fenil}acrilamida, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-{4-[hidroxi(2-piridinil)metil]fenil}acrilamida, (2E)-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]-N-[4-(4-morfolinilmetil)fenil]acrilamida, (2E)-N-{4-[(etilsulfonil)metil]fenil}-3-[5-(4-fluorofenil)-1-metil-1H-pirazol-4-il]acrilamida), inhibidores de PKC (por ejemplo, mesilato de ruboxistaurina)), inhibidores de AGE (por ejemplo, ALT946, pimagedina, bromuro de N-fenaciltiazolio (ALT-766), EXO-226, piridorina, Piridoxamina), eliminadores de oxígeno activo (por ejemplo, ácido tióctico), vasodilatadores cerebrales (por ejemplo, tiapurida, mexiletina), agonista de receptor de somatostatina (por ejemplo, BIM23190), inhibidores de cinasa 1 (ASK-1)

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reguladora de señal de apoptosis y similares.

Los ejemplos de agentes terapéuticos para hiperlipidemia incluyen inhibidores de HMG-CoA reductasa (por ejemplo, pravastatina, simvastatina, lovastatina, atorvastatina, fluvastatina, itavastatina, rosuvastatina, pitavastatina o una de sus sales (por ejemplo, sal de sodio, sal de calcio)), inhibidores de escualenosintetasa (por ejemplo, lapaquistat o su sal (con preferencia, acetato)), compuestos de fibrato (por ejemplo, bezafibrato, clofibrato, simfibrato, clinofibrato), inhibidores de ACAT (por ejemplo, Avasimibe, Eflucimibe), resinas de intercambio aniónico (por ejemplo, colestiramina), probucol, fármacos de ácido nicotínico (por ejemplo, nicomol, niceritrol), icosapentato de etilo, fitosteroles (por ejemplo, soisterol, γ-orizanol) y similares.

Ejemplos de agentes antihipertensivos incluyen inhibidores de la enzima convertidora de la angiotensina (por ejemplo, captopril, enalapril, delapril), antagonistas de angiotensina II (por ejemplo, candesartan cilexetilo, losartan, eprosartan, valsartan, telmisartan, irbesartan, olmesartan medoxomil, tasosartan, ácido 1-[[2'-(2.5-dihidro-5-oxo-4H-1,2,4-oxadiazol-3-il)bifenil-4-il]metil]-2-etoxi-1H-bencimidazol-7-carboxílico), bloqueadors del canal de calcio (por ejemplo, manidipina, nifedipina, nicardipina, amlodipina, efonidipina), abridores del canal de potasio (por

ejemplo, levcromakalim, L-27152, AL0671, NIP-121), clonidina y similares.

Los ejemplos de agentes antiobesidad incluyen agentes que actúan sobre el sistema nervioso central (por ejemplo, dexfenfluramina, fenfluramina, fentermina, sibutramina, amfepramona, dexamfetamina, mazindol, fenilpropanolamina, clobenzorex; antagonistas de receptor MCH (por ejemplo, SB-568849; SNAP-7941; compuestos descritos en WO01/82925 y WO01/87834); antagonistas de neuropéptido Y (por ejemplo, CP-422935); antagonistas de receptor de canabinoides (por ejemplo, SR-141716, SR-147778); antagonistas de ghrelina; inhibidores de 11β-hidroxiesteroide deshidrogenasa (por ejemplo, BVT-3498)), inhibidores de lipasa pancreática (por ejemplo, orlistat, cetilistat (ATL-962)), agonistas de β3 (por ejemplo, AJ-9677), anorexígenos peptídicos (por ejemplo, leptina, CNTF (factor neurotrópico ciliar)), agonistas de colecistoquinina (por ejemplo, lintitript, FPL-15849), inhibidores de alimentos (por ejemplo, P-57) y similares.

Los ejemplos de diuréticos incluyen derivados de xantina (por ejemplo, salicilato de sodio y teobromina, salicilato de calcio y teobromina), preparaciones de tiazida (por ejemplo, etiazida, ciclopentiazida, triclorometiazida, hidroclorotiazida, hidroflumetiazida, bencilhidroclorotiazida, penflutizida, politiazida,

meticlotiazida), preparaciones antialdosterona (por ejemplo, espironolactona, triamtereno), inhibidores de carbonato deshidratasa (por ejemplo, acetazolamida), preparaciones de clorobencensulfonamida (por ejemplo, clortalidona, mefrusida, indapamida), azosemida, isosorbida, ácido etacrínico, piretanida, bumetanida, furosemida y similares.

Los ejemplos de agentes quimioterapéuticos incluyen agentes alquilantes (por ejemplo, ciclofosfamida, ifosfamida), antagonistas metabólicos (por ejemplo, metotrexato, 5-fluorouracilo y uno de sus derivados), antibióticos antitumorales (por ejemplo, mitomicina, adriamicina), agentes antitumorales derivados de vegetales (por ejemplo, vincristina, vindesina, Taxol), cisplatino, carboplatino, etopósido y similares. De ellos, se prefieren Furtulon o NeoFurtulon, que son derivados 5-fluorouracilo y similares.

Los ejemplos de agentes inmunoterapéuticos incluyen componentes de microorganismos o bacterianos (por ejemplo, derivado de muramildipétido, picibanilo), polisacáridos con actividad potenciadora de inmunidad (por ejemplo, lentinano, esquizofilano, crestina), citocinas obtenidas mediante técnicas de ingeniería genética (por ejemplo, interferón, interleucina (IL)), factores estimulantes de colonias (por ejemplo, factor estimulante de colonias de granulocitos, eritropoyetina) y similares, con preferencia dada a

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interleucinas tales como IL-1, IL-2, IL-12 y similares.

Los ejemplos de agentes antitrombóticos incluyen heparina (por ejemplo, heparina sódica, heparina cálcica, dalt-heparina sódica), warfarina (por ejemplo, warfarina potásica), fármacos antitrombina (por ejemplo, aragatrobano), agentes trombolíticos (por ejemplo, urocinasa, tisocinasa, alteplasa, nateplasa, monteplasa, pamiteplasa), inhibidores de agregación plaquetaria (por ejemplo, clorhidrato de ticlopidina, cilostazol, icosapentato de etilo, beraprost sódico, clorhidrato de sarpogrelato) y similares.

Los ejemplos de agentes terapéuticos para osteoporosis incluyen alfacalcidol, calcitriol, elcatonina, calcitonina de salmón, estriol, ipriflavona, risedronato disódico, pamidronato disódico, alendronato sódico hidratado, incadronato disódico y similares.

Los ejemplos de agentes antidemencia incluyen tacrina, donepezilo, rivastigmina, galantamina y similares.

Los ejemplos de agentes que aminoran de disfunción eréctil incluyen apomorfina, citrato de sildenafil y similares.

Los ejemplos de agentes terapéuticos para incontinencia urinaria o polaquiuria incluyen clorhidrato de flavoxato, clorhidrato de oxibutinina, clorhidrato de propiverina y similares.

Los ejemplos de agentes terapéuticos para disuria

incluyen inhibidores de esterasa de acetilcolina (por ejemplo, distigmina) y similares.

Los ejemplos de fármacos de combinación incluyen fármacos con acción aliviadora de caquexia establecida en modelos animales y situaciones clínicas, tales como inhibidores de ciclooxigenasa (por ejemplo, indometacina), derivados de progesterona (por ejemplo, acetato de megestrol), glucosteroides (por ejemplo, dexametasona), agentes de metoclopramida, agentes de tetrahidrocanabinol, agentes mejoradores del metabolismo graso (por ejemplo, ácido eicosapentaenoico), hormonas de crecimiento, IGF-1, o anticuerpos contra factor inductor de caquexia tales como TNF-α, LIF, IL-6, oncostatina M y similares.

Como fármacos de combinación, se pueden mencionar fármacos promotores de regeneración nerviosa (por ejemplo, Y-128, VX853, prosaptida), antidepresivos (por ejemplo, desipramina, amitriptilina, imipramina), antiepilépticos (por ejemplo, lamotrigina), agentes antiarrítmicos (por ejemplo, mexiletina), ligandos de receptor de acetilcolina (por ejemplo, ABT-594), antagonistas de receptor de endotelina (por ejemplo, ABT-627), inhibidores de captación de monoaminas (por ejemplo, tramadol), analgésicos narcóticos (por ejemplo, morfina), agonistas de receptor de GABA (por ejemplo, gabapentina), agonistas de receptor de α2 (por ejemplo, clonidina), analgésicos locales (por ejemplo,

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capsaicina), fármacos ansiolíticos (por ejemplo, benzotiazepinas), agonistas de receptor de dopamina (por ejemplo, apomorfina), midazolam, quetoconazol y similares.

El fármaco de combinación de preferencia es una preparación de insulina, un sensibilizador de insulina, un inhibidor de α-glucosidasa, biguanida, secretagogo de insulina (de preferencia sulfonilurea) y similares.

Los fármacos de combinación antes mencionados se pueden usar en una mezcla de dos o más tipos en una proporción adecuada.

Si el compuesto de la presente invención se usa en combinación con un fármaco de combinación, se puede reducir la dosis de cada agente dentro de un rango de seguridad en consideración con sus efectos secundarios. En particular, las dosis de sensibilizador de insulinas, secretagogos de insulina y biguanidas se pueden reducir respecto de los niveles de dosis habituales. En consecuencia, es posible que se puedan prevenir con seguridad los efectos secundarios causados por estos agentes. Además, se pueden reducir las dosis de los agentes terapéuticos para complicaciones diabéticas, los agentes terapéuticos para hiperlipidemia y los agentes antihipertensivos, y como consecuencia, es posible prevenir efectivamente los efectos secundarios causados por estos agentes.

El método de producción del compuesto de la

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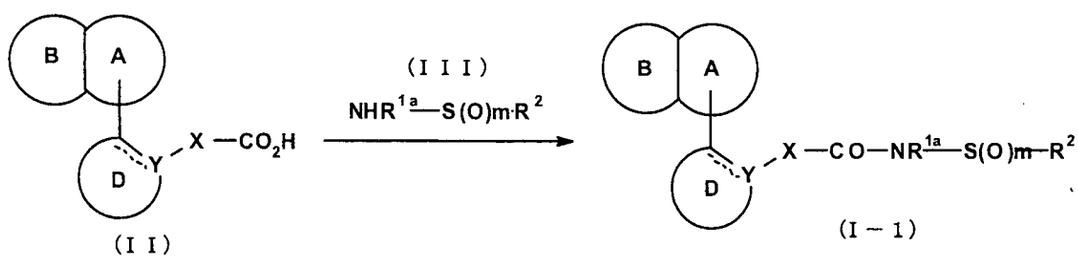
presente invención se explica a continuación.

El compuesto (I) se puede producir por un método conocido *per se*, por ejemplo, de acuerdo con los siguientes Método A1, Método A2, Método B a Método G, Método H1, Método H2, Método I a Método N, Método O1, Método O2, Método P a Método R, Método S1, Método S2, Método AA a Método AL, Método AU y Método AW o un método análogo.

En cada método de producción, se pueden usar los compuestos de material de inicio en forma de una sal. Como tales sales, se pueden usar aquellas similares a las sales de un compuesto representado por la fórmula (I).

El compuesto (I-1), que es el compuesto (I), en donde W es $-CONR^{1a}S(O)_mR^2$, en donde cada símbolo es como se definió, se produce, por ejemplo, de acuerdo con el siguiente Método A1.

[Método A1]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-1) se puede producir al someter el compuesto (II) a una reacción de

condensación. Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, método de condensación directa del compuesto (II) con el compuesto (III), o método de reacción de un derivado reactivo del compuesto (II) con el compuesto (III), y similares. Como el derivado reactivo del compuesto (II), se pueden mencionar, por ejemplo, haluros de ácido (por ejemplo, cloruros de ácido, bromuros de ácido), imidazolida, anhídridos de ácido mixtos (por ejemplo, anhídridos con carbonato de metilo, carbonato de etilo o carbonato de isobutilo, etc.) y similares.

El método de condensación directa del compuesto (II) con el compuesto (III) se lleva a cabo en presencia de un agente de condensación, en un solvente que no afecte adversamente la reacción.

Como el agente de condensación, se pueden mencionar un agente de condensación conocido en el campo, por ejemplo, reactivos de condensación de carbodiimida tales como diciclohexilcarbodiimida, diisopropilcarbodiimida, N-[3-(dimetilamino)propil]-N'-etilcarbodiimida y su clorhidrato y similares; reactivos de condensación de ácido fosfórico tales como cianofosfato de dietilo, azidofosfato de difenilo y similares; anhídrido 2-metil-6-nitrobenzoico, N,N'-carbonildiimidazol, tetrafluoroborato de 2-cloro-1,3-dimetilimidazolio y similares.

Como el solvente que no afecte adversamente la

reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, propionitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (III) por usar es, en general, de 0.1 a 10 moles, con preferencia, 0.3 a 3 moles, por 1 mol del compuesto (II).

La cantidad del agente de condensación por usar es, en general, de 0.1 a 10 moles, con preferencia, 0.3 a 5 moles, por 1 mol del compuesto (II).

Cuando se usa un reactivo de condensación de carbodiimida o anhídrido 2-metil-6-nitrobenzoico como un agente de condensación, de ser necesario, se puede mejorar la eficacia de la reacción usando un promotor de la condensación apropiado (por ejemplo, 1-hidroxi-7-azabenzotriazol, 1-hidroxibenzotriazol, N-hidroxisuccinimida, N-hidroxiftalimida, 4-dimetilaminopiridina, etc.). Cuando se usa un reactivo de condensación de ácido fosfórico o anhídrido 2-metil-6-nitrobenzoico como un agente de condensación, en general, se puede mejorar la eficacia de la

reacción añadiendo una base de amina orgánica tales como trietilamina, diisopropiletilamina y similares.

La cantidad del promotor de la condensación y base de amina orgánica por usar es, en general, de 0.1 a 10 moles, con preferencia, 0.3 a 5 moles, por 1 mol del compuesto (II), respectivamente.

La temperatura de reacción es en general -30°C a 100°C.

El tiempo de reacción es, en general, de 0.1 a 100 h.

Cuando se usa un haluro de ácido como un derivado reactivo del compuesto (II), la reacción se lleva a cabo haciendo reaccionar el compuesto (II) con un agente de halogenación en un solvente que no afecte adversamente la reacción, y haciendo reaccionar el compuesto resultante con el compuesto (III) en presencia de una base.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; acetonitrilo, acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción

apropiada.

Como el agente de halogenación, se pueden mencionar, por ejemplo, cloruro de tionilo, cloruro de oxalilo, cloruro de fosforilo y similares.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros.

La cantidad del compuesto (III) por usar es, en general, de 0.1 a 10 moles, con preferencia, de 0.3 a 3 moles, por 1 mol del compuesto (II).

La cantidad del agente de halogenación por usar es, en general, de 1 a 50 moles, con preferencia, 1 a 10 moles, por 1 mol del compuesto (II).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

La temperatura de reacción es, en general, de -30°C a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

Cuando se usa un anhídrido de ácido mixto como un

derivado reactivo del compuesto (II), la reacción se lleva a cabo haciendo reaccionar el compuesto (II) con un clorocarbonato en presencia de una base, y haciendo reaccionar el compuesto resultante con el compuesto (III).

Como el clorocarbonato, se pueden mencionar, por ejemplo, clorocarbonato de metilo, clorocarbonato de etilo, clorocarbonato de isobutilo y similares.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros.

La cantidad del compuesto (III) por usar es, en general, de 0.1 a 10 moles, con preferencia, 0.3 a 3 moles, por 1 mol del compuesto (II).

La cantidad del clorocarbonato por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

La temperatura de reacción es, en general, de -30°C a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

Cuando se usa una imidazolida como un derivado reactivo de compuesto (II), la reacción se lleva a cabo haciendo reaccionar el compuesto (II) con N,N'-carbonildiimidazol, y haciendo reaccionar el compuesto resultante con el compuesto (III) en presencia de una base.

Como la base, se pueden mencionar aquellas similares a la base usada para la reacción antes mencionada usando un haluro de ácido.

La cantidad del compuesto (III) por usar es, en general, de 0.1 a 10 moles, con preferencia, de 0.3 a 3 moles, por 1 mol del compuesto (II).

La cantidad del N,N'-carbonildiimidazol por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

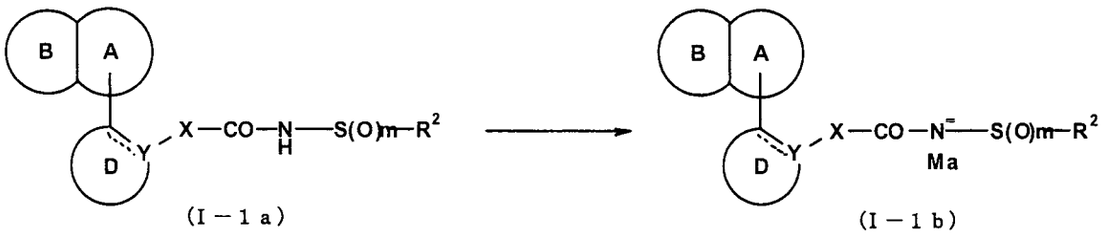
La temperatura de reacción es, en general, de -30°C a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

El compuesto (II) se puede producir, por ejemplo, de acuerdo con el Método T1 al Método T5 antes mencionados, Paso 1 del Método N o un método análogo. El compuesto (III) se puede producir de acuerdo con un método conocido *per se*.

La sal de metal alcalino (I-1b) del compuesto (I-1a), que es el compuesto (I) en donde W es $-CONR^{1a}S(O)_mR^2$ en donde R^{1a} es un átomo de hidrógeno y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método A2.

[Método A2]



en donde Ma es un metal alcalino, y los otros símbolos son como se definieron con anterioridad.

Como el metal alcalino para Ma, se pueden mencionar sodio, potasio y similares.

En este método, el compuesto (I-1b) se puede producir haciendo reaccionar el compuesto (I-1a) con una base. Esta reacción se lleva a cabo en presencia de una base, en un solvente que contiene agua, de acuerdo con un método conocido *per se*.

Como la base, se pueden mencionar, por ejemplo, carbonatos de metal alcalino tales como hidrógeno-carbonato de potasio, carbonato de sodio ácido y similares, y otros.

La cantidad de la base por usar es, en general, de 1 a 2 moles, por 1 mol del compuesto (I-1a).

Como el solvente que contiene agua, se pueden mencionar, por ejemplo, un solvente mixto de agua y 1 o varios solventes seleccionados de alcoholes tales como metanol, etanol y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; sulfóxido de dimetilo, acetona y similares, y otros.

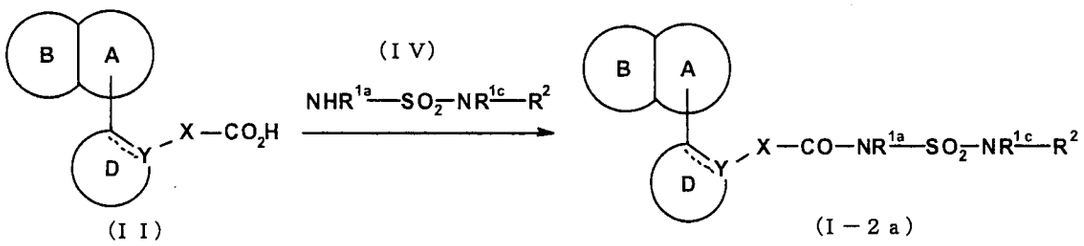
La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 50°C.

El tiempo de reacción es, en general, de 0.1 a 20 h.

El compuesto (I-1a) se puede producir, por ejemplo, de acuerdo con el Método A1 antes mencionado, el Método AI, Método AJ, Método AL mencionados más abajo o un método análogo.

El compuesto (I-2a), que es el compuesto (I) en donde W es $-CONR^{1a}S(O)_mNR^{1c}R^2$ en donde m es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método B.

[Método B]



(I I) (I-2a)

en donde cada símbolo es como se definió con

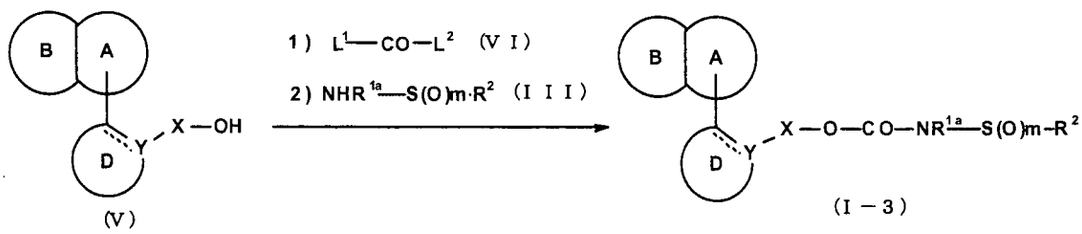
anterioridad.

En este método, el compuesto (I-2a) se puede producir haciendo reaccionar el compuesto (II) con el compuesto (IV). Esta reacción se lleva a cabo de la misma manera que en la reacción de condensación descrita en el Método A1 antes mencionado.

El compuesto (IV) se puede producir, por ejemplo, de acuerdo con el Método AT mencionado más abajo o un método análogo.

El compuesto (I-3), que es el compuesto (I) en donde W es $-OCONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método C o Método D.

[Método C]



en donde L^1 y L^2 son, de modo independiente, un grupo saliente, y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente L^1 o L^2, se pueden mencionar, por ejemplo, un grupo hidroxi, un átomo de halógeno, un grupo imidazolilo, un grupo succinimidooxi, $-OSO_2R^3$ en donde R^3 es

un grupo alquilo de C_{1-4} (con preferencia, metilo), un grupo arilo de C_{6-10} opcionalmente sustituido con grupos alquilo de C_{1-4} (con preferencia, tolilo), y similares.

Como el compuesto (VI), se pueden mencionar, por ejemplo, N,N'-carbonildiimidazol, difosgeno, trifosgeno y similares.

En este método, el compuesto (I-3) se puede producir a partir del compuesto (V). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (V) con el compuesto (VI) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 10 h, y haciendo reaccionar el compuesto obtenido con el compuesto (III) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 50 h.

Esta reacción se puede llevar a cabo en presencia de 1 a 5 moles de una base, por 1 mol del compuesto (V).

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio

ácido, carbonato de sodio, carbonato de potasio y similares, y otros. Estas bases se pueden usar en una mezcla en una proporción apropiada.

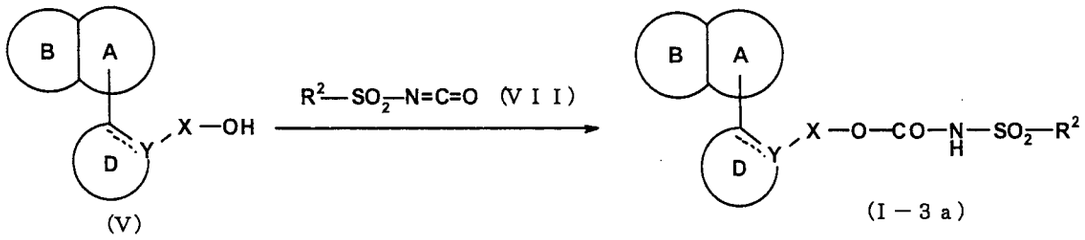
Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (VI) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

La cantidad del compuesto (III) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

El compuesto (V) se puede producir, por ejemplo, de acuerdo con el Método U1 o el Método U2 mencionados a continuación o un método análogo. El compuesto (VI) se puede producir de acuerdo con un método conocido *per se*.

[Método D]



(V) (I-3a)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-3a), que es el compuesto (I-3) en donde R^{1a} es un átomo de hidrógeno y m es 2, se puede producir haciendo reaccionar el compuesto (V) con el compuesto (VII). Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Esta reacción se puede llevar a cabo en presencia de 1 a 5 moles de una base, por 1 mol del compuesto (V).

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros. Estas bases se pueden usar en una

mezcla en una proporción apropiada.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (VII) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

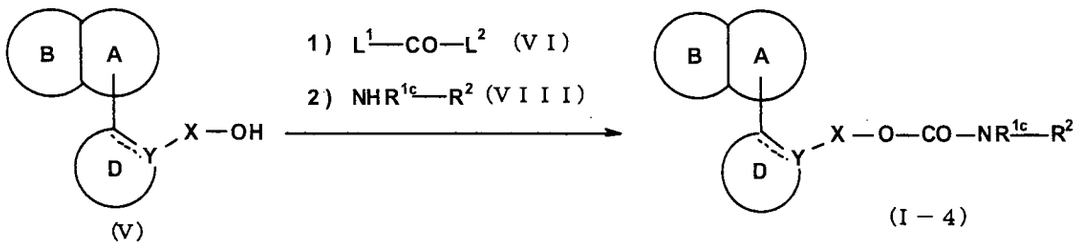
La temperatura de reacción es, en general, de -30°C a 100°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

El compuesto (VII) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-4), que es el compuesto (I) en donde W es $-OCONR^{1c}R^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método E o Método F.

[Método E]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-4) se puede producir a partir del compuesto (V). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (V) con el compuesto (VI) en un solvente que no afecte adversamente la reacción de -10°C a 100°C durante 0.5 a 10 h, y haciendo reaccionar el compuesto obtenido con el compuesto (VIII) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 30 h.

Esta reacción se puede llevar a cabo en presencia de 1 a 5 moles de una base, por 1 mol del compuesto (V).

Como la base y el solvente que no afecte adversamente la reacción, se pueden mencionar aquellos ejemplificados en el Método C antes mencionado.

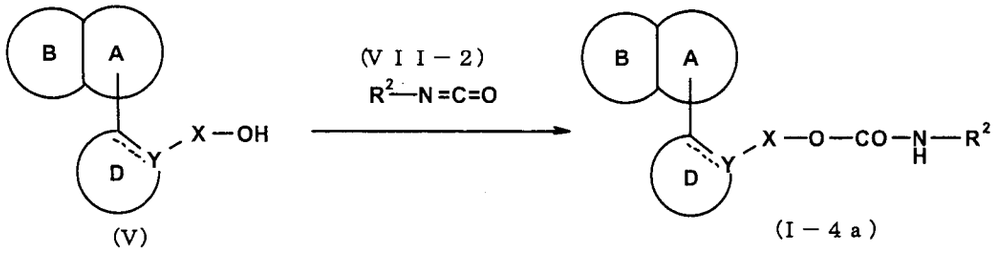
La cantidad del compuesto (VI) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

La cantidad del compuesto (VIII) por usar es, en

general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

El compuesto (VIII) se puede producir de acuerdo con un método conocido *per se*.

[Método F]



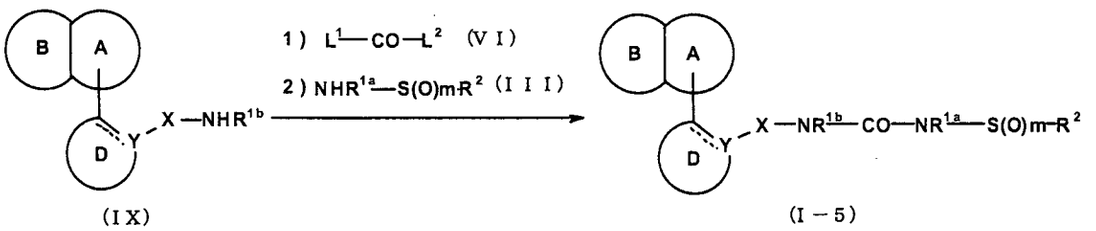
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-4a), que es el compuesto (I-4) en donde R^{1c} es un átomo de hidrógeno, se puede producir haciendo reaccionar el compuesto (V) con el compuesto (VII-2). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método D anteriormente mencionado.

El Compuesto (VII-2) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-5), que es el compuesto (I) en donde W es $-NR^{1b}CONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método G, Método H1 o Método H2.

[Método G]



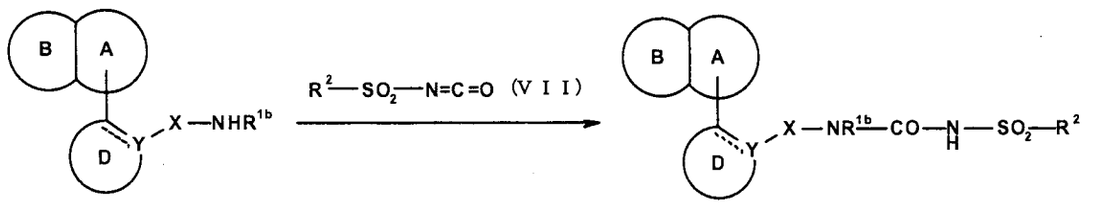
(IX) (I-5)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-5) se puede producir haciendo reaccionar el compuesto (IX) con el compuesto (VI) y (III) de manera sucesiva. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método C.

El compuesto (IX) se puede producir, por ejemplo, de acuerdo con el Método V1 o Método V2 mencionados más abajo o un método análogo.

[Método H1]



(IX) (I-5a)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-5a), que es el

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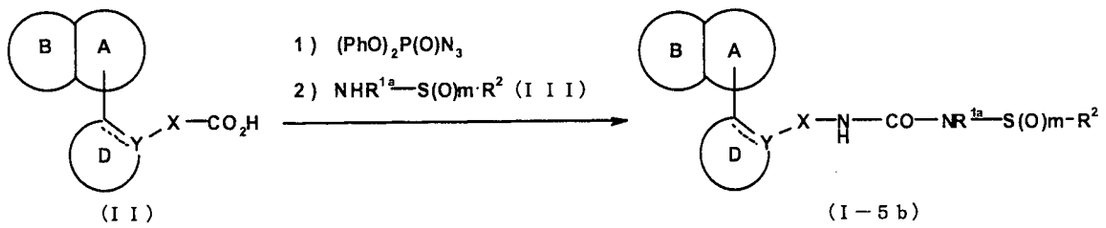
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compuesto (I-5) en donde R^{1a} es un átomo de hidrógeno y m es 2, se puede producir haciendo reaccionar el compuesto (IX) con el compuesto (VII). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método D anteriormente mencionado.

[Método H2]



(II) (I-5b)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-5b), que es el compuesto (I-5) en donde R^{1b} es un átomo de hidrógeno, se puede producir a partir del compuesto (II). Esta reacción se lleva a cabo haciendo reaccionar el compuesto (II) con azidofosfato de difenilo en presencia de una base, en un solvente que no afecte adversamente la reacción, de -10°C a 40°C durante 0.5 a 10 h, y haciendo reaccionar un isocianato generador por descomposición térmica a partir de la acilazida obtenida con el compuesto (III) en presencia de una base, en un solvente que no afecte adversamente la reacción, de 60°C a 150°C durante 0.5 a 30 h.

Como la base, se pueden mencionar, por ejemplo,

aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del azidofosfato de difenilo por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

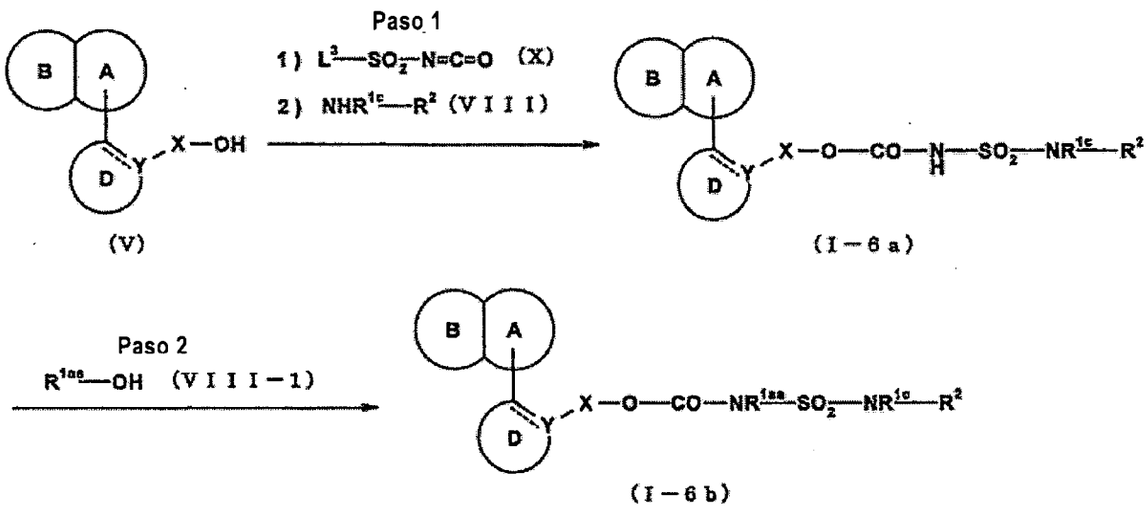
La cantidad de la base por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (II).

La cantidad del compuesto (III) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II).

El compuesto (I-6a), que es el compuesto (I) en

donde W es $-OCONR^{1a}S(O)_mNR^{1c}R^2$ en donde R^{1a} es un átomo de hidrógeno, m es 2 y los otros símbolos son como se definieron con anterioridad, y el compuesto (I-6b), que es el compuesto (I) en donde W es $-OCONR^{1a}S(O)_mNR^{1c}R^2$ en donde R^{1a} es un grupo alquilo de C_{1-6}, m es 2 y los otros símbolos son como se definieron con anterioridad, se producen, por ejemplo, de acuerdo con el siguiente Método I.

[Método I]



en donde L^3 es un grupo saliente, R^{1aa} es un grupo alquilo de C_{1-6}, y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^3, se pueden mencionar aquellos ejemplificados para los L^1 o L^2. De ellos, es preferentemente un átomo de halógeno, con preferencia particular, un átomo de cloro.

[Paso 1]

En este paso, el compuesto (I-6a) se puede producir a partir del compuesto (V). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (V) con el compuesto (X) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.1 a 10 h, y haciendo reaccionar el compuesto obtenido con el compuesto (VIII) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 50 h.

Esta reacción se puede llevar a cabo en presencia de 1 a 10 moles de una base, por 1 mol del compuesto (V).

Como ejemplos específicos de compuesto (X), se pueden mencionar isocianato de clorosulfonilo y similares.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales

como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, propionitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (X) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

La cantidad del compuesto (VIII) por usar es, en general, de 1 a 30 moles, con preferencia, 1 a 10 moles, por 1 mol del compuesto (V).

[Paso 2]

En este paso, el compuesto (I-6b) se puede producir haciendo reaccionar el compuesto (I-6a) con el compuesto (VIII-1). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, el método descrito en Synthesis, página 1, (1981) o un método análogo. Es decir, esta reacción en general se lleva a cabo en presencia de un compuesto de fósforo orgánico y un agente electrofílico, en un solvente que no afecte adversamente la reacción.

Como el compuesto de fósforo orgánico, se pueden mencionar, por ejemplo, trifenilfosfina, tributilfosfina y similares.

Como el agente electrofílico, se pueden mencionar, por ejemplo, azodicarboxilato de dietilo, azodicarboxilato de

diisopropilo, azodicarbonildipiperizina y similares.

La cantidad del compuesto de fósforo orgánico y agente electrofílico por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (I-6a), respectivamente.

La cantidad del compuesto (VIII-1) por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (I-6a).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

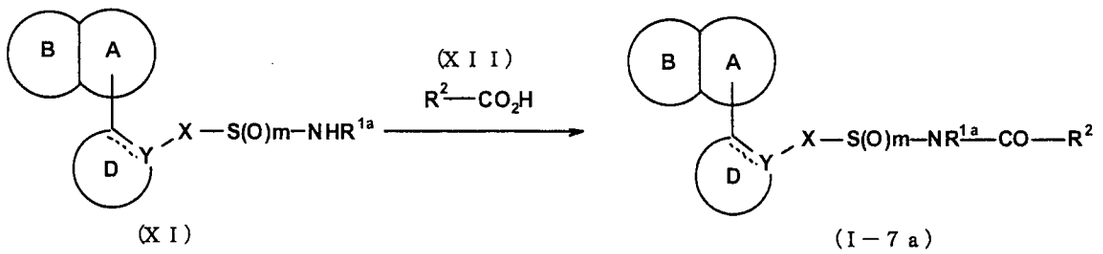
La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (X) y el compuesto (VIII-1) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-7a), que es el compuesto (I) en donde W es $-S(O)_mNR^{1a}CO_nR^2$ en donde n es 1 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método J.

[Método J]



(XI) (I-7a)

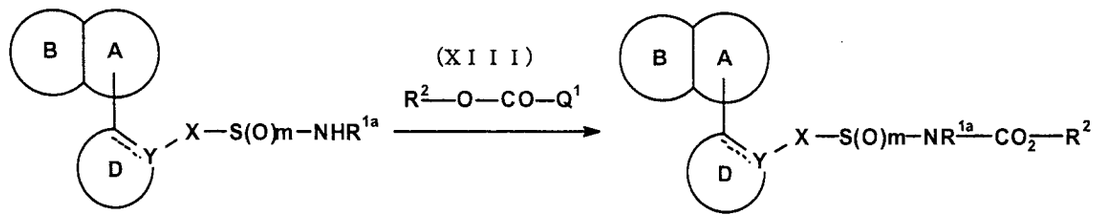
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-7a) se puede producir haciendo reaccionar el compuesto (XI) con el compuesto (XII). Esta reacción se lleva a cabo de la misma manera que la reacción de condensación descrita en el Método A1 antes mencionado.

El compuesto (XI) se puede producir, por ejemplo, de acuerdo con el Método W descrito más abajo o un método análogo. El compuesto (XII) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-7b), que es el compuesto (I) en donde W es $-S(O)_mNR^{1a}CO_nR^2$ en donde n es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método K o el Método AU mencionado más abajo.

[Método K]



(XI) (I-7b)

en donde Q^1 es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

El átomo de halógeno para Q^1 es preferentemente un átomo de cloro.

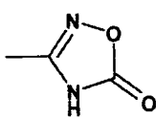
En este método, el compuesto (I-7b) se puede producir haciendo reaccionar el compuesto (XI) con el compuesto (XIII).

La cantidad del compuesto (XIII) por usar es, en general, 0.,5 a 200 moles, por 1 mol del compuesto (XI).

Esta reacción se lleva a cabo de la misma manera que en la reacción de condensación descrita en el Método A1 antes mencionado.

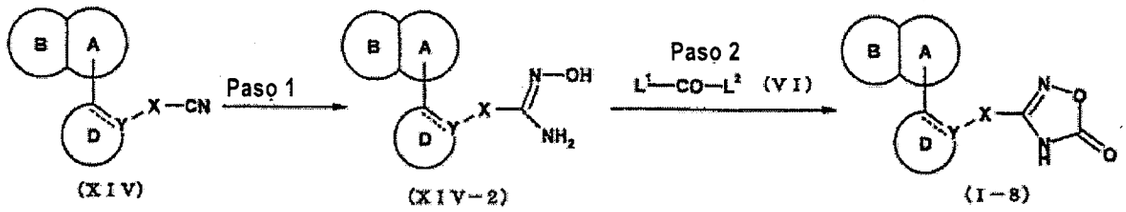
El compuesto (XIII) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-8), que es el compuesto (I) en donde W es



se produce, por ejemplo, de acuerdo con el siguiente Método L.

[Método L]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (XIV-2) se puede producir haciendo reaccionar el compuesto (XIV) con hidroxilamina (o cloruro de hidroxilamonio). Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares;

hidrocarburos halogenados tales como cloroformo, diclorometano, 1.2-dicloroetano y similares; hidrocarburos aromáticos tales como benceno, tolueno, nitrobenceno y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; cetonas tales como acetona y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del hidroxilamina por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XIV).

La cantidad de la base por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XIV).

La temperatura de reacción es, en general, de -30 a 180°C, con preferencia, -10 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

El compuesto (XIV) se puede producir, por ejemplo, de acuerdo con el Método X mencionado más abajo o un método análogo.

[Paso 2]

En este paso, el compuesto (I-8) se puede producir haciendo reaccionar el compuesto (XIV-2) con el compuesto (VI). Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como el compuesto (VI), se pueden mencionar, por

ejemplo, N,N'-carbonildiimidazol, difosgeno, trifosgeno y similares.

La cantidad del compuesto (VI) por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XIV-2).

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos de C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares, y otros.

La cantidad de la base por usar es, en general, de 1 a 50 moles, con preferencia, 1 a 10 moles, por 1 mol del compuesto (XIV-2).

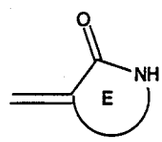
Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos

halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; cetonas tales como acetona y similares; acetonitrilo y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

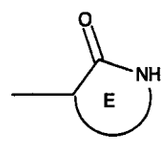
La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

El compuesto (I-9a), que es el compuesto (I) en donde W es un grupo representado por la fórmula:



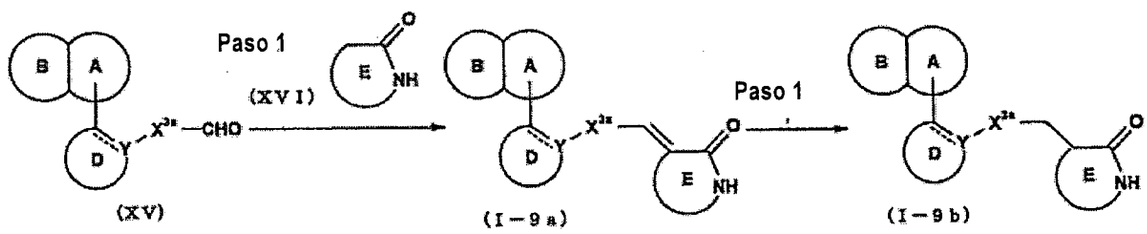
en donde el anillo E es un heterociclo que contiene C-CO-NH de 5 ó 6 miembros, que está opcionalmente sustituido, y X es $-X^{3a}-CH=$ en donde X^{3a} es como se definió con anterioridad, y el compuesto (I-9b), que es el compuesto (I) en donde W es un grupo representado por la fórmula:



en donde el anillo E es un heterociclo que contiene C-CO-NH de 5 ó 6 miembros, que está opcionalmente sustituido,

y X es $-X^{3a}-CH_2-$ en donde X^{3a} es como se definió con anterioridad, se producen, por ejemplo, de acuerdo con el siguiente Método M.

[Método M]



en donde cada símbolo es como se definió con anterioridad.

Como el "heterociclo que contiene C-CO-NH de 5 ó 6 miembros" del "heterociclo que contiene C-CO-NH de 5 ó 6 miembros, que está opcionalmente sustituido" para el anillo E, se pueden mencionar anillos que contienen C-CO-NH como miembro constitutivo del anillo (por ejemplo, 2,5-dioxopirrolina, 2-oxopirrolidina, 2,5-dioxopirrolidina, 2,4-dioxoimidazolidina, 2,6-dioxopiperidina, 2,4-dioxotiazolidina, 1,1-dióxido-3-oxoisotiazolidina, 2,6-dioxohexahidropirimidina, 1,1-dióxido-3-oxo-1.2-tiazinano), de entre anillos correspondientes al "grupo heterocíclico que contiene NH de 5 ó 6 miembros" del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" antes mencionado para W. Como los sustituyentes del "heterociclo que contiene C-CO-NH de 5 ó 6 miembros, que

está opcionalmente sustituido" para el anillo E, se pueden mencionar aquellos similares a los sustituyentes del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W.

[Paso 1]

En este paso, el compuesto (I-9a) se puede producir haciendo reaccionar el compuesto (XV) con el compuesto (XVI). Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción.

La cantidad del compuesto (XVI) por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XV).

Como la base, se pueden mencionar, por ejemplo, aminas tales como piperidina, pirrolidina, morfolina, piridina, dietilamina y similares; carbonatos de metal alcalino tales como carbonato de potasio, carbonato de sodio y similares; alcóxidos de C_{1-6} de metal alcalino tales como metóxido de sodio y similares; hidróxidos de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, hidróxido de litio y similares, y otros.

La cantidad de la base por usar es, en general, de 0.01 a 10 moles, con preferencia, de 0.05 a 5 moles, por 1 mol del compuesto (XV).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol,

butanol, isobutanol, alcohol ter-butílico y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; ácido acético y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 150°C, con preferencia, de 20 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (XV) se puede producir, por ejemplo, de acuerdo con el Método Z1 - Método Z3, Paso 2 del Método T4, Método AO, Método AQ, Método AV mencionados más abajo o un método análogo. El compuesto (XVI) se puede producir de acuerdo con un método conocido *per se*.

[Paso 2]

En este paso, el compuesto (I-9b) se puede producir al someter el compuesto (I-9a) a una reacción de hidrogenación. Esta reacción se puede llevar a cabo, por ejemplo, en presencia de un catalizador metálico tales como

paladio-carbón, negro de paladio, cloruro de paladio, óxido de platino, negro de paladio, platino-paladio, níquel Raney, cobalto Raney y similares y una fuente de hidrógeno, en un solvente que no afecte adversamente la reacción.

La cantidad del catalizador metálico por usar es, en general, de 0.001 a 1000 moles, con preferencia, de 0.01 a 100 moles, por 1 mol del compuesto (I-9a).

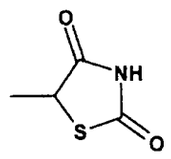
Como la fuente de hidrógeno, se pueden mencionar, por ejemplo, gas hidrógeno, ácido fórmico, una sal de amina de ácido fórmico, fosfinato, hidracina y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, alcohol ter-butílico y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1.2-dicloroetano, 1,1,2,2-tetracloroetano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; acetato de etilo, ácido acético y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 120°C, con preferencia, 10 a 80°C.

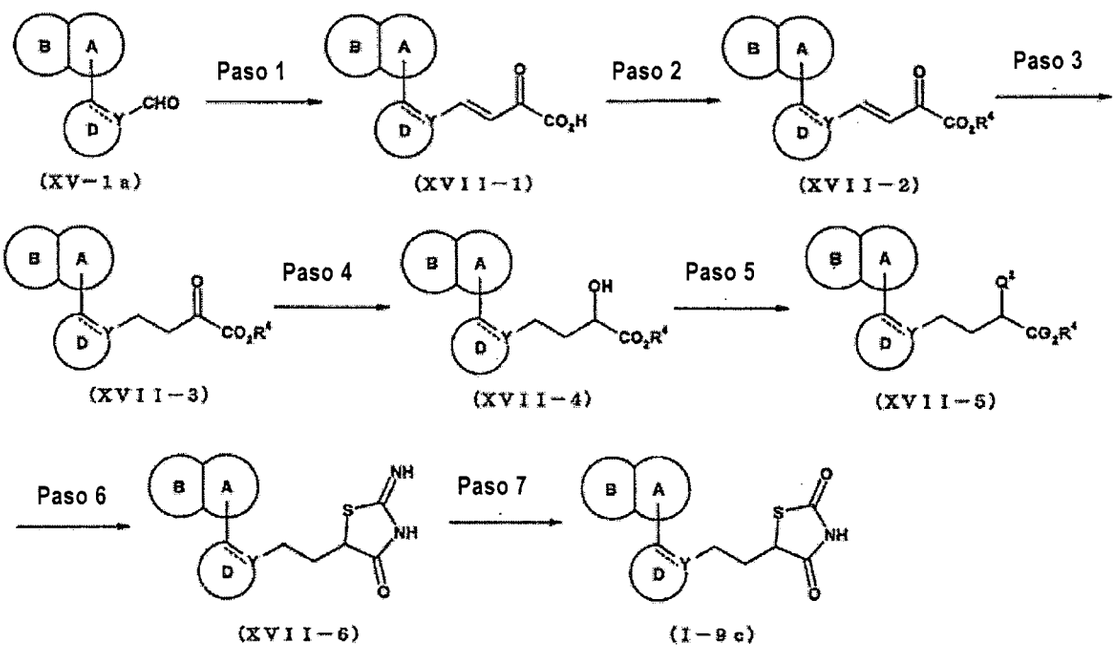
El tiempo de reacción es, en general, de 0.5 a 200 h.

El compuesto (I-9c), que es el compuesto (I) en donde W es



y X es $-CH_2CH_2-$, se produce, por ejemplo, de acuerdo con el siguiente Método N.

[Método N]



en donde R^4 es un grupo alquilo de C_{1-6}, Q^2 es un átomo de halógeno, y los otros símbolos son como se

definieron con anterioridad.

El "grupo alquilo de C_{1-6}" para R^4 es preferentemente metilo, etilo, ter-butilo o similares. "

El "átomo de halógeno" para Q^2 es preferentemente un átomo de cloro o un átomo de bromo.

[Paso 1]

En este paso, el compuesto (XVII-1) se puede producir haciendo reaccionar el compuesto (XV-1a) con ácido pirúvico. Esta reacción se lleva a cabo en presencia de una base, en un solvente que contiene agua.

La cantidad del ácido pirúvico por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XV-1a).

Como la base, se pueden mencionar, por ejemplo, aminas tales como piperidina, pirrolidina, morfolina, piridina, dietilamina y similares; carbonatos de metal alcalino tales como carbonato de potasio, carbonato de sodio y similares; alcóxidos de C_{1-6} de metal alcalino tales como metóxido de sodio y similares; hidróxidos de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, hidróxido de litio y similares, y otros.

La cantidad de la base por usar es, en general, de 0.01 a 10 moles, con preferencia, de 0.05 a 5 moles, por 1 mol del compuesto (XV-1a).

Como el solvente que contiene agua, se pueden mencionar, por ejemplo, un solvente mixto de 1 o varios

solventes seleccionados de alcoholes (por ejemplo, metanol, etanol y similares) y similares y agua, y similares.

La temperatura de reacción es, en general, de 0 a 150°C, con preferencia, de 20 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (XV-1a) se puede producir, por ejemplo, de acuerdo con el Método Z1, Método Z2, Método AO, Método AQ, Método AV mencionados más abajo o un método análogo.

[Paso 2]

En este paso, el compuesto (XVII-2) se puede producir al someter el compuesto (XVII-1) a una reacción de esterificación. Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (XVII-1) o un derivado reactivo del compuesto (XVII-1) con un alcohol. Como el derivado reactivo del compuesto (XVII-1), se pueden mencionar, por ejemplo, haluros de ácido (por ejemplo, cloruros de ácido, bromuros de ácido), imidazolida, anhídridos de ácido mixtos (por ejemplo, anhídridos con carbonato de metilo, carbonato de etilo o carbonato de isobutilo, etc.) y similares.

La reacción de compuesto (XVII-1) con un alcohol se lleva a cabo en presencia de un ácido.

Como el alcohol, se pueden mencionar metanol,

etanol y similares.

La gran cantidad en exceso del alcohol se usa como un solvente de reacción.

Como el ácido, se pueden mencionar ácidos minerales tales como ácido clorhídrico, ácido sulfúrico, y similares, y otros.

La cantidad del ácido por usar es, en general, de 0.05 a 1000 moles, por 1 mol del compuesto (XVII-1).

La temperatura de reacción es, en general, de 0 a 200°C, con preferencia, de 20 a 120°C.

El tiempo de reacción es, en general, de 0.1 a 200 h.

El método que usa un derivado reactivo de compuesto (XVII-1) se lleva a cabo de la misma manera que en el método que usa un derivado reactivo de compuesto (II) en el Método A1 antes mencionado o un método análogo.

[Paso 3]

En este paso, el compuesto (XVII-3) se puede producir al someter el compuesto (XVII-2) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

[Paso 4]

En este método, el compuesto (XVII-4) se puede producir al someter el compuesto (XVII-3) a una reacción de

reducción. Esta reacción se lleva a cabo, en general, en presencia de un agente de reducción, en un solvente que no afecte adversamente la reacción.

Como el agente de reducción, se pueden mencionar, por ejemplo, compuestos hidrogenados metálicos tales como hidruro de sodio y bis(2-metoxietoxi)aluminio, hidruro de diisobutilalumino y similares; compuestos de complejo de hidrógeno y metal tales como borohidruro de sodio, cianoborohidruro de sodio, hidruro de litio y aluminio, hidruro de sodio y aluminio y similares, y otros.

La cantidad del agente de reducción por usar es, en general, de 0.5 a 20 moles, por 1 mol del compuesto (XVII-3).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, alcohol ter-butílico y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1.2-dicloroetano, 1,1,2,2-tetracloroetano y similares; agua y similares. Estos

solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 100 h.

[Paso 5]

En este paso, el compuesto (XVII-5) se puede producir al someter el compuesto (XVII-4) a halogenación. Esta reacción se lleva a cabo en presencia de un agente de halogenación, en un solvente que no afecte adversamente la reacción.

Como el agente de halogenación, se pueden mencionar, por ejemplo, cloruro de tionilo, cloruro de oxalilo, cloruro de fosforilo, tricloruro de fósforo, tribromuro de fósforo y similares.

La cantidad del agente de halogenación por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (XVII-4).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano,

dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1.2-dicloroetano, 1,1,2,2-tetracloroetano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 50 h.

[Paso 6]

En este paso, el compuesto (XVII-6) se puede producir haciendo reaccionar el compuesto (XVII-5) con tiourea. Esta reacción se lleva a cabo en presencia de acetato de sodio o acetato de potasio, en un solvente que no afecte adversamente la reacción. Además, se puede mejorar la eficacia de la reacción añadiendo 1 a 1.5 moles de yoduro de sodio o yoduro de potasio, por 1 mol del compuesto (XVII-5).

La cantidad del tiourea por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XVII-5).

La cantidad del acetato de sodio o acetato de potasio por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XVII-5).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales

como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, alcohol ter-butílico y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo, sulforano y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 180°C, con preferencia, de 50 a 150°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

[Paso 7]

En este paso, el compuesto (I-9c) se puede producir al someter el compuesto (XVII-6) a hidrólisis. Esta reacción se lleva a cabo en presencia de un ácido, en un solvente que no afecte adversamente la reacción.

Como el ácido, se pueden mencionar ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares, y otros.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, por 1 mol del compuesto (XVII-6).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, alcohol ter-butílico y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-

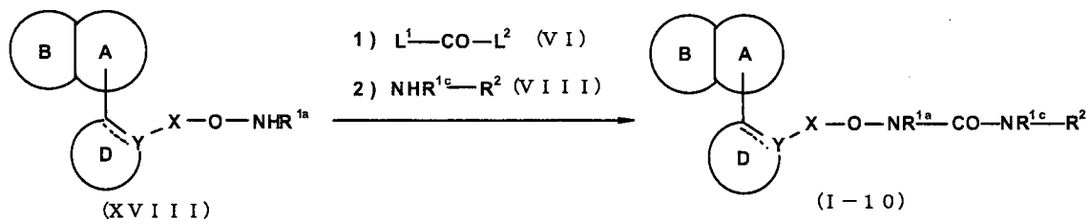
metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo, sulforano y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 20 a 150°C, con preferencia, de 50 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (I-10), que es el compuesto (I) en donde W es $-ONR^{1a}CONR^{1c}R^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método O1 o Método O2.

[Método O1]



(XVIII) (I-10)

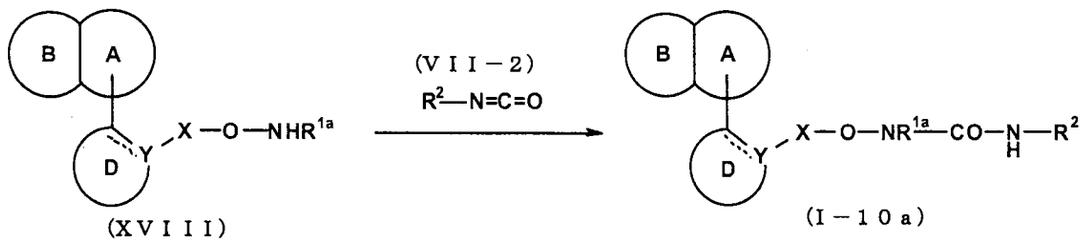
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-10) se puede producir haciendo reaccionar el compuesto (XVIII) con el compuesto (VI) y (VIII) de manera sucesiva. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método E.

El compuesto (XVIII) se puede producir, por

ejemplo, de acuerdo con el Método Y mencionado más abajo o un método análogo.

[Método O2]

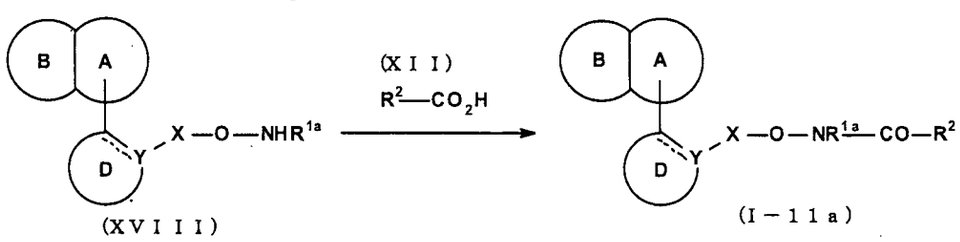


en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-10a), que es el compuesto (I-10) en donde R^{1c} es un átomo de hidrógeno, se puede producir haciendo reaccionar el compuesto (XVIII) con el compuesto (VII-2). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método D anteriormente mencionado.

El compuesto (I-11a), que es el compuesto (I) en donde W es $-ONR^{1a}CO_nR^2$ en donde n es 1 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método P.

[Método P]

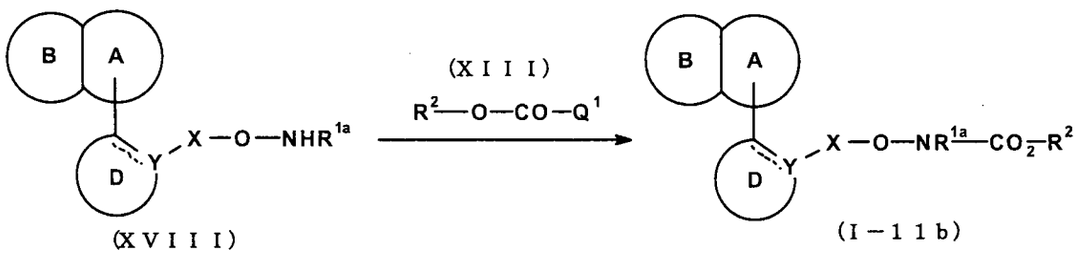


en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-11a) se puede producir haciendo reaccionar el compuesto (XVIII) con el compuesto (XII). Esta reacción se lleva a cabo de la misma manera que en el Método A1 antes mencionado.

El compuesto (I-11b), que es el compuesto (I) en donde W es $-ONR^{1a}CO_nR^2$ en donde n es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método Q.

[Método Q]



(XVIII) (I-11b)

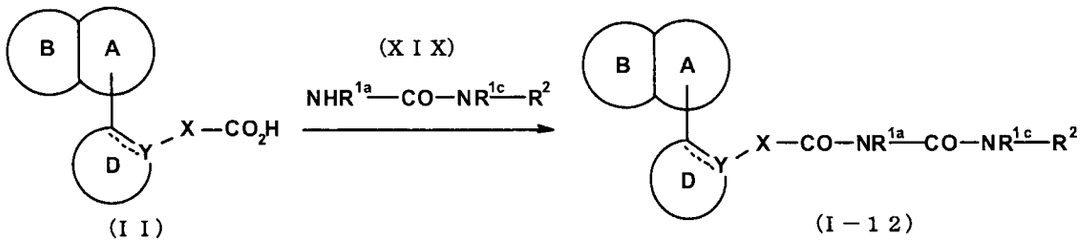
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-11b) se puede producir haciendo reaccionar el compuesto (XVIII) con el compuesto (XIII). Esta reacción se lleva a cabo de la misma manera que en el Método A1 antes mencionado.

El compuesto (I-12), que es el compuesto (I) en donde W es $-CONR^{1a}CONR^{1c}R^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo

con el siguiente Método R.

[Método R]

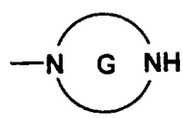


en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-12) se puede producir haciendo reaccionar el compuesto (II) con el compuesto (XIX). Esta reacción se lleva a cabo de la misma manera que en el Método A1 antes mencionado.

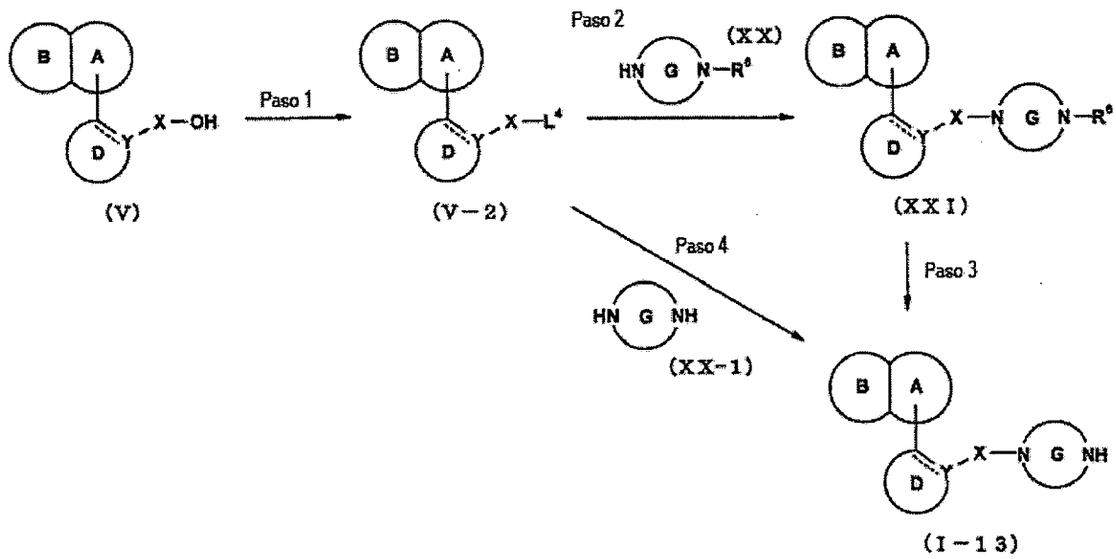
El compuesto (XIX) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-13), que es el compuesto (I) en donde W es un grupo representado por



en donde el anillo G es un heterociclo de 5 ó 6 miembros que contiene NH y también que contiene, además de NH, al menos un átomo de nitrógeno, que está opcionalmente sustituido, se produce, por ejemplo, de acuerdo con el siguiente Método S1.

[Método S1]



en donde L^4 es un grupo saliente, R^6 es un grupo protector de un átomo de nitrógeno, y los otros símbolos son como se definieron con anterioridad.

Como el "heterociclo de 5 ó 6 miembros que contiene NH y que también contiene, además de NH, al menos un átomo de nitrógeno" del "heterociclo de 5 ó 6 miembros que contiene NH y que también contiene, además del NH, al menos un átomo de nitrógeno, que está opcionalmente sustituido" para el anillo G, se pueden mencionar anillos que también contienen, como miembro constitutivo del anillo, además de "NH", al menos un átomo de nitrógeno (por ejemplo, imidazolidina, 2-oxoimidazolidina, 2,4-dioxoimidazolidina, tetrahidropirimidina, 2,6-dioxohexahidropirimidina, 1,1-dióxido-3-oxotiadiazolidina, 2-oxopiperazina), de entre anillos correspondientes al "grupo heterocíclico que contiene

NH de 5 ó 6 miembros" del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W. Como los sustituyentes para el anillo G, se pueden mencionar aquellos similares a los sustituyentes del "grupo heterocíclico que contiene NH de 5 ó 6 miembros, que está opcionalmente sustituido" para W.

Como el "grupo saliente" para L^4, se pueden mencionar un átomo de halógeno, $-OSO_2R^3$ en donde R^3 es como se definió con anterioridad, y similares.

Como el "grupo protector del átomo de nitrógeno" para R^6, se pueden mencionar un alcoxi de C_{1-6}-carbonilo (por ejemplo, ter-butoxicarbonilo), un aralquil C_{7-13}-oxi-carbonilo (por ejemplo, benciloxicarbonilo), ter-butilo, bencilo, un bencilo sustituido (por ejemplo, 4-metoxibencilo, 2,4-dimetoxibencilo) y similares.

[Paso 1]

En este paso, el compuesto (V-2) se puede producir al someter el compuesto (V) a sulfonilación o halogenación.

La sulfonilación del compuesto (V) se lleva a cabo usando un haluro de sulfonilo en presencia de una base, en un solvente que no afecte adversamente la reacción.

El haluro de sulfonilo es preferentemente cloruro de metansulfonilo, cloruro de p-toluensulfonilo, o similares.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio,

hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; acetonitrilo y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del haluro de sulfonilo por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

La cantidad de la base por usar es, en general, de

1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V).

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 50 h.

La halogenación de compuesto (V) se lleva a cabo de la misma manera que en la reacción descrita en el anterior Paso 5 del Método N.

[Paso 2]

En este paso, el compuesto (XXI) se puede producir haciendo reaccionar el compuesto (V-2) con el compuesto (XX). Esta reacción se lleva a cabo, en general, en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (XX) por usar es, en general, de 1 a 20 moles, con preferencia, 1 a 10 moles, por 1 mol del compuesto (V-2).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (V-2).

La temperatura de reacción es, en general, de -30 a 180°C, con preferencia, de -10 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (XX) se puede producir de acuerdo con un método conocido *per se*.

[Paso 3]

En este paso, el compuesto (I-13) se puede producir

al someter el compuesto (XXI) a desprotección.

Cuando R^6 es ter-butoxicarbonilo, ter-butilo, 4-metoxibencilo o 2,4-dimetoxibencilo, la reacción se lleva a cabo en presencia de un ácido, en un solvente que no afecte adversamente la reacción.

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido trifluoroacético, ácido p-toluensulfónico y similares; soluciones preparadas por disolución de cloruro de hidrógeno en metanol, acetato de etilo y similares, tales como solución de cloruro de hidrógeno-metanol, solución de cloruro de hidrógeno-acetato de etilo y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, con preferencia, de 0.1 a 100 moles, por 1 mol del compuesto (XXI).

La temperatura de reacción es, en general, de -80 a

150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

Cuando R^6 es benciloxicarbonilo o bencilo, por ejemplo, la reacción se puede llevar a cabo en presencia de un catalizador metálico tales como paladio-carbón, negro de paladio, cloruro de paladio, óxido de platino, negro de paladio, platino-paladio, níquel Raney, cobalto Raney y similares y una fuente de hidrógeno, en un solvente que no afecte adversamente la reacción.

La cantidad del catalizador metálico por usar es, en general, de 0.001 a 1000 moles, con preferencia, de 0.01 a 100 moles, por 1 mol del compuesto (XXI).

Como la fuente de hidrógeno, se pueden mencionar, por ejemplo, gas hidrógeno, ácido fórmico, una sal de amina de ácido fórmico, fosfinato, hidracina y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, alcohol ter-butílico y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos

halogenados tales como diclorometano, cloroformo, 1.2-dicloroetano, 1,1,2,2-tetracloroetano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; acetato de etilo, ácido acético y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 120°C, con preferencia, de 10 a 80°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

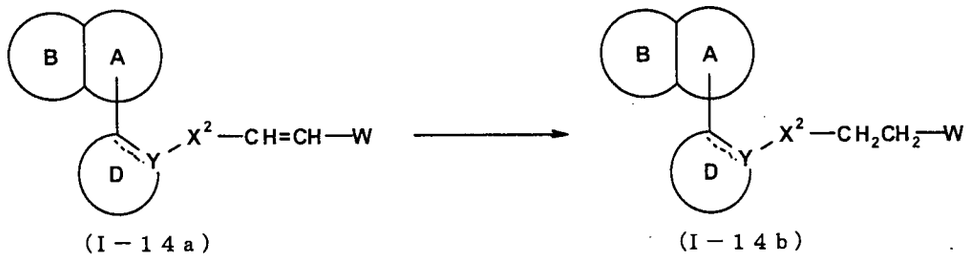
[Paso 4]

En este paso, el compuesto (I-13) se puede producir haciendo reaccionar el compuesto (V-2) con el compuesto (XX-1). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Paso 2 de este método.

El compuesto (XX-1) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-14b), que es el compuesto (I) en donde X es $-X^2-CH_2CH_2-$ en donde X^2 es un enlace o un alquileno de C_{1-2} de cadena lineal, se produce, por ejemplo, de acuerdo con el siguiente Método S2.

[Método S2]



(I−14a) (I−14b)

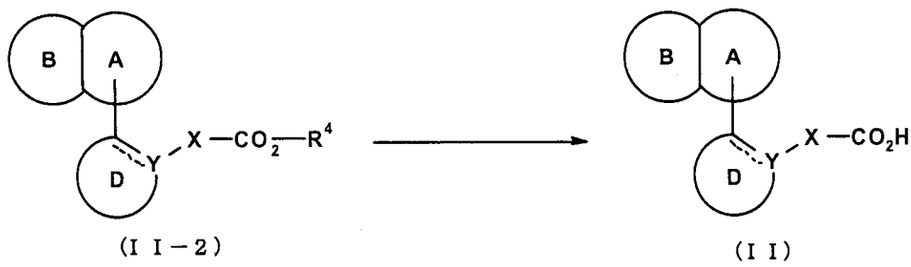
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-14b) se puede producir al someter el compuesto (I-14a) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (I-14a) se puede producir, por ejemplo, de acuerdo con el Método A1 antes mencionado, Método B, Método J, Método K, Método L, Método R, el Método AA al Método AC, Método AF al Método AL o Método AU mencionados más abajo, o un método análogo.

El compuesto (II) usado en el Método A1 antes mencionado, Método B, Método H2 y Método R como compuesto de material de partida se produce, por ejemplo, de acuerdo con el siguiente Método T1 - Método T5.

[Método T1]



(I I−2) (I I)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (II) se puede producir al someter el compuesto (II-2) a hidrólisis. Esta reacción se lleva a cabo en presencia de un ácido o una base, en un solvente que contiene agua, de acuerdo con un método conocido *per se*.

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido clorhídrico, ácido sulfúrico, ácido bromhídrico y similares; soluciones preparadas por disolución de cloruro de hidrógeno en metanol, acetato de etilo y similares, tales como solución de cloruro de hidrógeno-metanol, solución de cloruro de hidrógeno-acetato de etilo y similares; ácidos orgánicos tales como ácido trifluoroacético, ácido p-toluensulfónico, ácido acético y similares, y otros.

Como la base, se pueden mencionar, por ejemplo, carbonatos de metal alcalino tales como carbonato de potasio, carbonato de sodio y similares; alcóxidos C_{1-6} de metal

alcalino tales como metóxido de sodio y similares; hidróxidos de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, hidróxido de litio y similares, y otros.

La cantidad del ácido o base por usar es, en general, una cantidad en exceso, por 1 mol del compuesto (II-2). La cantidad del ácido por usar es preferentemente 2 a 100 moles, por 1 mol del compuesto (II-2). La cantidad de la base por usar es 1 a 10 moles, por 1 mol del compuesto (II-2).

Como el solvente que contiene agua, se pueden mencionar, por ejemplo, un solvente mixto o 1 o varios solventes seleccionados de alcoholes tales como metanol, etanol y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; sulfóxido de dimetilo, acetona y similares, y agua, y similares.

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

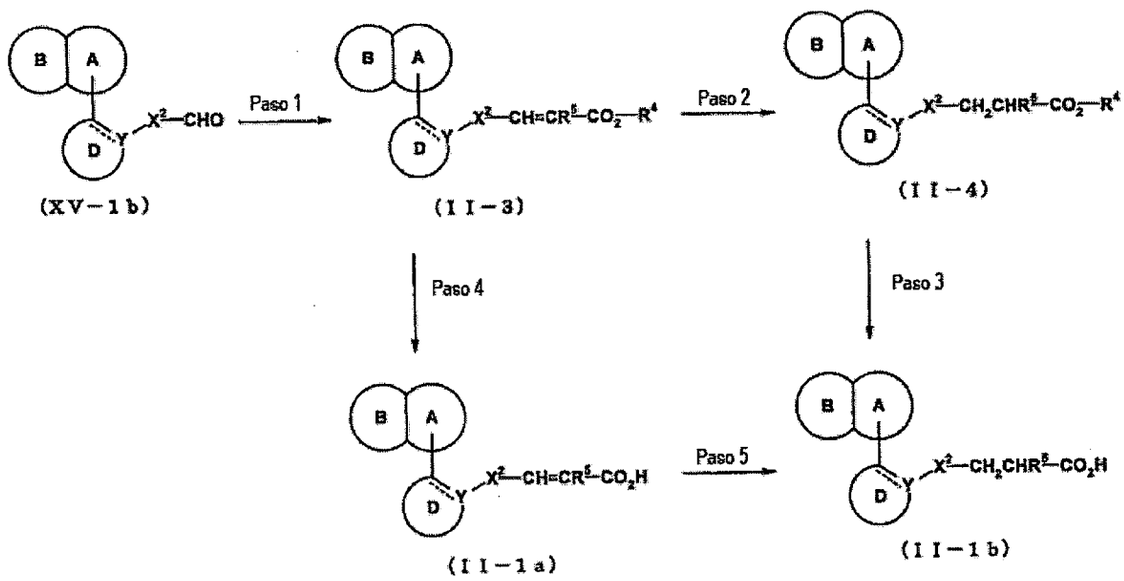
El tiempo de reacción es, en general, de 0.1 a 50 h.

El compuesto (II-2) se puede producir, por ejemplo, de acuerdo con la Paso 3 a la Paso 5 del Método N antes mencionado, Paso 1 o Paso 2 del Método T2, Método AM, Método AN, Método AP mencionados más adelante o un método análogo.

El compuesto (II-1a), que es el compuesto (II) en donde X es $-X^2-CH=CR^5-$ en donde R^5 es como se define más abajo, y X^2 es como se definió con anterioridad, y el

compuesto (II-1b), que es el compuesto (II) en donde X es $-X^2-CH_2CHR^5-$ en donde R^5 es como se define más adelante, y X^2 es como se definió con anterioridad, se producen, por ejemplo, de acuerdo con el siguiente Método T2.

[Método T2]



en donde R^5 es un grupo alquilo de C_{1-3}, y los otros símbolos son como se definieron con anterioridad.

[Paso 1]

En este paso, el compuesto (II-3) se puede producir al someter el compuesto (XV-1b) a una reacción de adición de carbonos. Esta reacción se lleva a cabo, en general, usando un reactivo de fósforo orgánico, en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio,

hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como el reactivo de fósforo orgánico, se pueden mencionar, por ejemplo, (dietoxifosforil)acetato de etilo, 2-(dietoxifosforil)propanoato de etilo, (dietoxifosforil)acetato de ter-butilo y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; alcoholes tales como metanol, etanol y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XV-1b).

La cantidad del reactivo de fósforo orgánico por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XV-1b).

La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

El compuesto (XV-1b) se puede producir, por ejemplo, de acuerdo con la Paso 2 del Método T4 mencionado más abajo, Método Z1 a Método Z3, Método AO, Método AQ, Método AV o un método análogo.

[Paso 2]

En este paso, el compuesto (II-4) se puede producir al someter el compuesto (II-3) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

[Paso 3]

En este paso, el compuesto (II-1b) se puede producir al someter el compuesto (II-4) a hidrólisis. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método T1.

[Paso 4]

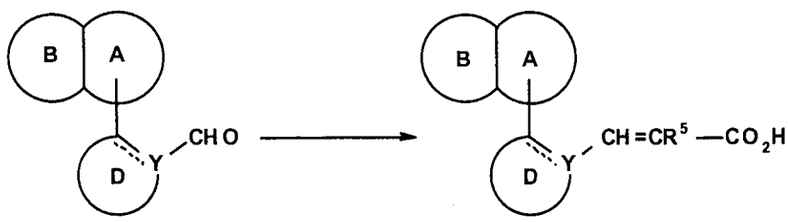
En este paso, el compuesto (II-1a) se puede producir al someter el compuesto (II-3) a hidrólisis. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método T1.

[Paso 5]

En este paso, el compuesto (II-1b) se puede producir al someter el compuesto (II-1a) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (II-1c), que es el compuesto (II) en donde X es $-CH=CR^{5a}-$ en donde R^{5a} es un átomo de hidrógeno o un grupo alquilo de C_{1-3}, se produce, por ejemplo, de acuerdo con el siguiente Método T3.

[Método T3]



(XV-1a) (II-1c)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (II-1c) se puede producir al someter el compuesto (XV-1a) a una reacción de

adición de carbonos. Esta reacción se lleva a cabo, en general, usando ácido malónico o un ácido malónico sustituido, en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como el ácido malónico sustituido, se pueden mencionar malonato de metilo, malonato de etilo, malonato de propilo y similares.

La cantidad del ácido malónico o ácido malónico sustituido por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 20 moles, por 1 mol del compuesto (XV-1a).

Como la base, se pueden mencionar, por ejemplo, aminas tales como piperidina, pirrolidina, morfolina, piridina, dietilamina y similares; carbonatos de metal alcalino tales como carbonato de potasio, carbonato de sodio y similares; alcóxidos de C_{1-6} de metal alcalino tales como metóxido de sodio y similares; hidróxidos de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, hidróxido de litio y similares, y otros.

La cantidad de la base por usar es, en general, de 0.1 a 50 moles, con preferencia, de 1 a 20 moles, por 1 mol del compuesto (XV-1a).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol,

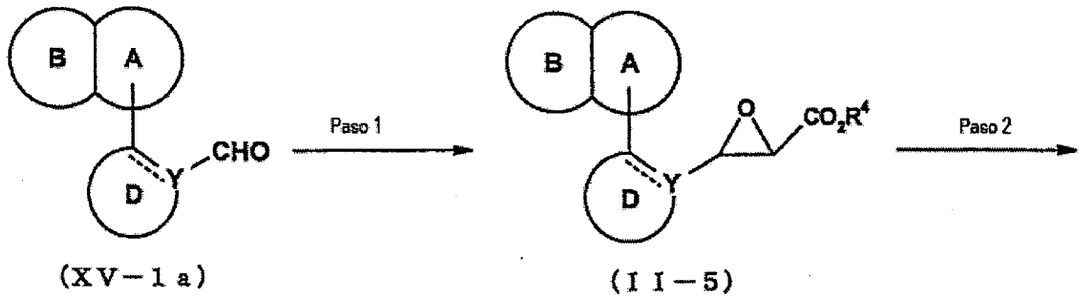
butanol, isobutanol, alcohol ter-butílico y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; ácido acético, piridina y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 200°C, con preferencia, de 20 a 150°C.

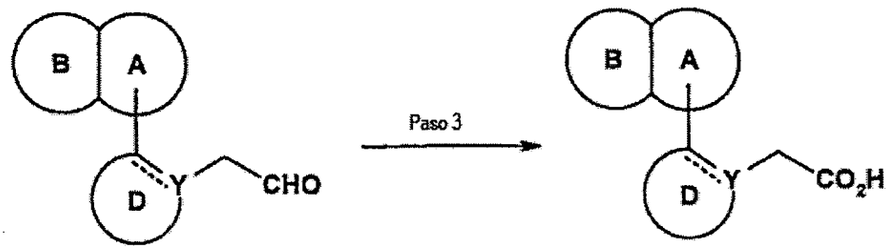
El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (II-1d), que es el compuesto (II) en donde X es metileno, se produce, por ejemplo, de acuerdo con el siguiente Método T4.

[Método T4]



(XV-1a) (II-5)



(XV-1c) (II-1d)

en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (II-5) se puede producir haciendo reaccionar el compuesto (XV-1a) con un haloacetato. Esta reacción se lleva a cabo, en general, en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como el haloacetato, se pueden mencionar bromoacetato de etilo, cloroacetato de etilo y similares.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio,

hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del haloacetato por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (XV-1a).

La cantidad de la base por usar es, en general, de

1 a 30 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (XV-1a).

La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -20 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 20 h.

[Paso 2]

En este paso, el compuesto (XV-1c) se puede producir al someter el compuesto (II-5) a hidrólisis, y someter el carboxílico ácido obtenido a una reacción de descarboxilación en presencia de un ácido.

La hidrólisis de compuesto (II-5) se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método T1.

La reacción de descarboxilación del carboxílico ácido obtenido por hidrólisis de compuesto (II-5) se lleva a cabo en presencia de un ácido, en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar aquellos similares al solvente que contiene agua usado para la hidrólisis del Método T1 antes mencionado.

Como el ácido, se pueden mencionar ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido acético y similares, y

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otros.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, por 1 mol del compuesto (II-5).

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

[Paso 3]

En este paso, el compuesto (II-1d) se puede producir al someter el compuesto (XV-1c) a una reacción de oxidación. Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, usando fosfato de sodio diácido, clorito de sodio y 2-metil-2-buteno, en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, un solvente mixto de alcohol ter-butílico y agua; un solvente mixto de ter-butilo alcohol, tetrahidrofurano y agua, y similares.

La cantidad del fosfato de sodio diácido, clorito de sodio y 2-metil-2-butene por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 20 moles, por 1 mol del compuesto (XV-1c), respectivamente.

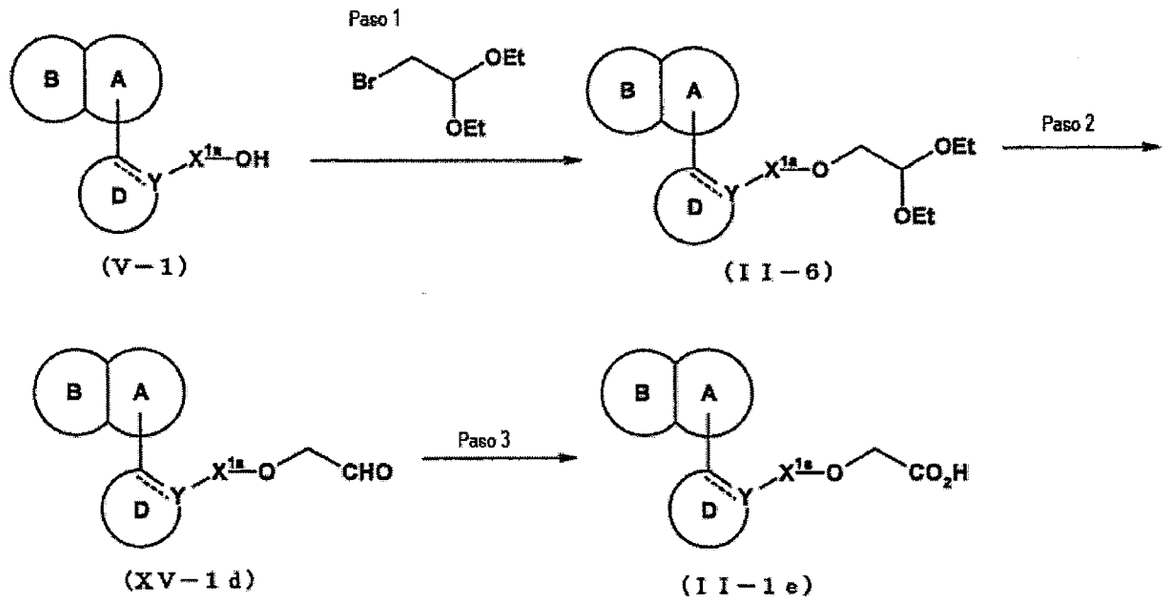
La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 80°C.

El tiempo de reacción es, en general, de 0.5 a 30

h.

El compuesto (II-1e), que es el compuesto (II) en donde X es $-X^{1a}-O-CH_2-$ en donde X^{1a} es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método T5.

[Método T5]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (II-6) se puede producir haciendo reaccionar el compuesto (V-1) con 2-bromo-1,1-dietoxietano. Esta reacción se lleva a cabo, en general, en presencia de una base, en un solvente que no afecte adversamente la reacción.

Como la base, se pueden mencionar, por ejemplo,

sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos de C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del 2-bromo-1,1-dietoxietano por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (V-1).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del

compuesto (V-1).

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (V-1) se puede producir, por ejemplo, de acuerdo con el Método U1 o Método U2 mencionados más abajo o un método análogo.

[Paso 2]

En este paso, el compuesto (XV-1d) se puede producir al someter el compuesto (II-6) a una reacción de desacetilación. Esta reacción se lleva a cabo en presencia de un ácido, en un solvente que no afecte adversamente la reacción, de acuerdo con un método conocido *per se*.

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido trifluoroacético, ácido p-toluensulfónico y similares; soluciones preparadas por disolución de cloruro de hidrógeno en metanol, acetato de etilo y similares, tales como solución de cloruro de hidrógeno-metanol, solución de cloruro de hidrógeno-acetato de etilo y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico,

tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, por 1 mol del compuesto (II-6).

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 20 h.

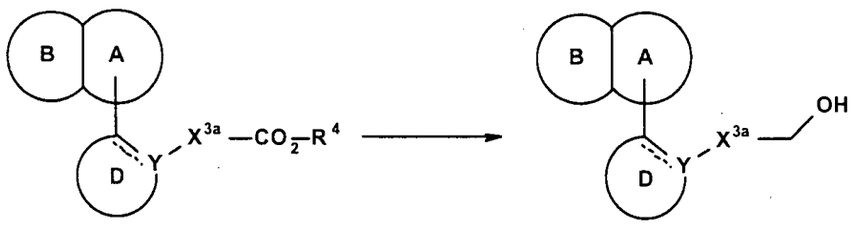
[Paso 3]

En este paso, el compuesto (II-1e) se puede producir al someter el compuesto (XV-1d) a una reacción de oxidación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 3 del Método T4 antes mencionado.

El compuesto (V) usado como compuesto de material de partida en el Método C, Método D, Método E, Método F, Método I y Método S1 antes mencionados, y el Método Y mencionado más abajo, el compuesto (V-1) usado como compuesto de material de partida en el Método T5 antes mencionado, y el compuesto (V-1a) usado como compuesto de material de partida en el Método Z3 mencionado más abajo, se producen, por ejemplo, de acuerdo con el siguiente Método U1 o Método U2.

El compuesto (V-1a), que es el compuesto (V) en donde X es $-X^{3a}-CH_2-$ en donde X^{3a} es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método U1 o Método U2.

[Método U1]



(II-7) (V-1a)

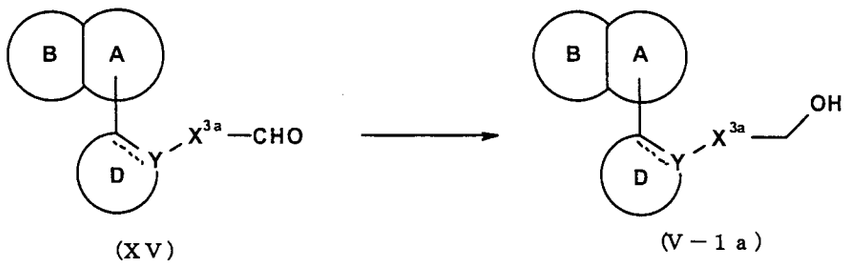
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (V-1a) se puede producir al someter el compuesto (II-7) a una reacción de reducción. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 4 del Método N antes mencionado.

El compuesto (II-7) se puede producir, por ejemplo, de acuerdo con la Paso 1 o Paso 2 del Método T2 antes mencionado, el Método AM, Método AN, Método AP mencionados más abajo o un método análogo.

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[Método U2]



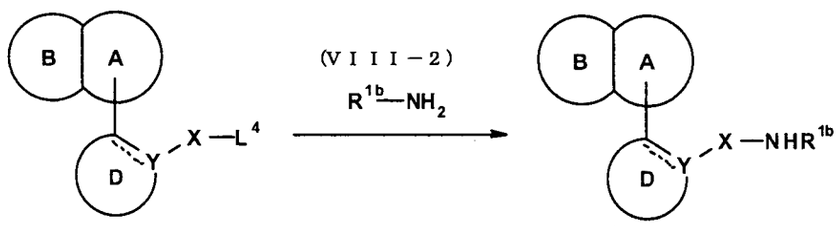
(XV) (V−1a)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (V-1a) se puede producir al someter el compuesto (XV) a una reacción de reducción. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 4 del Método N antes mencionado.

El compuesto (IX) usado como compuesto de material de partida en el Método G y Método H1 antes mencionados se produce, por ejemplo, de acuerdo con el siguiente Método V1 o Método V2.

[Método V1]



(V−2) (IX)

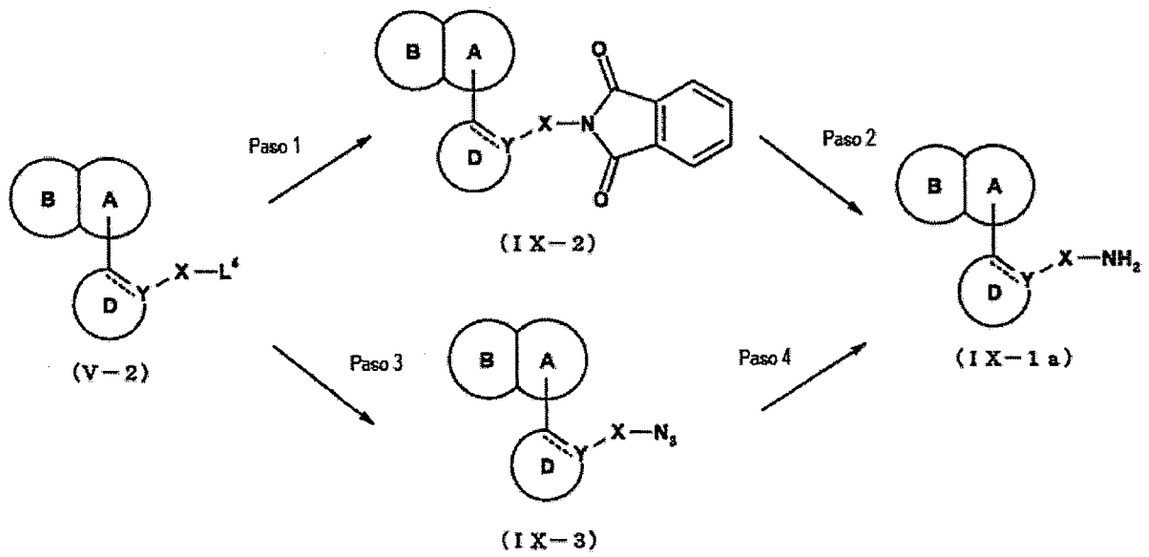
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (IX) se puede producir haciendo reaccionar el compuesto (V-2) con el compuesto (VIII-2). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método S1 antes mencionado.

El compuesto (VIII-2) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (IX-1a), que es el compuesto (IX) en donde R^{1b} es un átomo de hidrógeno, se produce, por ejemplo, de acuerdo con el siguiente Método V2.

[Método V2]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (IX-2) se puede producir haciendo reaccionar el compuesto (V-2) con ftalimida de

potasio. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del potasio ftalimida por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V-2).

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

[Paso 2]

En este paso, el compuesto (IX-1a) se puede producir al someter el compuesto (IX-2) a hidrólisis usando un ácido o una base. Esta reacción se lleva a cabo en un

solvente que no afecte adversamente la reacción.

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido sulfúrico y similares. Como la base, se pueden mencionar, por ejemplo, hidrato de hidracina. De ellos, se prefiere hidrato de hidracina.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares; agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del ácido o base por usar es, en general, de 1 a 100 moles, por 1 mol del compuesto (IX-2).

La temperatura de reacción es, en general, de -10 a 150°C, con preferencia, de 10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

[Paso 3]

En este paso, el compuesto (IX-3) se puede producir haciendo reaccionar el compuesto (V-2) con un compuesto de

azida. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el compuesto de azida, se pueden mencionar azida de sodio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto de azida por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (V-2).

La temperatura de reacción es, en general, de -10 a 150°C, con preferencia, 0 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

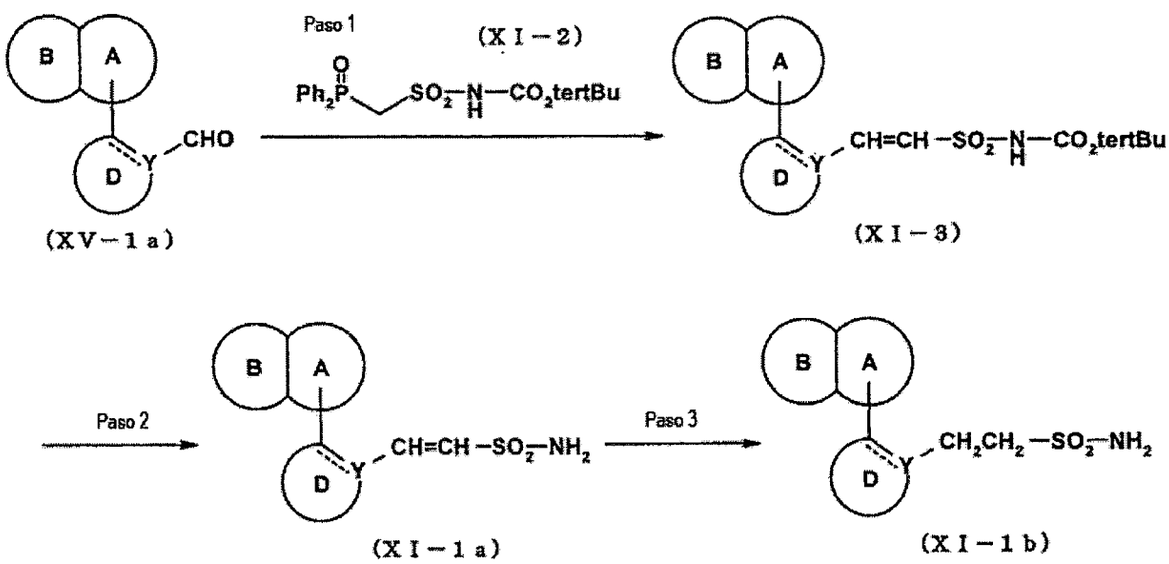
[Paso 4]

En este paso, el compuesto (IX-1a) se puede

producir al someter el compuesto (IX-3) a una reacción de reducción. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado o Paso 4 del Método N antes mencionado.

El compuesto (XI-1a), que es el compuesto (XI) (usado como compuesto de material de partida en el Método J y Método K antes mencionados) en donde R^{1a} es un átomo de hidrógeno, m es 2, y X es -CH=CH-, y el compuesto (XI-1b), que es el compuesto (XI) en donde R^{1a} es un átomo de hidrógeno, m es 2, y X es $-CH_2CH_2-$, se producen, por ejemplo, de acuerdo con el siguiente Método W.

[Método W]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (XI-3) se puede producir haciendo reaccionar el compuesto (XV-1a) con el compuesto (XI-2). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se* (por ejemplo, el método descrito en Synthesis, página 2321 (2003), Paso 1 del Método T2 antes mencionado o un método análogo etc.).

El compuesto (XI-2) se puede producir de acuerdo con un método conocido *per se*.

[Paso 2]

En este paso, el compuesto (XI-1a) se puede producir al someter el compuesto (XI-3) a desprotección. Esta reacción se lleva a cabo en presencia de un ácido, en un solvente que no afecte adversamente la reacción, de acuerdo con un método conocido *per se*.

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos orgánicos tales como ácido trifluoroacético, ácido p-toluensulfónico y similares; soluciones preparadas por disolución de cloruro de hidrógeno en metanol, acetato de etilo y similares, tales como solución de cloruro de hidrógeno-metanol, solución de cloruro de hidrógeno-acetato de etilo y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar éteres tales como éter

dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares; acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, por 1 mol del compuesto (XI-3).

La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -10 a 100°C.

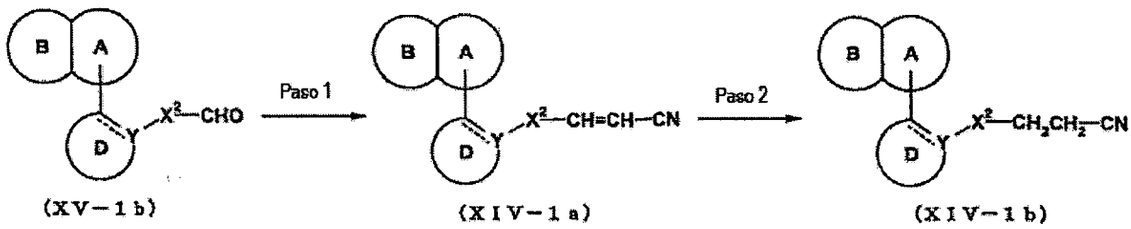
El tiempo de reacción es, en general, de 0.1 a 30 h.

[Paso 3]

En este paso, el compuesto (XI-1b) se puede producir al someter el compuesto (XI-1a) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (XIV-1a), que es el compuesto (XIV) (usado como compuesto de material de partida en el Método L antes mencionado) en donde X es $-X^2-CH=CH-$ en donde X^2 es como se definió con anterioridad, y el compuesto (XIV-1b), que es el compuesto (XIV) en donde X es $-X^2-CH_2CH_2-$ en donde X^2 es como se definió con anterioridad, se producen, por ejemplo, de acuerdo con el siguiente Método X.

[Método X]



(XV-1b) (XIV-1a) (XIV-1b)

en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

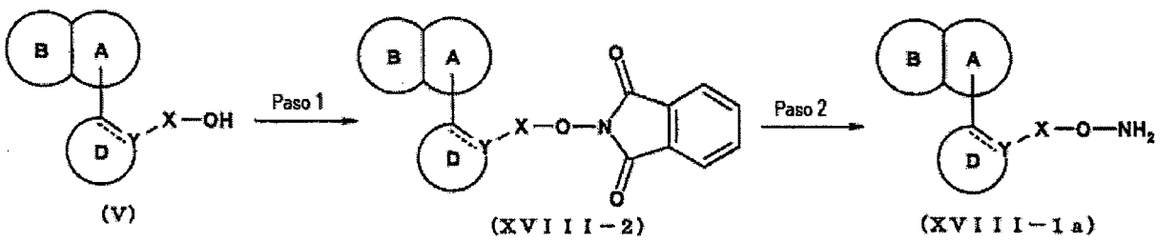
En este paso, el compuesto (XIV-1a) se puede producir haciendo reaccionar el compuesto (XV-1b) con (cianometil)fosfonato de dietilo. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 1 del Método T2 antes mencionado.

[Paso 2]

En este paso, el compuesto (XIV-1b) se puede producir al someter el compuesto (XIV-1a) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (XVIII-1a), que es el compuesto (XVIII) (usado como compuesto de material de partida en el Método O1, Método O2, Método P y Método Q antes mencionados) en donde R^{1a} es un átomo de hidrógeno, se produce, por ejemplo, de acuerdo con el siguiente Método Y.

[Método Y]



(V) (XVIII-2) (XVIII-1a)

en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (XVIII-2) se puede producir haciendo reaccionar el compuesto (V) con N-hidroxiftalimida. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método I antes mencionado.

[Paso 2]

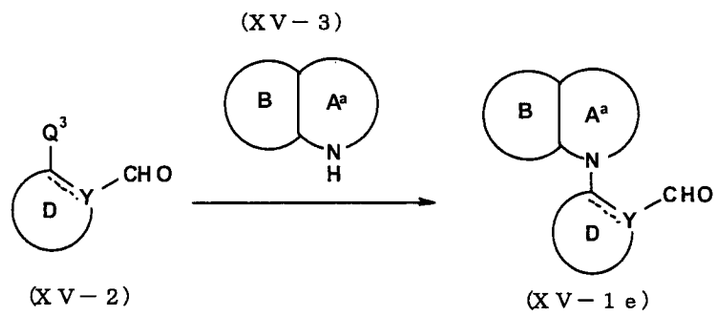
En este paso, el compuesto (XVIII-1a) se puede producir al someter el compuesto (XVIII-2) a hidrólisis. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método V2 antes mencionado.

El compuesto (XV-1a) usado como compuesto de material de partida en el Método N, Método T3, Método T4 y Método W antes mencionado, el compuesto (XV) usado como compuesto de material de partida en el Método M y Método U2 antes mencionados, el compuesto (XV-1b) usado como compuesto

de material de partida en el Método T2 y Método X antes mencionados, el compuesto (XV-1f) usado como compuesto de material de partida en el Método AL mencionado más abajo, el compuesto (XV-1h) usado como compuesto de material de partida en el Método AO mencionado más abajo, el compuesto (XV-1k) usado como compuesto de material de partida en el Método AQ mencionado más abajo, y el compuesto (XV-1m) usado como compuesto de material de partida en el Método AV mencionado más abajo, se producen, por ejemplo, de acuerdo con el siguiente Método Z1 a Método Z3.

El compuesto (XV-1e), que es el compuesto (XV-1a) en donde el anillo D está unido con el átomo de nitrógeno en el anillo A, se produce, por ejemplo, de acuerdo con el siguiente Método Z1.

[Método Z1]



(XV-2) (XV-1e)

en donde Q^3 es un átomo de halógeno o trifluorometilsulfoniloxi, el anillo A^a es un monociclo de 5 a 7 miembros que contiene NH, que está opcionalmente sustituido, y los otros símbolos son como se definieron con

anterioridad.

Como el "monociclo de 5 a 7 miembros que contiene NH, que está opcionalmente sustituido" para el anillo A^a, se pueden mencionar anillos que contienen, como miembro constitutivo del anillo, al menos un NH no sustituido (-NH-) (por ejemplo, pirrol, pirazol, imidazol), de entre los cuales se puede mencionar el "monociclo de 5 a 7 miembros que contiene NH, que está opcionalmente sustituido" para el anillo A.

En este método, el compuesto (XV-1e) se puede producir haciendo reaccionar el compuesto (XV-2) con el compuesto (XV-3). Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción. Esta reacción se puede llevar a cabo en presencia de un catalizador metálico orgánico y un ligando de fosfina, de ser necesario.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio,

etóxido de sodio, ter-butóxido de potasio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

Como el catalizador metálico orgánico, se pueden mencionar acetato de paladio (II), tetraquis(trifenilfosfina)paladio (0), diclorobis(trifenilfosfina)paladio (II) y similares.

Como el ligando de fosfina, se pueden mencionar 2.2'-bis(difenilfosfino)-1,1'-binaftilo (BINAP), tris(2-metilfenil)fosfina, 1,1'-bis(difenilfosfino)ferroceno y similares.

La cantidad del compuesto (XV-3) por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XV-2).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del

compuesto (XV-2).

La cantidad del catalizador metálico orgánico por usar es, en general, de 0.001 a 1 mol, con preferencia, de 0.01 a 0.5 moles, por 1 mol del compuesto (XV-2).

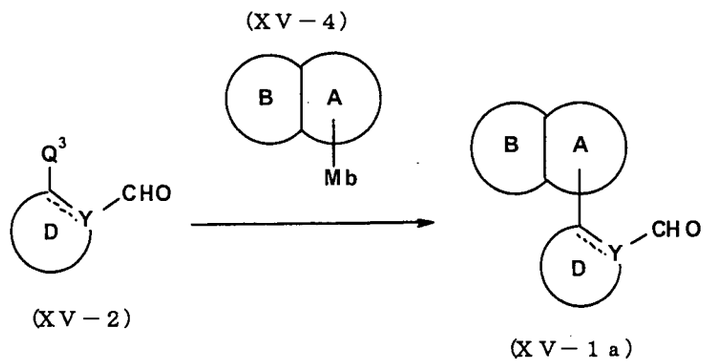
La cantidad del ligando de fosfina por usar es, en general, de 0.001 a 1 mol, con preferencia, de 0.01 a 0.5 moles, por 1 mol del compuesto (XV-2).

La temperatura de reacción es, en general, de -10 a 250°C, con preferencia, de 20 a 150°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (XV-2) se puede producir, por ejemplo, de acuerdo con el Método AR mencionado más abajo o un método análogo. El compuesto (XV-3) se puede producir de acuerdo con un método conocido *per se*.

[Método Z2]



en donde Mb es un átomo de boro sustituido cuando el compuesto (XV-4) es un ácido borónico orgánico o un boronato orgánico, o un átomo de estaño sustituido cuando el

compuesto (XV-4) es un reactivo de estaño orgánico, y los otros símbolos son como se definieron con anterioridad.

Como el átomo de boro sustituido para Mb, se pueden mencionar grupo dihidroxiborilo, grupo 4.4,5.5-tetrametil-1.3,2-dioxaborolan-2-ilo y similares.

Como el átomo de estaño sustituido para Mb, se pueden mencionar grupo trimetilestanilo, grupo tributilestanilo y similares.

En este método, el compuesto (XV-1a) se puede producir al someter el compuesto (XV-2) y el compuesto (XV-4) a una reacción de acoplamiento usando un catalizador metálico orgánico. Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción, de ser necesario. Esta reacción se puede llevar a cabo, en presencia de un ligando de fosfina, de ser necesario.

Como el catalizador metálico orgánico, se pueden mencionar acetato de paladio (II), tetraquis(trifenilfosfina)paladio (0), tris(dibencilidenacetona)dipaladio (0), diclorobis(trifenilfosfina)paladio (II) y similares.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio, carbonato de cesio y similares; hidruros de metal tales como hidruro de potasio, hidruro de

sodio y similares, y otros.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; alcoholes tales como metanol, etanol, isopropanol, alcohol ter-butílico y similares; agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (XV-4) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XV-2).

La cantidad del catalizador metálico orgánico por usar es, en general, de 0.001 a 1 mol, con preferencia, de 0.01 a 0.5 moles, por 1 mol del compuesto (XV-2).

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (XV-2).

Como el ligando de fosfina, se pueden mencionar 2.2'-bis(difenilfosfino)-1,1'-binaftilo (BINAP), tris(2-

metilfenil)fosfina, 1,1'-bis(difenilfosfino)ferroceno, 2-diciclohexilfosfino-2',6'-dimetoxibifenilo y similares.

La cantidad del ligando de fosfina por usar es, en general, de 0.001 a 1 mol, con preferencia, de 0.01 a 0.5 moles, por 1 mol del compuesto (XV-2).

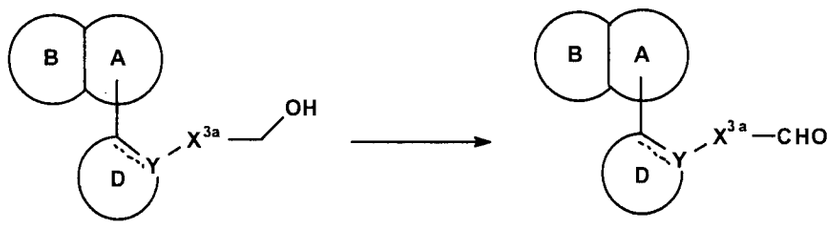
La temperatura de reacción es, en general, de 0 a 200°C, con preferencia, de 50 a 150°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (XV-4) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (XV) usado como compuesto de material de partida en el Método M antes mencionado, y el compuesto (XV-1b) usado como compuesto de material de partida en el Método T2 y Método X antes mencionados, se producen, por ejemplo, de acuerdo con el siguiente Método Z3.

[Método Z3]



(V−1a) (XV)

en donde cada símbolo es como se definió con anterioridad.

En esta reacción, el compuesto (XV) se puede

producir al someter el compuesto (V-1a) a una reacción de oxidación. Esta reacción se lleva a cabo, en general, en presencia de un oxidante, en un solvente que no afecte adversamente la reacción.

Como el oxidante, se pueden mencionar, por ejemplo, oxidantes de metal tales como dióxido de manganeso, clorocromato de piridinio, dicromato de piridinio, óxido de rutenio y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del oxidante por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (V-1a).

La temperatura de reacción es, en general, de -50 a 150°C, con preferencia, de -10 a 100°C.

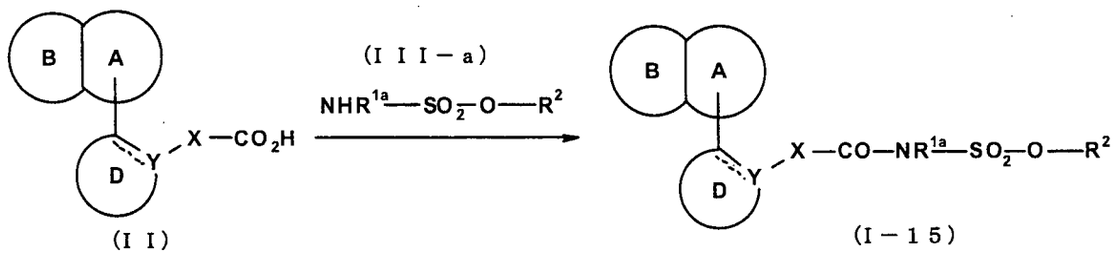
El tiempo de reacción es, en general, de 0.5 a 50 h.

El compuesto (V-1a) se puede producir, por ejemplo, de acuerdo con el Método U1 antes mencionado o un método

análogo.

El compuesto (I-15), que es el compuesto (I) en donde W es $-CONR^{1a}S(O)_mOR^2$ en donde m es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AA.

[Método AA]



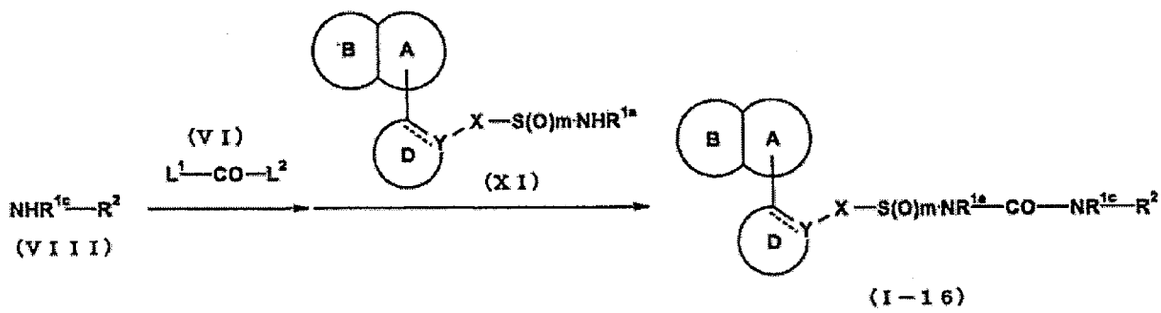
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-15) se puede producir haciendo reaccionar el compuesto (II) con el compuesto (III-a). Esta reacción se lleva a cabo de la misma manera que en la reacción de condensación descrita en el Método A1 antes mencionado.

El compuesto (III-a) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-16), que es el compuesto (I) en donde W es $-S(O)_mNR^{1a}CONR^{1c}R^2$ en donde cada símbolo es como se definió con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AB.

[Método AB]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-16) se puede producir a partir del compuesto (XI). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (VIII) con el compuesto (VI) en un solvente que no afecte adversamente la reacción, de -10°C a 120°C durante 0.5 a 10 h, y haciendo reaccionar el compuesto obtenido con el compuesto (XI) en un solvente que no afecte adversamente la reacción, de -10°C a 120°C durante 0.5 a 50 h. Esta reacción se puede llevar a cabo en presencia de 1 a 20 mol de una base, por 1 mol del compuesto (XI), de ser necesario.

Como el compuesto (VI), se pueden mencionar, por ejemplo, N,N'-carbonildiimidazol, difosgeno, trifosgeno y similares.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-

diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros. Estas bases se pueden usar en una mezcla en una proporción apropiada.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

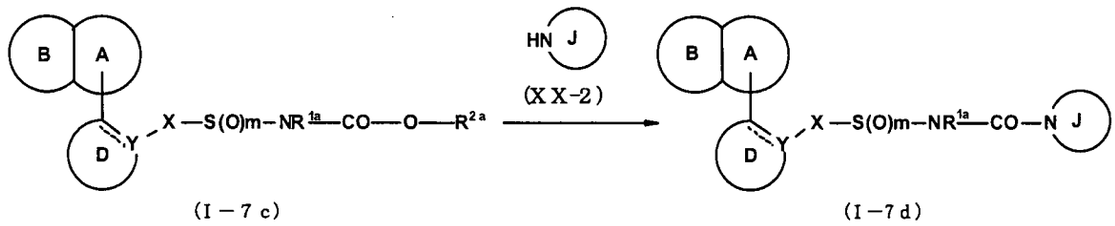
La cantidad del compuesto (VI) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XI).

La cantidad del compuesto (VIII) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XI).

El compuesto (I-7d), que es el compuesto (I-7a) (compuesto (I) en donde W es $-S(O)_mNR^{1a}CO_nR^2$ en donde n es 1 y los otros símbolos son como se definieron con anterioridad) en donde R^2 es un grupo heterocíclico no aromático que

contiene NH, se produce, por ejemplo, de acuerdo con el siguiente Método AC.

[Método AC]



(I-7c) (I-7d)

en donde R^{2a} es un grupo alquilo de C_{1-6}, el anillo J es un heterociclo no aromático que contiene NH, y los otros símbolos son como se definieron con anterioridad.

El "grupo alquilo de C_{1-6}" para R^{2a} es preferentemente etilo, propilo o butilo.

Como el "heterociclo no aromático que contiene NH" para el anillo J, se pueden mencionar pirrolidina, morfolina, piperizina y similares.

En este método, el compuesto (I-7d) se puede producir haciendo reaccionar el compuesto (I-7c) con el compuesto (XX-2). Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como

tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

Esta reacción se puede llevar a cabo en presencia de 1 a 5 moles de una base, por 1 mol del compuesto (I-7c), de ser necesario.

Como la base que no afecta adversamente la reacción, se pueden mencionar aquellas ejemplificadas en el Método AB antes mencionado.

La cantidad del compuesto (XX-2) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (I-7c).

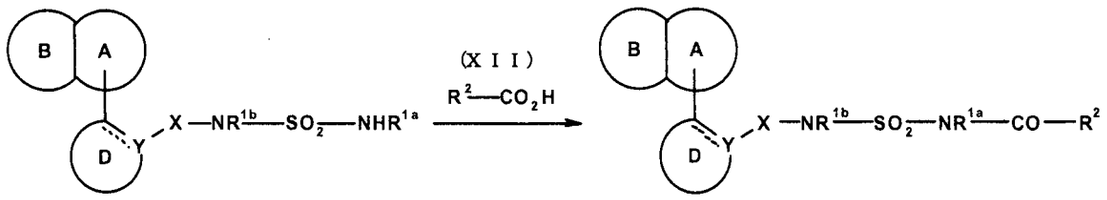
La temperatura de reacción es, en general, de -30°C a 150°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

El compuesto (I-7c) se puede producir, por ejemplo, de acuerdo con el Método AU mencionado después o un método análogo. El compuesto (XX-2) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-17a), que es el compuesto (I) en donde W es $-NR^{1b}S(O)_mNR^{1a}CO_nR^2$ en donde m es 2, n es 1 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AD.

[Método AD]



(XXII) (I-17a)

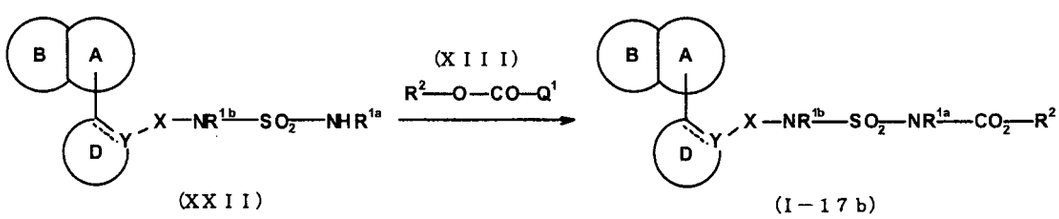
en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-17a) se puede producir haciendo reaccionar el compuesto (XXII) con el compuesto (XII). Esta reacción se lleva a cabo de la misma manera que en la reacción de condensación descrita en el Método A1 antes mencionado.

El compuesto (XXII) se puede producir, por ejemplo, de acuerdo con el Método AS mencionado más abajo o un método análogo.

El compuesto (I-17b), que es el compuesto (I) en donde W es $-NR^{1b}S(O)_mNR^{1a}CO_nR^2$ en donde m es 2, n es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AE.

[Método AE]



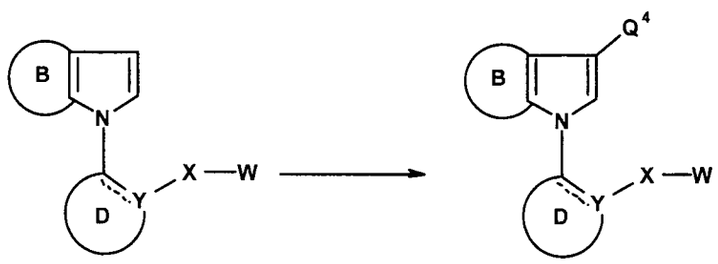
(XXII) (I-17b)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-17b) se puede producir haciendo reaccionar el compuesto (XXII) con el compuesto (XIII). Esta reacción se lleva a cabo de la misma manera que en la reacción de condensación descrita en el Método A1 antes mencionado.

El compuesto (I-18b), que es el compuesto (I) en donde el anillo A es pirrol unido con el anillo D en la posición 1 y que tiene un átomo de halógeno en la posición 3, se produce, por ejemplo, de acuerdo con el siguiente Método AF.

[Método AF]



(I-18a) (I-18b)

en donde Q^4 es un átomo de halógeno, y los otros símbolos son como se definieron con anterioridad.

El "átomo de halógeno" para Q^4 es preferentemente un átomo de cloro o un átomo de bromo.

En este método, el compuesto (I-18b) se puede producir haciendo reaccionar el compuesto (I-18a) con un agente de halogenación. Esta reacción se lleva a cabo en un

solvente que no afecte adversamente la reacción.

Como agente de halogenación, se pueden mencionar N-clorosuccinimida, N-bromosuccinimida y similares.

La cantidad del agente de halogenación por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (I-18a).

La temperatura de reacción es, en general, de -10°C a 150°C, con preferencia, de 0 a 80°C.

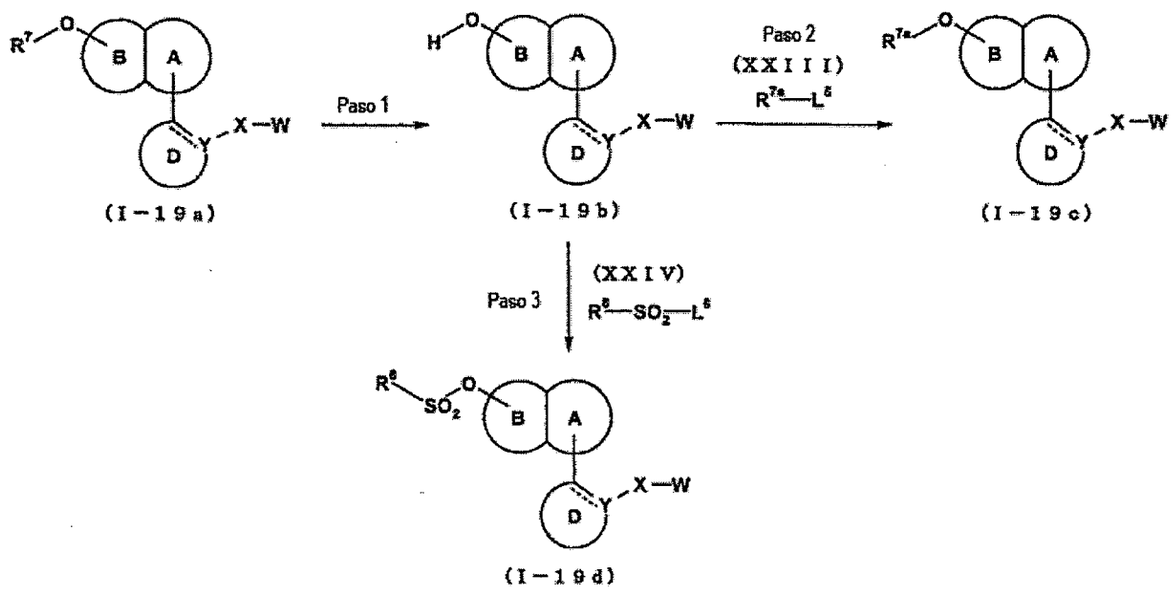
El tiempo de reacción es 0.5 a 50 h.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; acetonitrilo y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

El compuesto (I-18a) se puede producir, por ejemplo, de acuerdo con el Método A1 antes mencionado, Método B a Método G, Método H1, Método H2, Método I a Método N, Método O1, Método O2, Método P a Método R, Método S1, Método S2, Método AA a Método AE, Método AG a Método AL mencionados más abajo, Método AU o un método análogo.

El compuesto (I-19b), que es el compuesto (I) que tiene un grupo hidroxilo en el anillo B, el compuesto (I-19c), que es el compuesto (I) que tiene un grupo alcoxi de C_{1-6} opcionalmente sustituido en el anillo B, y el compuesto (I-19d), que es el compuesto (I) que tiene un grupo alquil de C_{1-6}-sulfoniloxi opcionalmente sustituido en el anillo B, se producen, por ejemplo, de acuerdo con el siguiente Método AG.

[Método AG]



en donde R^7 es metilo o bencilo, R^{7a} es un grupo alquilo de C_{1-6} opcionalmente sustituido, R^8 es un grupo alquilo de C_{1-6}, L^5 y L^6 son iguales o diferentes y cada uno es un grupo saliente, y los otros símbolos son como se definieron con anterioridad.

Como el "grupo saliente" para L^5 o L^6, se pueden mencionar aquellos ejemplificados para los L^1 o L^2 antes

mencionados.

Como el sustituyente del "grupo alquilo de C_{1-6} opcionalmente sustituido" para R^{7a}, se pueden mencionar 1 a 3 sustituyentes seleccionados de (a) un grupo arilo de C_{6-14}, (b) un grupo alcoxi de C_{1-6}, (c) un grupo cicloalquilo de C_{3-10} y (d) un grupo alquil C_{1-6}-carbonilo.

[Paso 1]

En este paso, el compuesto (I-19b) se puede producir a partir del compuesto (I-19a).

Cuando R^7 es metilo o bencilo, la reacción se lleva a cabo en presencia de tribromuro de boro, en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar hidrocarburos halogenados tales como diclorometano y similares, y otros.

La cantidad del tribromuro de boro por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (I-19a).

La temperatura de reacción es, en general, de -100 a 150°C, con preferencia, de -80 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

Cuando R^7 es bencilo, la reacción se puede llevar a cabo en presencia de un catalizador metálico tales como paladio-carbón, negro de paladio, cloruro de paladio, óxido de platino, negro de paladio, platino-paladio, níquel Raney,

cobalto Raney y similares y una fuente de hidrógeno, o en presencia de un ácido, en un solvente que no afecte adversamente la reacción.

La cantidad del catalizador metálico por usar es, en general, de 0.001 a 1000 moles, con preferencia, de 0.01 a 100 moles, por 1 mol del compuesto (I-19a).

Como la fuente de hidrógeno, se pueden mencionar, por ejemplo, gas hidrógeno, ácido fórmico, una sal de amina de ácido fórmico, fosfinato, hidracina y similares.

Como el ácido, se pueden mencionar, por ejemplo, ácidos orgánicos tales como ácido trifluoroacético y similares.

La cantidad del ácido por usar es, en general, de 0.01 a 1000 moles, con preferencia, de 0.1 a 100 moles, por 1 mol del compuesto (I-19a).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol, propanol, 2-propanol, 2-metoxietanol, butanol, isobutanol, ter-butanol y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1.2-

dicloroetano, 1,1,2,2-tetracloroetano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; acetato de etilo; ácido acético y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 150°C, con preferencia, de 10 a 80°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (I-19a) se puede producir, por ejemplo, de acuerdo con el Método A1, Método B, Método J, Método K, Método L, Método R, Método AA, Método AB antes mencionados o el Método AU mencionado más abajo, o un método análogo.

[Paso 2]

En este paso, el compuesto (I-19c) se puede producir haciendo reaccionar el compuesto (I-19b) con el compuesto (XXIII). Esta reacción se lleva a cabo, en general, en presencia de una base, en un solvente que no afecte adversamente la reacción. La eficacia de la reacción se puede mejorar usando yoduro de sodio, de ser necesario.

La cantidad del compuesto (XXIII) por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (I-19b).

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio,

hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

La cantidad de la base por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (I-19b).

La cantidad del yoduro de sodio por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (I-19b).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, acetona, acetonitrilo y similares. Estos solventes se pueden usar en una mezcla en

una proporción apropiada.

La temperatura de reacción es, en general, de -30 a 150°C, con preferencia, de -10 a 100°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (XXIII) se puede producir de acuerdo con un método conocido *per se*.

[Paso 3]

En este paso, el compuesto (I-19d) se puede producir haciendo reaccionar el compuesto (I-19b) con el compuesto (XXIV). Esta reacción se lleva a cabo, en general, en presencia de una base, en un solvente que no afecte adversamente la reacción.

La cantidad del compuesto (XXIV) por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 10 moles, por 1 mol del compuesto (I-19b).

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido

de potasio y similares.

La cantidad de la base por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (I-19b).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -10 a 100°C.

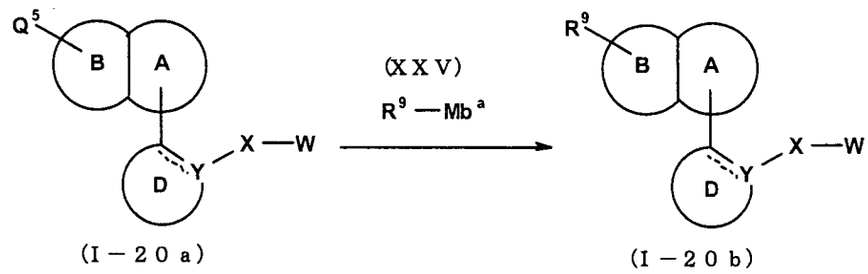
El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (XXIV) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-20b), que es el compuesto (I) que tiene un grupo arilo de C_{6-14}, un grupo heterocíclico aromático o un grupo cicloalquilo de C_{3-10} en el anillo B, se

produce, por ejemplo, de acuerdo con el siguiente Método AH.

[Método AH]



(I-20a) (I-20b)

en donde Q^5 es un átomo de halógeno, Mb^a es un átomo de boro sustituido cuando el compuesto (XXV) es un ácido borónico orgánico o un boronato orgánico, o un átomo de estaño sustituido cuando el compuesto (XXV) es un reactivo de estaño orgánico, R^9 es un grupo arilo de C_{6-14}, un grupo heterocíclico aromático o un grupo cicloalquilo de C_{3-10}, y los otros símbolos son como se definieron con anterioridad.

El "átomo de halógeno" para Q^5 es preferentemente un átomo de bromo o un átomo de yodo.

Como el "átomo de boro sustituido" o "átomo de estaño sustituido" para Mb^a, se pueden mencionar aquellos ejemplificados para el Mb antes mencionado.

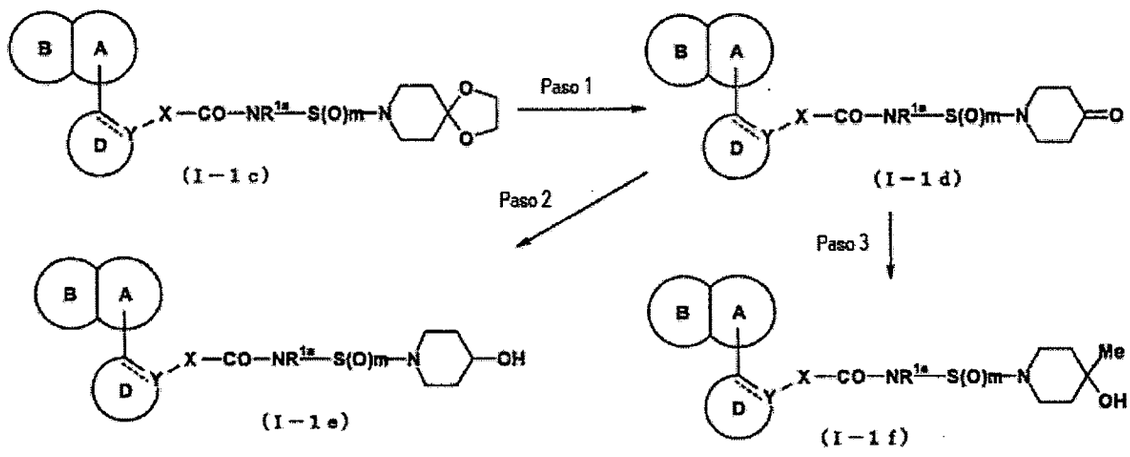
En este método, el compuesto (I-20b) se puede producir al someter el compuesto (I-20a) y el compuesto (XXV) a una reacción de acoplamiento usando un catalizador metálico orgánico. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método Z2.

El compuesto (I-20a) se puede producir, por

ejemplo, de acuerdo con el Método A1, Método B a Método G, Método H1, Método H2, Método I a Método N, Método O1, Método O2, Método P a Método R, Método S1, Método S2, Método AA a Método AG, Método AI a Método AL, Método AU antes mencionados o un método análogo. El compuesto (XXV) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (I-1d), que es el compuesto (I-1) (compuesto (I) en donde W es $-CONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió con anterioridad) en donde R^2 es grupo 4-oxopiperidin-1-ilo), el compuesto (I-1e), que es el compuesto (I-1) en donde R^2 es grupo 4-hidroxipiperidin-1-ilo, y el compuesto (I-1f), que es el compuesto (I-1) en donde R^2 es grupo 4-hidroxi-4-metilpiperidin-1-ilo, se producen, por ejemplo, de acuerdo con el siguiente Método AI.

[Método AI]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (I-1d) se puede producir al someter el compuesto (I-1c) a una reacción de descetalación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método T5 antes mencionado.

El compuesto (I-1c) se puede producir, por ejemplo, de acuerdo con el Método A1 antes mencionado o un método análogo.

[Paso 2]

En este paso, el compuesto (I-1e) se puede producir al someter el compuesto (I-1d) a una reacción de reducción. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 4 del Método N antes mencionado.

[Paso 3]

En este paso, el compuesto (I-1f) se puede producir haciendo reaccionar el compuesto (I-1d) con un agente de metilación. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el agente de metilación, se pueden mencionar cloruro de metilmagnesio, bromuro de metilmagnesio, metil-litio, y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares;

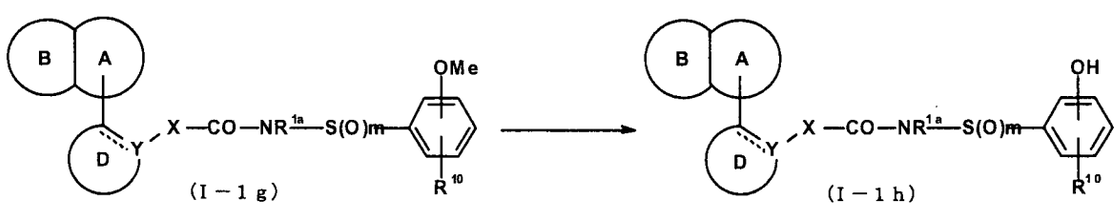
hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -80 a 150°C, con preferencia, de -10 a 80°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

El compuesto (I-1h), que es el compuesto (I-1) (compuesto (I) en donde W es $-CONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió con anterioridad) en donde R^2 es un grupo hidroxifenilo opcionalmente sustituido, se produce, por ejemplo, de acuerdo con el siguiente Método AJ.

[Método AJ]



en donde R^{10} es un grupo alquilo de C_{1-6} opcionalmente sustituido, y los otros símbolos son como se definieron con anterioridad.

Como los sustituyentes del "grupo alquilo de C_{1-6}

opcionalmente sustituido" para R^{10}, se pueden mencionar 1 a 3 átomos de halógeno (con preferencia, un átomo de flúor).

En este método, el compuesto (I-1h) se puede producir haciendo reaccionar el compuesto (I-1g) con tribromuro de boro. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar hidrocarburos halogenados tales como diclorometano y similares, y otros.

La cantidad del tribromuro de boro por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (I-1g).

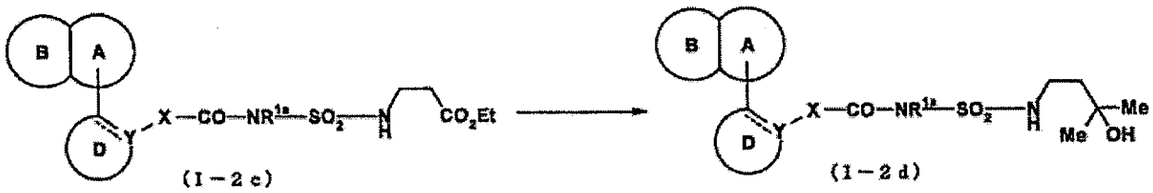
La temperatura de reacción es, en general, de -100 a 150°C, con preferencia, de -80 a 100°C.

El tiempo de reacción es, en general, de 0.1 a 50 h.

El compuesto (I-1g) se puede producir, por ejemplo, de acuerdo con el Método A1 antes mencionado o un método análogo.

El compuesto (I-2d), que es el compuesto (I-2a) (compuesto (I) en donde W es $-CONR^{1a}S(O)_mNR^{1c}R^2$ en donde m es 2 y los otros símbolos son como se definieron con anterioridad) en donde $NR^{1c}R^2$ es grupo (3-hidroxi-3-metilbutil)amino, se produce, por ejemplo, de acuerdo con el siguiente Método AK.

[Método AK]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-2d) se puede producir al someter el compuesto (I-2c) a una reacción de dimetilación. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

Como el agente de metilación, se pueden mencionar cloruro de metilmagnesio, bromuro de metilmagnesio, metil-litio y similares.

La cantidad del agente de metilación por usar es, en general, 2 - 20 moles, con preferencia, de 2 a 10 moles, por 1 mol del compuesto (I-2c).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares,

y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

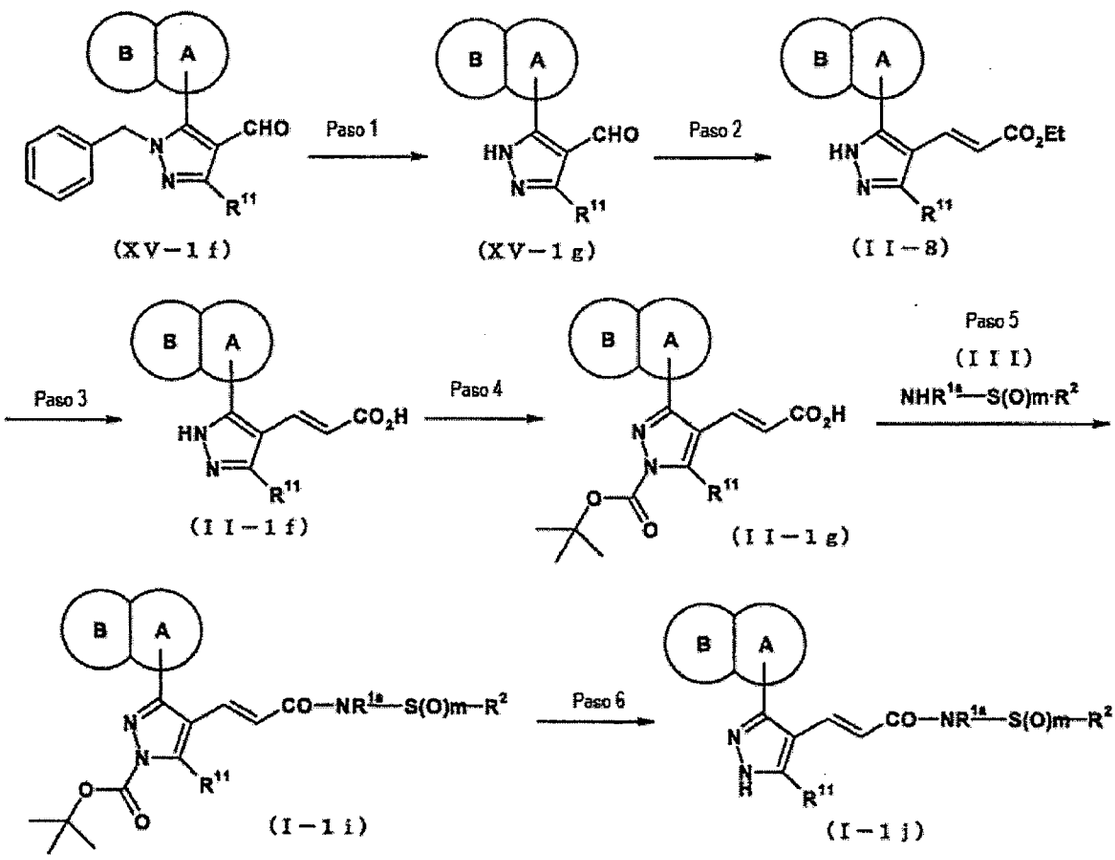
La temperatura de reacción es, en general, de -80 a 100°C, con preferencia, de -10 a 60°C.

El tiempo de reacción es, en general, de 0.1 a 30 h.

El compuesto (I-2c) se puede producir, por ejemplo, de acuerdo con el Método B antes mencionado o un método análogo.

El compuesto (I-1i), que es el compuesto (I-1) (compuesto (I) en donde W es $-CONR^{1a}S(O)_mR^2$ en donde cada símbolo es como se definió con anterioridad) en donde X es -CH=CH- y el anillo D es pirazol (unido con el anillo A en la posición 3 y unido con X en la posición 4) que tiene grupo ter-butoxicarbonilo en la posición 1, y el compuesto (I-1j), que es el compuesto (I-1) en donde X es -CH=CH- y el anillo D es pirazol (unido con el anillo A en la posición 3 y unido con X en la posición 4) que no tiene sustituyentes en las posiciones 1 y 2, se producen, por ejemplo, de acuerdo con el siguiente Método AL.

[Método AL]



en donde R^{11} es un grupo alquilo de C_{1-6} opcionalmente sustituido o un grupo cicloalquilo de C_{1-6}, y los otros símbolos son como se definieron con anterioridad."

Como los sustituyentes del "grupo alquilo de C_{1-6} opcionalmente sustituido" para R^{11}, se pueden mencionar 1 a 3 átomos de halógeno (con preferencia, un átomo de flúor) y un grupo alcoxi de C_{1-6}.

[Paso 1]

En este paso, el compuesto (XV-1g) se puede producir al someter el compuesto (XV-1f) a una reacción de

desbencilación. Esta reacción se lleva a cabo en ácido trifluoroacético a 0°C a 80°C durante 1 a 200 h.

La cantidad del ácido trifluoroacético por usar es, en general, de 5 a 1000 moles, por 1 mol del compuesto (XV-1f).

El compuesto (XV-1f) se puede producir, por ejemplo, de acuerdo con el Método Z1, Método Z2 antes mencionados, Método AO, Método AQ mencionados más abajo o un método análogo.

[Paso 2]

En este paso, el compuesto (II-8) se puede producir haciendo reaccionar el compuesto (XV-1g) con (trifenilfosforaniliden)acetato de etilo. Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

La cantidad del (trifenilfosforaniliden)acetato de etilo por usar es, en general, de 1 a 20 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XV-1g).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1,2-dimetoxietano y similares; hidrocarburos

halogenados tales como cloroformo, diclorometano y similares, acetonitrilo y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -10 a 150°C, con preferencia, de 10 a 120°C.

El tiempo de reacción es, en general, de 0.5 a 50 h.

[Paso 3]

En este paso, el compuesto (II-1f) se puede producir al someter el compuesto (II-8) a hidrólisis. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método T1 antes mencionado.

[Paso 4]

En este paso, el compuesto (II-1g) se puede producir haciendo reaccionar el compuesto (II-1f) con dicarbonato de di-ter-butilo. Esta reacción se lleva a cabo en presencia de una base, en un solvente que no afecte adversamente la reacción.

La cantidad del dicarbonato de di-ter-butilo por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (II-1f).

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares; aminas tales como

piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares.

La cantidad de la base por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (II-1f).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; acetonitrilo, acetato de etilo, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de 0 a 150°C, con preferencia, de 10 a 80°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

[Paso 5]

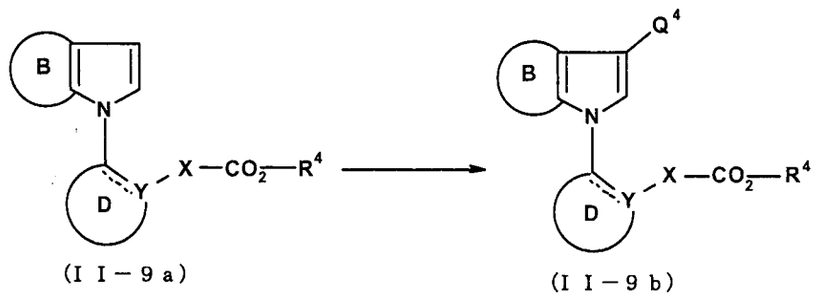
En este paso, el compuesto (I-1i) se puede producir haciendo reaccionar el compuesto (II-1g) con el compuesto (III). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método A1 antes mencionado.

[Paso 6]

En este paso, el compuesto (I-1j) se puede producir al someter el compuesto (I-1i) a desprotección. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 3 del Método S1 antes mencionado.

El compuesto (II-9b), que es el compuesto (II-2) en donde el anillo A es pirrol unido con el anillo D en la posición 1 y que tiene un átomo de halógeno en la posición 3, se produce, por ejemplo, de acuerdo con el siguiente Método AM.

[Método AM]



en donde cada símbolo es como se definió con anterioridad.

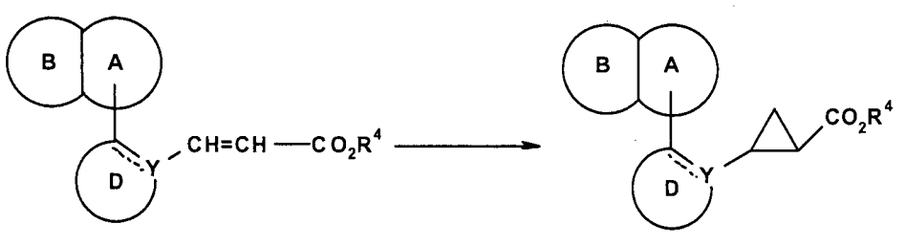
En este método, el compuesto (II-9b) se puede producir haciendo reaccionar el compuesto (II-9a) con un

agente de halogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el Método AF antes mencionado.

El compuesto (II-9a) se puede producir, por ejemplo, de acuerdo con la Paso 1 o Paso 2 del Método T2 antes mencionado, el Método AN, Método AP mencionados más abajo o un método análogo.

El compuesto (II-10b), que es el compuesto (II-2) en donde X es anillo ciclopropano, se produce, por ejemplo, de acuerdo con el siguiente Método AN.

[Método AN]



(II-10a) (II-10b)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (II-10b) se puede producir al someter el compuesto (II-10a) a una reacción de ciclopropanación usando una base o un catalizador metálico orgánico.

La reacción de ciclopropanación usando una base se lleva a cabo usando un agente de ciclopropanación, en presencia de una base, en un solvente que no afecte

adversamente la reacción.

Como el agente de ciclopropanación, se pueden mencionar yoduro de trimetilsulfoxonio, bromuro de metiltrifenilfosfonio, nitrometano y similares.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio, carbonato de potasio y similares; aminas tales como piridina, trietilamina, tributilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares; metales orgánicos tales como metil-litio, butil-litio y similares; fluoruros de metal alcalino tales como fluoruro de cesio, fluoruro de potasio y similares, y otros.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, 1.2-dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida,

N-metilpirrolidona y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; nitrilos tales como acetonitrilo, propionitrilo y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -70 a 150°C, con preferencia, de -20 a 80°C.

El tiempo de reacción es en general 1 a 100 h, con preferencia, 1 a 60 h.

La cantidad del agente de ciclopropanación por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II-10a).

La cantidad de la base por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II-10a).

La reacción de ciclopropanación usando un catalizador metálico orgánico se lleva a cabo usando un diazoalcano en un solvente que no afecte adversamente la reacción, en presencia de un ligando, de ser necesario.

Como el catalizador metálico orgánico, se pueden mencionar, por ejemplo, acetato de paladio (II), triflato de cobre (I), dímero de acetato de rodio (II) y similares.

Como el diazoalcano, se pueden mencionar diazometano y similares.

Como el ligando, se pueden mencionar 2.2'-

diisopropilidenbis[(4S)-4-ter-butil-2-oxazolina] y similares.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; hidrocarburos halogenados tales como diclorometano, cloroformo, 1.2-dicloroetano, 1,1,2,2-tetracloroetano y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -70 a 150°C, con preferencia, de -20 a 80°C.

El tiempo de reacción es, en general, de 0.1 a 100 h, con preferencia, 0.1 a 40 h.

La cantidad del catalizador metálico orgánico por usar es, en general, de 0.01 a 2 moles, con preferencia, 0.01 a 0.5 moles, por 1 mol del compuesto (II-10a).

La cantidad del diazoalcano por usar es, en general, de 1 a 50 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (II-10a).

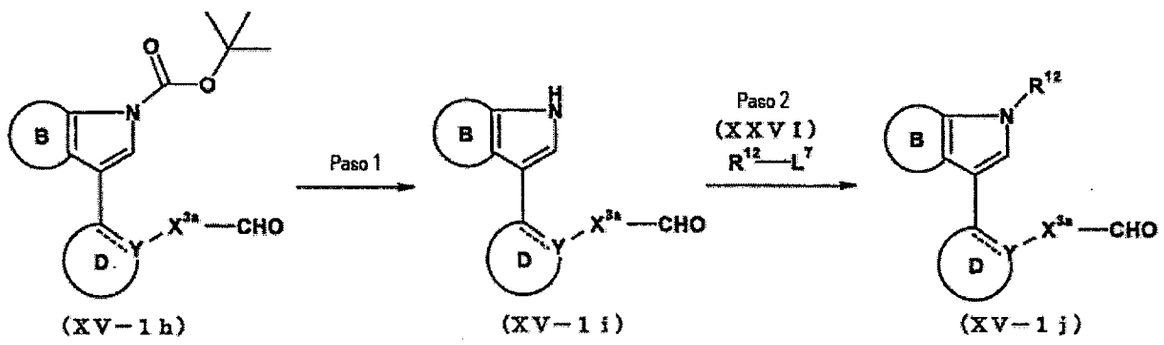
La cantidad del ligando por usar es, en general, de 0.01 a 2 moles, con preferencia, de 0.01 a 0.5 moles, por 1 mol del compuesto (II-10a).

El compuesto (II-10a) se puede producir, por ejemplo, de acuerdo con la Paso 1 del Método T2 antes

mencionado o un método análogo.

El compuesto (XV-1j), que es el compuesto (XV) en donde el anillo A es un pirrol N-sustituido unido con el anillo D en la posición 3, se produce, por ejemplo, de acuerdo con el siguiente Método AO.

[Método AO]



(XV-1h) (XV-1i) (XV-1j)

en donde R^{12} es un grupo alquilo de C_{1-6}, L^7 es un grupo saliente, y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^7, se pueden mencionar aquellos ejemplificados para los L^1 o L^2 antes mencionados.

[Paso 1]

En este paso, el compuesto (XV-1i) se puede producir al someter el compuesto (XV-1h) a desprotección. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 3 del Método S1 antes mencionado.

El compuesto (XV-1h) se puede producir, por ejemplo, de acuerdo con el Método Z2 antes mencionado o un

método análogo.

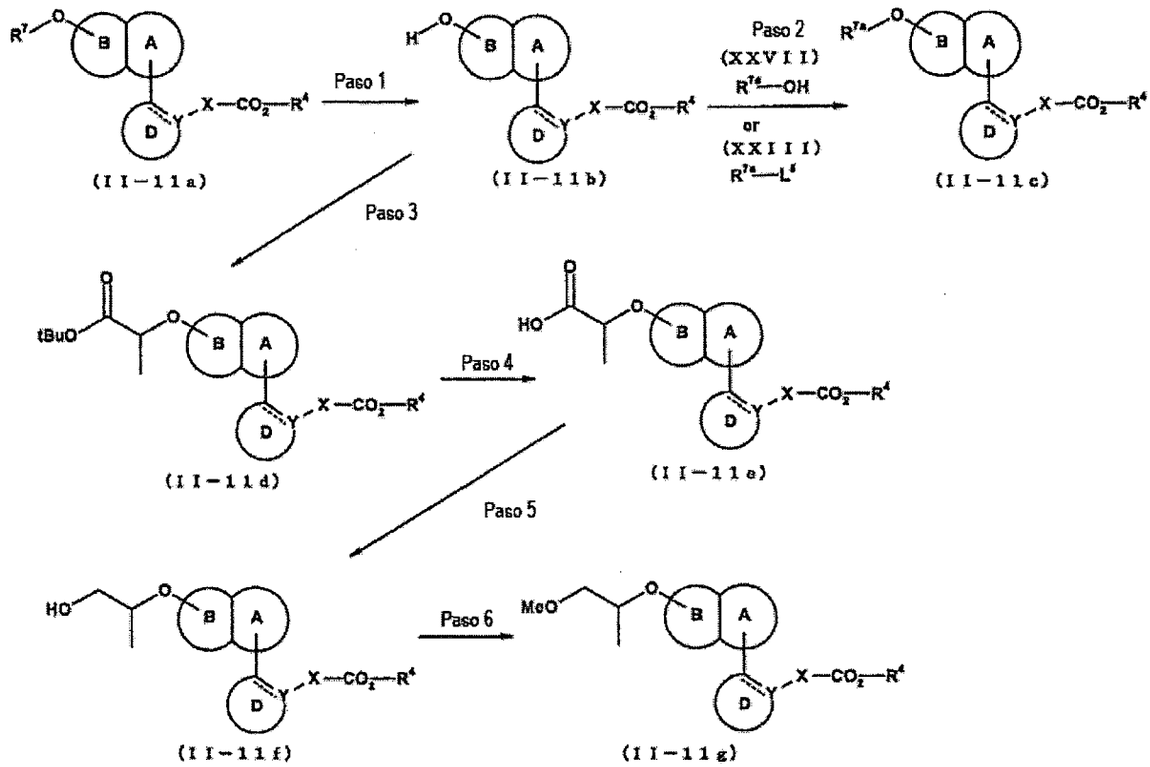
[Paso 2]

En este paso, el compuesto (XV-1j) se puede producir haciendo reaccionar el compuesto (XV-1i) con el compuesto (XXVI). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método AG antes mencionado.

El compuesto (XXVI) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (II-11c), que es el compuesto (II-2) que tiene un grupo alcoxi de C_{1-6} opcionalmente sustituido en el anillo B, y el compuesto (II-11g), que es el compuesto (II-2) que tiene grupo 2-metoxi-1-metiletoxi en el anillo B, se producen, por ejemplo, de acuerdo con el siguiente Método AP.

[Método AP]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

En este paso, el compuesto (II-11b) se puede producir a partir del compuesto (II-11a). Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 1 del Método AG antes mencionado.

El compuesto (II-11a) se puede producir, por ejemplo, de acuerdo con la Paso 1 o Paso 2 del Método T2, Método AM, Método AN antes mencionados o un método análogo.

[Paso 2]

En este paso, el compuesto (II-11c) se puede producir haciendo reaccionar el compuesto (II-11b) con el compuesto (XXVII) o compuesto (XXIII).

La reacción del compuesto (II-11b) con el compuesto (XXVII) se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método I antes mencionado.

La reacción del compuesto (II-11b) con el compuesto (XXIII) se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método AG antes mencionado.

El compuesto (XXVII) se puede producir de acuerdo con un método conocido *per se*.

[Paso 3]

En este paso, el compuesto (II-11d) se puede producir haciendo reaccionar el compuesto (II-11b) con 2-bromopropionato de ter-butilo. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método AG antes mencionado.

[Paso 4]

En este paso, el compuesto (II-11e) se puede producir al someter el compuesto (II-11d) a hidrólisis. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método T1.

[Paso 5]

En este paso, el compuesto (II-11f) se puede

producir a partir del compuesto (II-11e). Esta reacción se lleva a cabo por ejemplo, sometiendo el compuesto (II-11e) a halogenación de -10°C a 100°C durante 0.5 a 30 h, y sometiendo el compuesto obtenido a una reacción de reducción de -10°C a 100°C durante 0.1 a 50 h.

La halogenación se lleva a cabo de la misma manera que en la reacción descrita en el anterior Paso 5 del Método N o la halogenación en el Método A1 antes mencionado.

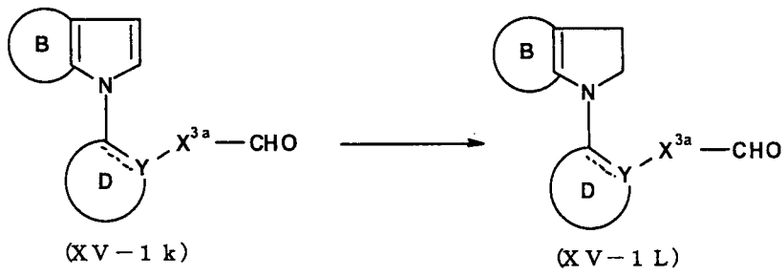
La reacción de reducción del compuesto obtenido por la halogenación se lleva a cabo de la misma manera que en la reacción descrita en la Paso 4 del Método N antes mencionado.

[Paso 6]

En este paso, el compuesto (II-11g) se puede producir haciendo reaccionar el compuesto (II-11f) con yoduro de metilo. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método AG antes mencionado.

El compuesto (XV-1L), que es el compuesto (XV) en donde el anillo A es 2,3-dihidropirrol unido con el anillo D en la posición 1, se produce, por ejemplo, de acuerdo con el siguiente Método AQ.

[Método AQ]



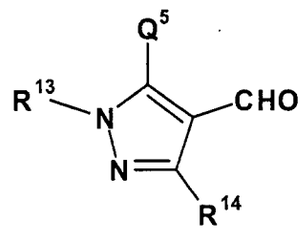
(XV-1k) (XV-1L)

en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (XV-1L) se puede producir al someter el compuesto (XV-1k) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (XV-1k) se puede producir, por ejemplo, de acuerdo con la Paso 2 del Método T4 antes mencionado, el Método Z1, Método Z3 antes mencionados o un método análogo.

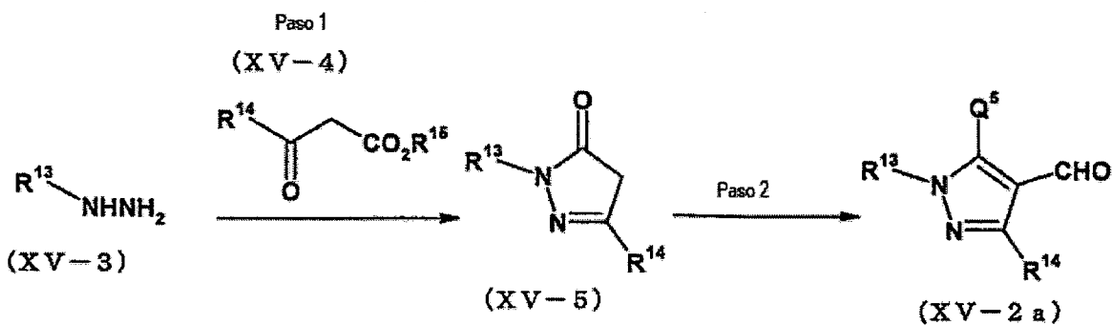
Del compuesto (XV-2), el compuesto (XV-2a) representado por la fórmula:



en donde R^{13} es grupo alquilo de C_{1-6} opcionalmente sustituido con grupos arilo de C_{6-14}, R^{14} es un grupo alquilo

de C_{1-6} opcionalmente sustituido con 1 a 3 sustituyentes seleccionados de (a) un átomo de halógeno y (b) un grupo alcoxi de C_{1-6}, o un grupo cicloalquilo de C_{3-10}, Q^5 es un átomo de cloro, un átomo de bromo o un átomo de yodo, y los otros símbolos son como se definieron con anterioridad, se puede producir, por ejemplo, de acuerdo con el siguiente Método AR.

[Método AR]



en donde R^{15} es un grupo alquilo de C_{1-10}, un grupo bencilo opcionalmente sustituido con grupos alquilo de C_{1-6}, o un grupo arilo de C_{6-14} opcionalmente sustituido con grupos alquilo de C_{1-6}, y los otros símbolos son como se definieron con anterioridad.

R^{15} es preferentemente metilo, etilo, ter-butilo, bencilo, fenilo o similares.

[Paso 1]

En este paso, el compuesto (XV-5) se puede producir haciendo reaccionar el compuesto (XV-3) con el compuesto (XV-4). Esta reacción se lleva a cabo en un solvente que no afecte adversamente la reacción.

La cantidad del compuesto (XV-3) por usar es, en general, de 0.1 a 10 moles, con preferencia, de 0.5 a 5 moles, por 1 mol del compuesto (XV-4).

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, éteres tales como éter dietílico, tetrahidrofurano, dioxano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; amidas tales como N,N-dimetilformamida y similares; sulfóxidos tales como sulfóxido de dimetilo y similares; cetonas tales como acetona, 2-butanone y similares; agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -80 a 200°C, con preferencia, de 0 a 150°C.

El tiempo de reacción es, en general, de 0.5 a 100 h.

El compuesto (XV-3) y el compuesto (XV-4) se pueden producir de acuerdo con un método conocido *per se*.

[Paso 2]

En este paso, el compuesto (XV-2a) se puede producir haciendo reaccionar el compuesto (XV-5) con N,N-dimetilformamida y a compuesto de oxihaluro de fósforo. Esta reacción se lleva a cabo sin un solvente o en un solvente que

no afecte adversamente la reacción.

La cantidad del N,N-dimetilformamida por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (XV-5).

Como el compuesto de oxihaluro de fósforo, se pueden mencionar, por ejemplo, oxicloruro de fósforo, oxibromuro de fósforo y similares.

La cantidad del compuesto de oxihaluro de fósforo por usar es, en general, de 1 a 20 moles, por 1 mol del compuesto (XV-5).

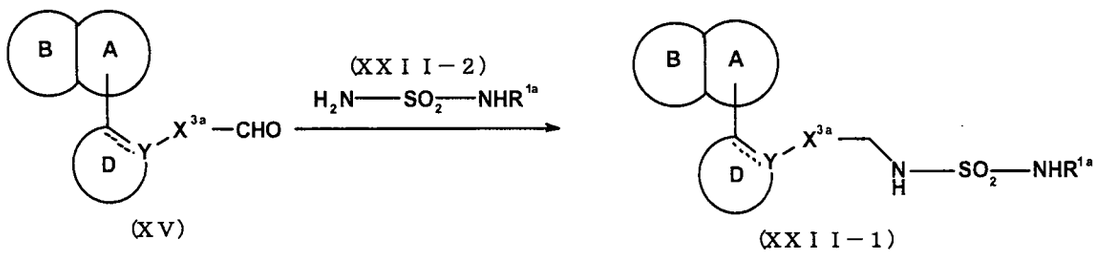
Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como nitrobenceno y similares; amidas tales como N,N-dimetilformamida y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La temperatura de reacción es, en general, de -80 a 200°C, con preferencia, de 0 a 150°C.

El tiempo de reacción es, en general, de 0.5 a 30 h.

El compuesto (XXII-1), que es el compuesto (XXII) en donde X es $-X^{3a}-CH_2-$ en donde X^{3a} es como se definió con anterioridad, y R^{1b} es un átomo de hidrógeno, se produce, por ejemplo, de acuerdo con el siguiente Método AS.

[Método AS]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (XXII-1) se puede producir al someter el compuesto (XV) a una reacción de aminación reductiva con el compuesto (XXII-2). Esta reacción se lleva a cabo sometiendo el compuesto (XV) a una reacción de iminación con el compuesto (XXII-2) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.1 a 30 h, y sometiendo el compuesto obtenido a una reacción de reducción de -10°C a 100°C durante 0.1 a 50 h.

La reacción de iminación se puede llevar a cabo en presencia de un ácido o una base.

La cantidad del compuesto (XXII-2) por usar es, en general, de 1 a 10 moles, por 1 mol del compuesto (XV).

Como el ácido, se pueden mencionar, por ejemplo, ácidos minerales tales como ácido clorhídrico, ácido sulfúrico y similares; ácidos de Lewis tales como tricloruro de boro, tribromuro de boro y similares; ácidos orgánicos tales como ácido acético, ácido trifluoroacético, ácido p-

toluensulfónico y similares, y otros.

Como la base, se pueden mencionar, por ejemplo, sales de metal alcalino tales como hidróxido de potasio, hidróxido de sodio, carbonato de sodio ácido, carbonato de potasio y similares; aminas tales como piridina, trietilamina, N,N-diisopropiletilamina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piperidina y similares; hidruros de metal tales como hidruro de potasio, hidruro de sodio y similares; alcóxidos C_{1-6} de metal alcalino tales como metóxido de sodio, etóxido de sodio, ter-butóxido de potasio y similares, y otros.

La cantidad del ácido o base por usar es, en general, de 0.1 a 50 moles, con preferencia, de 0.5 a 20 moles, por 1 mol del compuesto (XV), respectivamente.

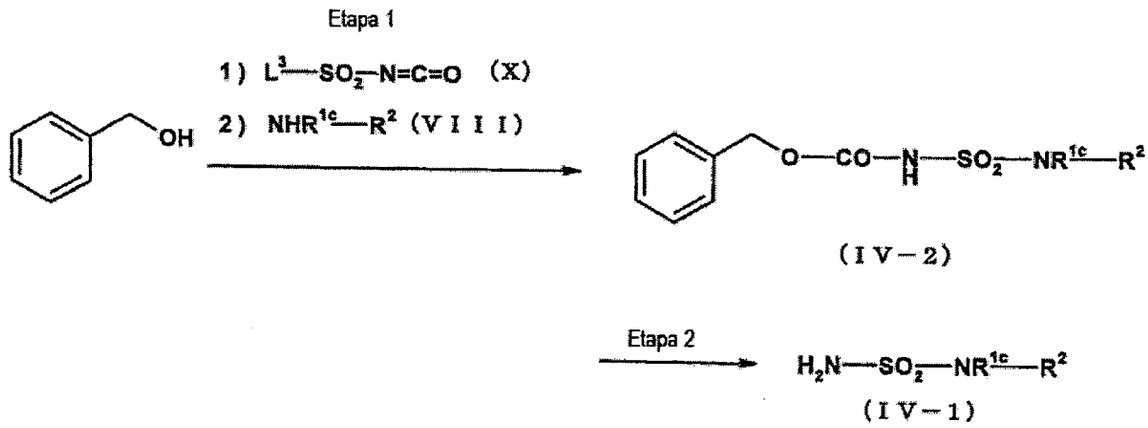
Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, alcoholes tales como metanol, etanol y similares; hidrocarburos aromáticos tales como benceno, tolueno, xileno y similares; hidrocarburos alifáticos tales como hexano, heptano y similares; éteres tales como éter dietílico, éter diisopropílico, éter ter-butilmetílico, tetrahidrofurano, dioxano, dimetoxietano y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares, y otros. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La reacción de reducción del compuesto obtenido por la reacción de iminación se lleva a cabo de la misma manera que en la reacción descrita en la Paso 4 del Método N antes mencionado.

El compuesto (XXII-2) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (IV-1), que es el compuesto (IV) en donde R^{1a} es un átomo de hidrógeno, se produce, por ejemplo, de acuerdo con el siguiente Método AT.

[Método AT]



en donde cada símbolo es como se definió con anterioridad.

[Paso 1]

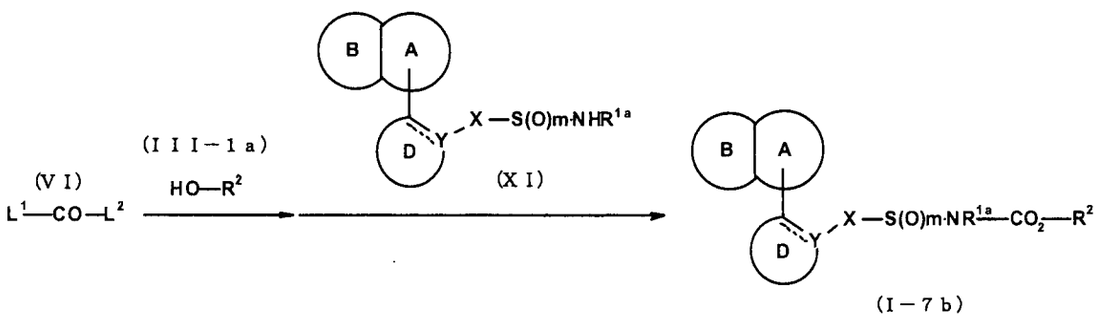
En este paso, el compuesto (IV-2) se puede producir haciendo reaccionar alcohol bencílico con el compuesto (X) y el compuesto (VIII) de manera sucesiva. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 1 del Método I antes mencionado.

[Paso 2]

En este paso, el compuesto (IV-1) se puede producir al someter el compuesto (IV-2) a una reacción de hidrogenación. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en la Paso 2 del Método M antes mencionado.

El compuesto (I-7b), que es el compuesto (I) en donde W es $-S(O)_mNR^{1a}CO_nR^2$ en donde n es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AU.

[Método AU]



en donde cada símbolo es como se definió con anterioridad.

En este método, el compuesto (I-7b) se puede producir a partir del compuesto (XI). Esta reacción se lleva a cabo de acuerdo con un método conocido *per se*, por ejemplo, haciendo reaccionar el compuesto (VI) con el compuesto (III-1a) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 10 h, y haciendo reaccionar el

compuesto obtenido con el compuesto (XI) en un solvente que no afecte adversamente la reacción, de -10°C a 100°C durante 0.5 a 50 h. Esta reacción se puede llevar a cabo en presencia de 1 a 20 mol de una base, por 1 mol del compuesto (XI), de ser necesario.

Como la base, se pueden mencionar, por ejemplo, aminas tales como trietilamina, N,N-diisopropiletilamina, N-metilmorfolina, N,N-dimetilanilina, 1,8-diazabiciclo[5.4.0]undec-7-eno, piridina, 4-dimetilaminopiridina y similares; sales de metal alcalino tales como carbonato de sodio ácido, carbonato de sodio, carbonato de potasio y similares, y otros. Estas bases se pueden usar en una mezcla en una proporción apropiada.

Como el solvente que no afecte adversamente la reacción, se pueden mencionar, por ejemplo, amidas tales como N,N-dimetilformamida, N,N-dimetilacetamida y similares; hidrocarburos halogenados tales como cloroformo, diclorometano y similares; hidrocarburos aromáticos tales como benceno, tolueno y similares; éteres tales como tetrahidrofurano, dioxano, éter dietílico y similares; acetonitrilo, acetato de etilo, piridina, agua y similares. Estos solventes se pueden usar en una mezcla en una proporción apropiada.

La cantidad del compuesto (VI) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles,

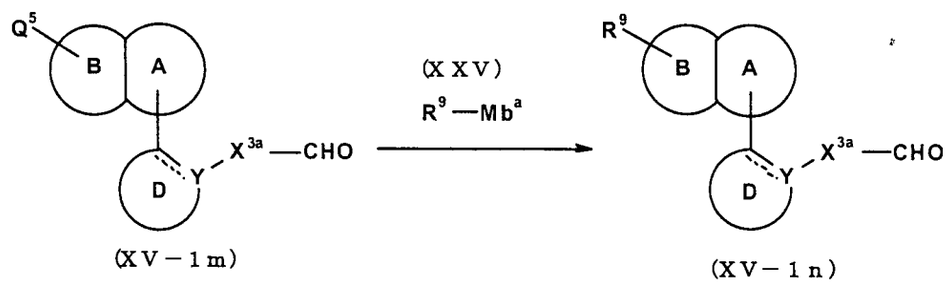
por 1 mol del compuesto (XI).

La cantidad del compuesto (III-1a) por usar es, en general, de 1 a 10 moles, con preferencia, de 1 a 5 moles, por 1 mol del compuesto (XI).

El compuesto (III-1a) se puede producir de acuerdo con un método conocido *per se*.

El compuesto (XV-1n), que es el compuesto (XV) que tiene un grupo arilo de C_{6-14}, un grupo heterocíclico aromático o un grupo cicloalquilo de C_{3-10} en el anillo B, se produce, por ejemplo, de acuerdo con el siguiente Método AV.

[Método AV]



en donde cada símbolo es como se definió con anterioridad.

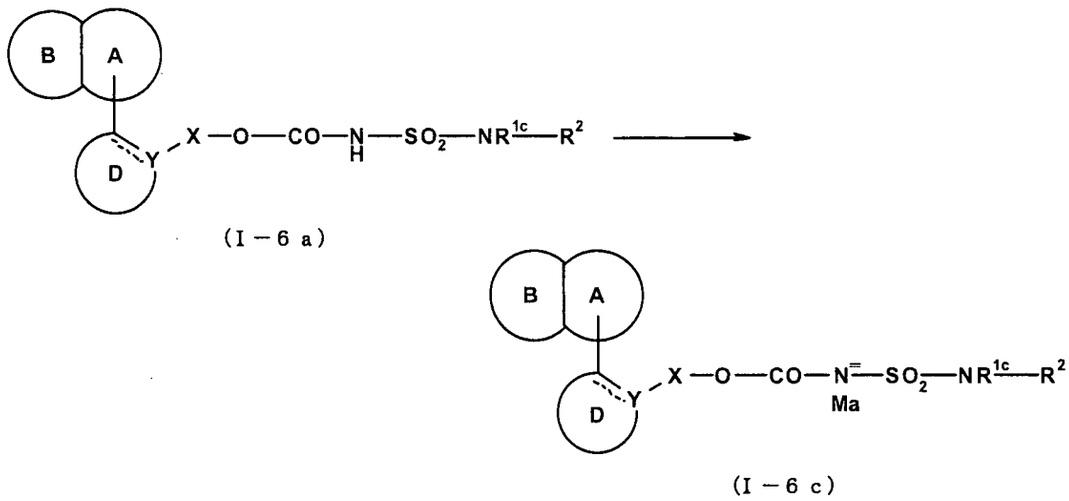
En este método, el compuesto (XV-1n) se puede producir al someter el compuesto (XV-1m) y el compuesto (XXV) a una reacción de acoplamiento usando un catalizador metálico orgánico. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método Z2.

El compuesto (XV-1m) se puede producir, por ejemplo, de acuerdo con el Método Z1 a Método Z3 antes

mencionados o un método análogo.

La sal de metal alcalino (I-6c) de compuesto (I-6a), que es el compuesto (I) en donde W es $-OCONR^{1a}S(O)_mNR^{1c}R^2$ en donde R^{1a} es un átomo de hidrógeno, m es 2 y los otros símbolos son como se definieron con anterioridad, se produce, por ejemplo, de acuerdo con el siguiente Método AW.

[Método AW]



en donde cada símbolo es como se definió con anterioridad.

Como el metal alcalino para Ma, se pueden mencionar sodio, potasio y similares.

En este método, el compuesto (I-6c) se puede producir haciendo reaccionar el compuesto (I-6a) con una base. Esta reacción se lleva a cabo de la misma manera que en la reacción descrita en el anterior Método A2.

El compuesto (I-6a) se puede producir, por ejemplo,

de acuerdo con el Método I antes mencionado o un método análogo.

En cada una de las reacciones antes mencionadas, cuando el compuesto de material de partida tiene un grupo amino, un grupo carboxilo, un grupo hidroxi o un grupo carbonilo como sustituyente, se pueden introducir un grupo protector usado en general en la química de los péptidos y similares en estos grupos, y el compuesto objeto se puede obtener por eliminación del grupo protector de ser necesario después de la reacción.

Los ejemplos del grupo protector de amino incluyen un grupo formilo; un grupo alquil de C_{1-6}-carbonilo, un grupo alcoxi de C_{1-6}-carbonilo, un grupo benzoílo, un grupo aralquil de C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo), un grupo aralquil de C_{7-13}-oxi-carbonilo (por ejemplo, benciloxicarbonilo, 9-fluorenilmetoxicarbonilo), un grupo tritilo, un grupo ftaloílo, un grupo N,N-dimetilaminometileno, un grupo sililo trisustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo de C_{2-6} (por ejemplo, 1-alilo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo alcoxi de C_{1-6}, un grupo nitro y similares.

Los ejemplos del grupo protector de carboxilo incluyen un grupo alquilo de C_{1-6}, un grupo aralquilo de C_{7-20} (por ejemplo, bencilo), un grupo fenilo, un grupo tritilo, un grupo sililo trisustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo de C_{2-6} (por ejemplo, 1-alilo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo alcoxi de C_{1-6}, un grupo nitro y similares.

Los ejemplos del grupo protector de hidroxi incluyen un grupo alquilo de C_{1-6}, un grupo fenilo, un grupo tritilo, un grupo aralquilo de C_{7-13} (por ejemplo, bencilo), un grupo formilo, un grupo alquil de C_{1-6}-carbonilo, un grupo benzoílo, un grupo aralquil de C_{7-13}-carbonilo (por ejemplo, bencilcarbonilo), un grupo 2-tetrahidropiranilo, un grupo 2-tetrahidrofuranilo, un grupo sililo trisustituido (por ejemplo, trimetilsililo, trietilsililo, dimetilfenilsililo, ter-butildimetilsililo, ter-butildietilsililo), un grupo alquenilo de C_{2-6} (por ejemplo, 1-alilo) y similares. Estos grupos están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, un grupo alquilo de C_{1-6}, un grupo alcoxi de C_{1-6}, un grupo nitro y similares.

Los ejemplos del grupo protector del carbonilo

incluyen un acetal cíclico (por ejemplo, 1,3-dioxano), un acetal no cíclico (por ejemplo, un di-alquil de C_{1-6}-acetal) y similares.

Para eliminar el grupo protector antes mencionado, se puede mencionar un método conocido *per se*, por ejemplo, un método descrito en Protective Groups in Organic Synthesis, John Wiley and Sons (1980) y similares. Por ejemplo, se emplea un método que usa ácido, base, luz UV, hidracina, fenilhidracina, N-metilditiocarbamato de sodio, fluoruro de tetrabutilamonio, acetato de paladio, haluro de trialquilsililo (por ejemplo, yoduro de trimetilsililo, bromuro de trimetilsililo y similares) y similares, reducción y similares.

El compuesto de la presente invención obtenido por medio de cada método de producción mencionado con anterioridad se puede aislar y purificar por un medio conocido, tales como concentración, concentración a presión reducida, extracción del solvente, cristalización, recristalización, transferencia de fase, cromatografía y similares. Cada compuesto de material de partida usado en cada uno de los métodos de producción antes mencionados se puede aislar y purificar por un medio conocido similar a los mencionados anteriormente. También se posible usar el compuesto de material de partida como tal en una mezcla de reacción sin aislamiento, como un material de partida para el

siguiente paso.

Cuando el compuesto (I) contiene un isómero óptico, un estereoisómero, un isómero de posición o un isómero rotacional, también están incluidos en el compuesto (I) y se pueden obtener como productos individuales por medio de técnicas de síntesis y técnicas de separación conocidas *per se*. Por ejemplo, cuando el compuesto (I) contiene un isómero óptico, también está comprendido en el compuesto (I) un isómero óptico separado del compuesto.

La presente invención se explica con detalle a continuación haciendo referencia al Ejemplo experimental, Ejemplos de referencia, Ejemplos y Ejemplos de formulación que no se construyeron para ser limitativos.

Ejemplos

En los siguientes Ejemplos de referencia y Ejemplos, "%" significa % en peso salvo que se especifique otra cosa, y "temperatura ambiente" significa una temperatura de 1°C a 30°C salvo que se especifique otra cosa.

Ejemplo de referencia 1

5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una solución de 1H-indol (719 mg) en N,N-dimetilformamida (10 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 275 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Se

añadió 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (900 mg) a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 60°C durante 5 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 80:20, v/v) para dar el compuesto del título (1.10 g, rendimiento del 81%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.81 (d, J = 3.0 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 7.19 (d, J = 3.4 Hz, 1 H), 7.20 - 7.31 (m, 2 H), 7.70 - 7.73 (m, 1 H), 9.52 (s, 1 H).

Ejemplo de referencia 2

ácido (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

A una solución de 5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 1 (1.09 g) en ácido acético (10 ml) se añadieron ácido malónico (573 mg) y pirrolidina (495 mg), y la mezcla se agitó con calentamiento a 100°C durante 5 h. Se añadieron ácido malónico (239 mg) y pirrolidina (648 mg) nuevamente a la mezcla de reacción, y la mezcla se agitó con calentamiento a 100°C durante 15 h. Después de dejar enfriar la mezcla de

reacción hasta temperatura ambiente, se añadieron ácido clorhídrico 1 N (1 ml) y agua (20 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Los cristales resultantes se recogieron por filtración, y se disolvieron en acetato de etilo. La solución obtenida se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.11 g, rendimiento del 87%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.38 (s, 3 H), 3.47 (s, 3 H), 5.40 (d, J = 16.2 Hz, 1 H), 6.86 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 7.11 (m, 2 H), 7.15 - 7.27 (m, 2 H), 7.57 (d, J = 3.3 Hz, 1 H), 7.71 - 7.77 (m, 1 H), 12.13 (s, 1 H).

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvieron 5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído del Ejemplo de referencia 3, que es un compuesto menos polar, y 5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-carbaldehído del Ejemplo de referencia 4, que es un compuesto más polar a partir de 1H-indazol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

Ejemplo de referencia 3

5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

^{1}H-NMR (300 MHz, $CDCl_3$) (: 2.58 (s, 3 H), 3.70 (s, 3 H), 7.28 - 7.38 (m, 2 H), 7.47 - 7.55 (m, 1 H), 7.84 - 7.87

(m, 1 H), 8.35 (d, J = 0.9 Hz, 1 H), 9.58 (s, 1 H).

Ejemplo de referencia 4

5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.86 (s, 3 H), 7.17 - 7.22 (m, 1 H), 7.39 - 7.44 (m, 1 H), 7.73 - 7.79 (m, 2 H), 8.35 (d, J = 0.9 Hz, 1 H), 9.74 (s, 1 H).

Ejemplo de referencia 5

ácido (2E)-3-[5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 3 y ácido malónico.

1H-NMR (300 MHz, DMSO-d_6): 2.40 (s, 3 H), 3.51 (s, 3 H), 5.46 (d, J = 16.2 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.27 - 7.37 (m, 2 H), 7.49 - 7.55 (m, 1 H), 7.96 - 7.99 (m, 1 H), 8.60 (d, J = 1.1 Hz, 1 H), 12.16 (s, 1 H).

Ejemplo de referencia 6

ácido (2E)-3-[5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 4 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.39 (s, 3 H), 3.60 (s, 3 H), 5.67 (d, J = 16.2 Hz, 1 H), 7.16 (d, J = 16.2 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.37 - 7.44 (m, 1 H), 7.77 (dd, J = 8.9, 0.9 Hz, 1 H), 7.84 - 7.86 (m, 1 H), 8.85 (d, J = 0.9 Hz, 1 H), 12.26 (s, 1 H).

Ejemplo de referencia 7

5-(1H-bencimidazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H- bencimidazol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3 H), 3.64 (s, 3 H), 7.19 - 7.21 (m, 1 H), 7.33 - 7.45 (m, 2 H), 7.92 - 7.96 (m, 1 H), 8.03 (s, 1 H), 9.60 (s, 1 H).

Ejemplo de referencia 8

ácido (2E)-3-[5-(1H-bencimidazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(1H-bencimidazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 7 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.40 (s, 3 H), 3.54 (s, 3 H), 5.49 (d, J = 16.3 Hz, 1 H), 7.04 (d, J = 16.3 Hz, 1 H),

7.22 - 7.28 (m, 1 H), 7.32 - 7.45 (m, 2 H), 7.84 - 7.88 (m, 1 H), 8.55 (s, 1 H), 12.20 (s, 1 H).

Ejemplo de referencia 9

5-(1-benzotien-3-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una mezcla de ácido 1-benzotien-3-ilborónico (1.61 g), 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (1.20 g), una solución acuosa 2.0 M de carbonato de sodio (8.0 ml) y 1.2-dimetoxietano (25 ml) se añadió tetraquis(trifenilfosfina)paladio (0) (0.44 g), y la mezcla de reacción se calentó a reflujo durante 6 h bajo una atmósfera de nitrógeno. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30 - 50:50, v/v) para dar el compuesto del título (0.83 g, rendimiento del 42%) en forma de un aceite marrón.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3 H), 3.68 (s, 3 H), 7.38 - 7.51 (m, 3 H), 7.62 (s, 1 H), 7.97 (dd, J = 6.4, 3.0 Hz, 1 H), 9.57 (s, 1 H).

Ejemplo de referencia 10

ácido (2E)-3-[5-(1-benzotien-3-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(1-benzotien-3-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 9 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.39 (s, 3 H), 3.58 (s, 3 H), 5.75 (d, J = 16.3 Hz, 1 H), 7.17 (d, J = 16.3 Hz, 1 H), 7.36 - 7.51 (m, 3 H), 8.11 (s, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 12.00 (s, 1 H).

Ejemplo de referencia 11

1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

A una solución de 1H-pirrolo[2,3-b]piridina (5.60 g) en N,N-dimetilformamida (100 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 2.00 g) con agitación, y la mezcla se agitó a 0°C durante 1 h. Se agregó 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (5.00 g) a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 60(C durante 7 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El

filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v) para dar el compuesto del título (4.02 g, rendimiento del 53%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.68 (s, 3 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.9, 4.7 Hz, 1 H), 7.32 (d, J = 3.6 Hz, 1 H), 8.03 (dd, J = 7.9, 1.6 Hz, 1 H), 8.36 (dd, J = 4.7, 1.6 Hz, 1 H), 9.58 (s, 1 H).

Ejemplo de referencia 12

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

A una solución de (dietoxifosforil)acetato de etilo (845 mg) en tetrahidrofurano (15 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 163 mg) con agitación, y la mezcla se agitó a 0°C durante 15 min. Una solución de 1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 11 (780 mg) en tetrahidrofurano (8 ml) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 0°C durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 65:35, v/v) para

dar el compuesto del título (929 mg, rendimiento del 92%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.1 Hz, 3 H), 2.45 (s, 3 H), 3.58 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.70 (d, J = 16.3 Hz, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.30 (d, J = 16.3 Hz, 1 H), 8.03 (dd, J = 7.9, 1.5 Hz, 1 H), 8.35 (dd, J = 4.9, 1.5 Hz, 1 H).

Ejemplo de referencia 13

ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

A una solución de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 12 (925 mg) en un solvente mixto de tetrahidrofurano (6 ml) y etanol (6 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (6 ml), y la mezcla se agitó con calentamiento a 60°C durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se neutralizó con una solución acuosa (30 ml) de sulfato de potasio ácido (820 mg), y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (763 mg, rendimiento del 90%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3 H), 3.49 (s,

3 H), 5.48 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.2 Hz, 1 H), 7.27 (dd, J = 8.0, 4.9 Hz, 1 H), 7.70 (d, J = 3.6 Hz, 1 H), 8.16 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 (dd, J = 4.9, 1.5 Hz, 1 H), 12.15 (s, 1 H).

Ejemplo de referencia 14

1,3-dimetil-5-(1-naftil)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 9, se obtuvo el compuesto del título a partir de ácido 1-naftilborónico y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.61 (s, 3 H), 3.55 (s, 3 H), 7.42 - 7.63 (m, 5 H), 7.97 (d, J = 7.2 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H), 9.43 (s, 1 H).

Ejemplo de referencia 15

ácido (2E)-3-[1,3-dimetil-5-(1-naftil)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1-naftil)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 14 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.41 (s, 3 H), 3.45 (s, 3 H), 5.61 (d, J = 16.2 Hz, 1 H), 7.07 (d, J = 16.2 Hz, 1 H), 7.31 (d, J = 8.3 Hz, 1 H), 7.53 - 7.73 (m, 4 H), 8.07 - 8.10 (m, 1 H), 8.17 (d, J = 8.3 Hz, 1 H), 11.95 (s, 1 H).

Ejemplo de referencia 16

1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 4-metil-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 2.61 (s, 3 H), 3.58 (s, 3 H), 6.83 (dd, J = 3.4, 0.9 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 7.05 - 7.07 (m, 1 H), 7.16 - 7.19 (m, 2 H), 9.51 (s, 1 H).

Ejemplo de referencia 17

ácido (2E)-3-[1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 16 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 3 H), 2.55 (s, 3 H), 3.46 (s, 3 H), 5.45 (d, J = 16.2 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.89 (dd, J = 3.4, 0.9 Hz, 1 H), 6.98 - 7.01 (m, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.11 - 7.14 (m, 1 H), 7.54 (d, J = 3.4 Hz, 1 H), 12.13 (s, 1 H).

Ejemplo de referencia 18

5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 4-cloro-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.94 (dd, J = 3.4, 0.9 Hz, 1 H), 6.97 - 7.04 (m, 1 H), 7.15 - 7.30 (m, 3 H), 9.53 (s, 1 H).

Ejemplo de referencia 19

ácido (2E)-3-[5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 18 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.48 (s, 3 H), 5.39 (d, J = 15.9 Hz, 1 H), 6.89 (d, J = 3.2 Hz, 1 H), 6.99 - 7.09 (m, 2 H), 7.20 - 7.25 (m, 1 H), 7.27 - 7.31 (m, 1 H), 7.72 (d, J = 3.2 Hz, 1 H), 12.15 (s, 1 H).

Ejemplo de referencia 20

5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-fluoro-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.58 (s, 3 H), 6.77 (d, J = 3.3 Hz, 1 H), 7.00 - 7.03 (m, 2 H), 7.22 (d, J = 3.3 Hz, 1 H), 7.33 - 7.37 (m, 1 H), 9.51 (s, 1 H).

Ejemplo de referencia 21

ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 20 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.48 (s, 3 H), 5.38 (d, J = 16.2 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.99 - 7.10 (m, 3 H), 7.49 - 7.53 (m, 1 H), 7.66 (d, J = 3.4 Hz, 1 H), 12.15 (s, 1 H).

Ejemplo de referencia 22

5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-metoxi-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.58 (s, 3 H), 3.87 (s, 3 H), 6.73 (dd, J = 3.3, 0.9 Hz, 1 H), 6.90 (dd, J = 8.5, 2.4 Hz, 1 H), 6.99 (dd, J = 8.5, 1.5 Hz, 1 H), 7.14 - 7.15 (m, 2 H), 9.51 (s, 1 H).

Ejemplo de referencia 23

ácido (2E)-3-[5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 22 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 3 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 5.40 (d, J = 16.2 Hz, 1 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 6.81 - 6.85 (m, 1 H), 6.89 - 6.93 (m, 1 H), 7.07 (d, J = 16.2 Hz, 1 H), 7.22 (d, J = 2.1 Hz, 1 H), 7.51 (d, J = 3.4 Hz, 1 H), 12.13 (s, 1 H).

Ejemplo de referencia 24

5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 6-cloro-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.79 (dd, J = 3.4, 0.8 Hz, 1 H), 7.08 - 7.10 (m, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.5, 1.9 Hz, 1 H), 7.62 (d, J = 8.5 Hz, 1 H), 9.53 (s, 1 H).

Ejemplo de referencia 25

ácido (2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 24 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.48 (s, 3 H), 5.35 (d, J = 16.3 Hz, 1 H), 6.89 (d, J = 3.4 Hz, 1 H), 7.06 (d, J = 16.3 Hz, 1 H), 7.08 - 7.09 (m, 1 H), 7.23 (dd, J = 8.3, 1.9 Hz, 1 H), 7.62 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 12.15 (s, 1 H).

Ejemplo de referencia 26

5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 6-(benciloxi)-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.49 (s, 3 H), 4.99 - 5.08 (m, 2 H), 6.59 (d, J = 2.1 Hz, 1 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.98 (dd, J = 8.7, 2.1 Hz, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.29 - 7.48 (m, 5 H), 7.58 (d, J = 8.7 Hz, 1 H), 9.52 (s, 1 H).

Ejemplo de referencia 27

(2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 26 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.43 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.00 (s, 2 H), 5.64 (d, J = 16.4 Hz, 1 H), 6.50 (d, J = 2.1 Hz, 1 H), 6.72 (dd, J = 3.2, 0.8 Hz, 1 H), 6.93 - 6.99 (m, 2 H), 7.27 - 7.45 (m, 6 H), 7.58 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 28

ácido (2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 27.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.38 (s, 3 H), 3.44 (s, 3 H), 4.99 (d, J = 11.7 Hz, 1 H), 5.07 (d, J = 11.7 Hz, 1 H), 5.43 (d, J = 16.1 Hz, 1 H), 6.60 (d, J = 1.9 Hz, 1 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.92 (dd, J = 8.5, 1.9 Hz, 1 H), 7.08 (d, J = 16.1 Hz, 1 H), 7.27 - 7.44 (m, 6 H), 7.60 (d, J = 8.5 Hz, 1 H), 12.13 (s, 1 H).

Ejemplo de referencia 29

1,3-dimetil-5-(2-naftil)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 9, se obtuvo el compuesto del título a partir de ácido 2-naftilborónico y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 3.78 (s, 3 H), 7.47 (dd, J = 8.5, 1.7 Hz, 1 H), 7.58 - 7.64 (m, 2 H), 7.88 - 7.96 (m, 3 H), 8.00 (d, J = 8.5 Hz, 1 H), 9.67 (s, 1 H).

Ejemplo de referencia 30

ácido (2E)-3-[1,3-dimetil-5-(2-naftil)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(2-naftil)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 29 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.68 (s, 3 H), 5.89 (d, J = 16.2 Hz, 1 H), 7.29 (d, J = 16.2 Hz, 1 H), 7.53 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 - 7.70 (m, 2 H), 8.00 - 8.06 (m, 3 H), 8.12 (d, J = 8.5 Hz, 1 H), 12.04 (s, 1 H).

Ejemplo de referencia 31

1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 9, se obtuvo el compuesto del título a partir de ácido (quinolin-8-il)borónico y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.60 (s, 3 H), 3.60 (s, 3 H), 7.46 - 7.76 (m, 3 H), 8.04 (dd, J = 8.0, 1.9 Hz, 1 H), 8.28 (dd, J = 8.3, 1.9 Hz, 1 H), 8.96 (dd, J = 4.2, 1.5 Hz, 1 H), 9.51 (s, 1 H).

Ejemplo de referencia 32

(2E)-3-[1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 31 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.51 (s, 3 H), 3.55 (s, 3 H), 4.11 (q, J = 7.2 Hz, 2 H), 5.91 (d, J = 16.4 Hz, 1 H), 7.37 (d, J = 16.4 Hz, 1 H), 7.48 (dd, J = 8.3, 4.3 Hz, 1 H), 7.62 - 7.74 (m, 2 H), 7.96 - 8.05 (m, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 8.94 (d, J = 4.1 Hz, 1 H).

Ejemplo de referencia 33

ácido (2E)-3-[1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 32.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.39 (s, 3 H), 3.43 (s, 3 H), 5.69 (d, J = 16.3 Hz, 1 H), 7.10 (d, J = 16.3 Hz, 1 H), 7.64 (dd, J = 8.3, 4.2 Hz, 1 H), 7.73 - 7.88 (m, 2 H), 8.23 (dd, J = 6.8, 2.7 Hz, 1 H), 8.53 (dd, J = 8.3, 1.7 Hz, 1 H), 8.91 (dd, J = 4.2, 1.7 Hz, 1 H), 11.90 (s, 1 H).

Ejemplo de referencia 34

5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5,6-difluoro-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.76 (d, J = 2.3 Hz, 1 H), 6.88 (dd, J = 9.8, 6.8 Hz, 1 H), 7.20 (d, J = 3.4 Hz, 1 H), 7.46 (dd, J = 10.2, 7.6 Hz, 1 H), 9.54 (s, 1 H).

Ejemplo de referencia 35

(2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 34 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.50 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.59 (d, J = 16.3 Hz, 1 H), 6.72 - 6.83 (m, 2 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.27 (d, J = 16.3 Hz, 1 H), 7.45 (dd, J = 10.2, 7.6 Hz, 1 H).

Ejemplo de referencia 36

ácido (2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 35.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.49 (s, 3 H), 5.34 (d, J = 16.2 Hz, 1 H), 6.87 (dd, J = 3.4, 0.8 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.19 (dd, J = 10.7, 6.8 Hz, 1 H), 7.65 (d, J = 3.4 Hz, 1 H), 7.76 (dd, J = 10.9, 7.9 Hz, 1 H), 12.18 (s, 1 H).

Ejemplo de referencia 37

5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una solución de 5-cloro-1H-indol (2.00 g) en N,N-dimetilformamida (10 ml) se añadió hidruro de sodio al 60% (en aceite, 550 mg) con agitación, y la mezcla se agitó a temperatura ambiente durante 1 h. Se agregó 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (2.00 g) a esta mezcla de reacción a temperatura ambiente, y la mezcla se agitó con calentamiento a 70°C durante 2 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato

de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 85:15 - 65:35, v/v), y se cristalizó en hexano-éter diisopropílico para dar el compuesto del título (1.67 g, rendimiento del 49%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.19 - 7.27 (m, 2 H), 7.69 (d, J = 1.5 Hz, 1 H), 9.53 (s, 1 H).

Ejemplo de referencia 38

ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

A una solución de 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (1.91 g) en piridina (10 ml) se añadieron ácido malónico (2.90 g) y piperidina (1.7 ml), y la mezcla se agitó con calentamiento a 110°C durante 2.5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, la mezcla de reacción se concentró a presión reducida, y el residuo se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con solución acuosa saturada de cloruro de amonio y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo

se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 65:35 - 25:75, v/v) para dar el compuesto del título (1.74 g, rendimiento del 79%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3 H), 3.51 (s, 3 H), 5.54 (d, J = 15.9 Hz, 1 H), 6.74 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 2.3 Hz, 1 H), 7.32 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 39

5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Una mezcla de 3-cloro-1H-indazol (1.53 g), 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (1.00 g) y carbonato de potasio (1.38 g) en N,N-dimetilformamida (30 ml) se agitó con calentamiento a 120°C durante 12 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 95:5 - 75:25, v/v) para dar el compuesto del título (1.65 g, rendimiento del 60%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.73 (s, 3

H), 7.28 (dd, J = 7.5, 0.9 Hz, 1 H), 7.30 - 7.41 (m, 1 H), 7.54 - 7.58 (m, 1 H), 7.81 (dd, J = 7.5, 0.9 Hz, 1 H), 9.60 (s, 1 H).

Ejemplo de referencia 40

ácido (2E)-3-[5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Una solución de 5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 39 (1.65 g) y (dietoxifosforil)acetato de etilo (1.41 g) en tetrahidrofurano (30 ml) se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 252 mg) con agitación, y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se disolvió en un solvente mixto de tetrahidrofurano (30 ml) y metanol (30 ml). Una solución acuosa 4 N de hidróxido de sodio (4 ml) se añadió, y la mezcla se agitó a temperatura ambiente durante 3 h. Se agregó ácido clorhídrico 1 N (20 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró para dar el compuesto del título (1.59 g, rendimiento del 84%) en forma de cristales

incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3 H), 3.56 (s, 3 H), 5.50 (d, J = 16.2 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.61 - 7.66 (m, 1 H), 7.89 (d, J = 7.8 Hz, 1 H), 12.21 (br s, 1 H).

Ejemplo de referencia 41

1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 6-(trifluorometil)-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.59 (s, 3 H), 3.59 (s, 3 H), 6.71 - 6.99 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.43 - 7.58 (m, 1 H), 7.82 (d, J = 8.3 Hz, 1 H), 9.55 (s, 1 H).

Ejemplo de referencia 42

ácido (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 40, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 41.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3 H), 3.50 (s, 3 H), 5.35 (d, J = 16.3 Hz, 1 H), 6.87 - 7.19 (m, 2 H), 7.21 - 7.40 (m, 1 H), 7.44 - 7.65 (m, 1 H), 7.85 (d, J = 3.4 Hz, 1

H), 7.96 (d, J = 8.3 Hz, 1 H), 11.99 (s, 1 H).

Ejemplo de referencia 43

3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoato de etilo

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 12 (7.49 g) se disolvió en etanol (200 ml), se añadió paladio sobre carbón al 10% (800 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 5 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50 - 0:100, v/v) para dar el compuesto del título (6.64 g, rendimiento del 88%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.15 (t, J = 7.2 Hz, 3 H), 2.25 - 2.35 (m, 5 H), 2.55 - 2.64 (m, 2 H), 3.51 (s, 3 H), 4.00 (q, J = 7.2 Hz, 2 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.17 (dd, J = 7.8, 4.8 Hz, 1 H), 7.21 (d, J = 3.6 Hz, 1 H), 8.00 (dd, J = 7.8, 1.6 Hz, 1 H), 8.34 (dd, J = 4.8, 1.6 Hz, 1 H).

Ejemplo de referencia 44

3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoato de etilo

Por medio de un método similar al del Ejemplo de referencia 43, se obtuvo el compuesto del título (compuesto más polar, 0.48 g, rendimiento del 6%) en forma de un aceite

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incoloro, junto con el compuesto del Ejemplo de referencia 43, a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 12.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, J = 7.1 Hz, 3 H), 2.21 (s, 3 H), 2.36 - 2.45 (m, 2 H), 2.55 - 2.65 (m, 2 H), 3.17 - 3.27 (m, 2 H), 3.63 (s, 3 H), 3.85 (t, J = 8.6 Hz, 2 H), 4.05 (q, J = 7.1 Hz, 2 H), 6.59 (dd, J = 7.0, 5.3 Hz, 1 H), 7.34 (dd, J = 7.0, 1.0 Hz, 1 H), 7.88 (dd, J = 5.3, 1.0 Hz, 1 H).

Ejemplo de referencia 45

ácido 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoato de etilo obtenido en el Ejemplo de referencia 43.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.08 - 2.17 (m, 2 H), 2.19 (s, 3 H), 2.31 - 2.45 (m, 2 H), 3.40 (s, 3 H), 6.79 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.65 (d, J = 3.6 Hz, 1 H), 8.11 (dd, J = 7.8, 1.6 Hz, 1 H), 8.25 (dd, J = 4.7, 1.6 Hz, 1 H), 12.02 (s, 1 H).

Ejemplo de referencia 46

ácido 3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de 3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoato de etilo obtenido en el Ejemplo de referencia 44.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.08 (s, 3 H), 2.21 - 2.29 (m, 2 H), 2.37 - 2.44 (m, 2 H), 3.15 - 3.22 (m, 2 H), 3.49 (s, 3 H), 3.70 - 3.88 (m, 2 H), 6.61 (dd, J = 7.1, 5.2 Hz, 1 H), 7.43 (dd, J = 7.1, 1.5 Hz, 1 H), 7.73 (dd, J = 5.2, 1.5 Hz, 1 H), 12.02 (s, 1 H).

Ejemplo de referencia 47

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-2-metilacrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 11 y 2-(dietoxifosforil)propanoato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 2.29 (s, 3 H), 3.66 (s, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 6.65 (d, J = 3.4 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.0, 4.7 Hz, 1 H), 7.32 (s, 1 H), 7.97

(dd, J = 8.0, 1.5 Hz, 1 H), 8.34 - 8.40 (m, 1 H).

Ejemplo de referencia 48

ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-2-metilacrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-2-metilacrilato de etilo obtenido en el Ejemplo de referencia 47.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.06 (d, J = 1.3 Hz, 3 H), 2.20 (s, 3 H), 3.54 (s, 3 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 1.3 Hz, 1 H), 7.25 (dd, J = 7.9, 4.7 Hz, 1 H), 7.56 (d, J = 3.8 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H), 12.32 (s, 1 H).

Ejemplo de referencia 49

5-cloro-N-metoxi-N,1-dimetil-1H-pirazol-4-carboxamida

A una mezcla de clorhidrato de N,O-dimetilhidroxiamina (6.78 g) y N,N-dimetilformamida (50 ml) se añadió trietilamina (9.68 ml), y la mezcla se agitó a temperatura ambiente durante 10 min. Se añadieron ácido 5-cloro-1-metil-1H-pirazol-4-carboxílico (9.70 g), clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (13.32 g) y monohidrato de 1-hidroxibenzotriazol (10.64 g) a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente

durante 15 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó sucesivamente con solución acuosa de carbonato de potasio y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 67:33 - 25:75, v/v) para dar el compuesto del título (9.92 g, rendimiento del 81%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.33 (s, 3 H), 3.66 (s, 3 H), 3.88 (s, 3 H), 7.92 (s, 1 H).

Ejemplo de referencia 50

5-cloro-1-metil-1H-pirazol-4-carbaldehído

A una solución de 5-cloro-N-metoxi-N,1-dimetil-1H-pirazol-4-carboxamida obtenida en el Ejemplo de referencia 49 (9.47 g) en tetrahidrofurano (60 ml) se añadió gota a gota hidruro de diisobutilalumino (solución toluénica 1.5 M, 37.2 ml) con agitación a 0°C, y la mezcla de reacción se agitó a 0°C durante 1 h. Se añadió gradualmente sulfato de magnesio 10 hidratado (19.0 g), y la mezcla se agitó a temperatura ambiente durante 5 h. El precipitado se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 75:25 - 33:67, v/v), y se cristalizó en hexano-éter dietílico para dar el compuesto del título (2.88 g,

rendimiento del 43%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3 H), 7.96 (s, 1 H), 9.83 (s, 1 H).

Ejemplo de referencia 51

1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-cloro-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 50 y 1H-pirrolo[2,3-b]piridina.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 3.78 (s, 3 H), 6.79 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 7.9, 4.7 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.03 (dd, J = 7.9, 1.6 Hz, 1 H), 8.10 (s, 1 H), 8.36 (dd, J = 4.7, 1.6 Hz, 1 H), 9.62 (s, 1 H).

Ejemplo de referencia 52

(2E)-2-metil-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 51 y 2-(dietoxifosforil)propanoato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J = 7.1 Hz, 3 H), 2.10 (d, J = 1.1 Hz, 3 H), 3.70 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 6.74 (d, J = 3.6 Hz, 1 H), 7.08 (d, J = 1.1 Hz, 1 H),

7.17 - 7.24 (m, 2 H), 7.91 (s, 1 H), 8.02 (dd, J = 7.8, 1.6 Hz, 1 H), 8.36 (dd, J = 4.8, 1.6 Hz, 1 H).

Ejemplo de referencia 53

ácido (2E)-2-metil-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-2-metil-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 52.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.00 (s, 3 H), 3.59 (s, 3 H), 6.84 (s, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.28 (dd, J = 8.0, 4.5 Hz, 1 H), 7.73 (d, J = 3.6 Hz, 1 H), 8.02 (s, 1 H), 8.16 (dd, J = 8.0, 1.6 Hz, 1 H), 8.28 (dd, J = 4.5, 1.6 Hz, 1 H), 12.19 (s, 1 H).

Ejemplo de referencia 54

5-(6-hidroxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

5-[6-(Benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 26 (1.59 g) se disolvió en metanol (120 ml), se añadió paladio sobre carbón al 10% (330 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 24 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía

en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v) para dar el compuesto del título (574 mg, rendimiento del 48%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3 H), 3.14 - 3.22 (m, 2 H), 3.67 (s, 3 H), 3.83 - 3.95 (m, 1 H), 3.98 - 4.07 (m, 1 H), 5.54 (br s, 1 H), 5.80 (d, J = 2.1 Hz, 1 H), 6.28 (dd, J = 8.0, 2.1 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 1 H), 9.77 (s, 1 H).

Ejemplo de referencia 55

5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Una mezcla de 5-(6-hidroxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 54 (267 mg), yoduro de metilo (2.61 g) y carbonato de potasio (430 mg) en acetona (8 ml) se calentó a reflujo durante 24 h. La mezcla de reacción se concentró a presión reducida, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 75:25, v/v) para dar el compuesto del título (250 mg, rendimiento del 89%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.48 (s, 3 H), 3.14 - 3.26 (m, 2 H), 3.68 (s, 3 H), 3.69 (s, 3 H), 3.83 - 3.93 (m,

1 H), 3.97 - 4.07 (m, 1 H), 5.88 (d, J = 2.3 Hz, 1 H), 6.34 (dd, J = 8.0, 2.3 Hz, 1 H), 7.07 (d, J = 8.0 Hz, 1 H), 9.77 (s, 1 H).

Ejemplo de referencia 56

(2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 55 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, J = 7.2 Hz, 3 H), 2.38 (s, 3 H), 3.14 - 3.25 (m, 2 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 3.75 - 3.95 (m, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.76 (d, J = 2.3 Hz, 1 H), 5.94 (d, J = 16.1 Hz, 1 H), 6.31 (dd, J = 8.0, 2.3 Hz, 1 H), 7.06 (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 16.1 Hz, 1 H).

Ejemplo de referencia 57

ácido (2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 56.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.28 (s, 3 H), 3.10 - 3.18 (m, 2 H), 3.59 (s, 3 H), 3.60 (s, 3 H), 3.65 - 3.77 (m, 1 H), 3.87 - 3.97 (m, 1 H), 5.65 (d, J = 2.3 Hz, 1 H), 5.77 (d, J = 16.2 Hz, 1 H), 6.29 (dd, J = 8.1, 2.3 Hz, 1 H), 7.08 (d, J = 8.1 Hz, 1 H), 7.25 (d, J = 16.2 Hz, 1 H), 12.06 (s, 1 H).

Ejemplo de referencia 58

5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 6-metoxi-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 3.59 (s, 3 H), 3.78 (s, 3 H), 6.53 (d, J = 2.3 Hz, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.6, 2.3 Hz, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.6 Hz, 1 H), 9.54 (s, 1 H).

Ejemplo de referencia 59

(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 58 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 3.76 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.65 (d, J = 16.3 Hz, 1 H), 6.42 (d, J = 2.1 Hz, 1 H), 6.72 (d, J = 3.2 Hz, 1 H), 6.88 (dd, J = 8.7, 2.1 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.32 (d, J = 16.3 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 60

ácido (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 59.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.49 (s, 3 H), 3.69 (s, 3 H), 5.43 (d, J = 16.2 Hz, 1 H), 6.48 (d, J = 2.1 Hz, 1 H), 6.76 (dd, J = 3.4, 0.8 Hz, 1 H), 6.84 (dd, J = 8.7, 2.1 Hz, 1 H), 7.10 (d, J = 16.2 Hz, 1 H), 7.38 (d, J = 3.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 12.14 (s, 1 H).

Ejemplo de referencia 61

[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol

5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (4.08 g) se disolvió en un solvente mixto de tetrahidrofurano (24 ml) y metanol (6 ml), se añadió borohidruro de sodio (845 mg), y

la mezcla se agitó a 0°C durante 3 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (3.99 g, rendimiento del 97%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, J = 5.2 Hz, 1 H), 2.38 (s, 3 H), 3.50 (s, 3 H), 4.22 - 4.39 (m, 2 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.15 - 7.22 (m, 2 H), 7.66 (d, J = 1.5 Hz, 1 H).

Ejemplo de referencia 62

[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acetaldehído

5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (5.26 g) se disolvió en un solvente mixto de tetrahidrofurano (30 ml) y se agregaron alcohol ter-butílico (30 ml), ter-butóxido de potasio (2.59 g) y bromoacetato de etilo (3.53 g), y la mezcla se agitó a temperatura ambiente durante 5 h. Esta mezcla de reacción se filtró a través de celite®, y el filtrado se concentró. El residuo se disolvió en un solvente mixto de tetrahidrofurano (10 ml) y etanol (10 ml), se añadió una solución acuosa 8 N de hidróxido de sodio (5 ml), y la mezcla se agitó a temperatura ambiente durante 3 h. Se agregó

ácido acético (30 ml), y la mezcla se agitó a 60°C durante 3 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el compuesto del título (2.89 g, rendimiento del 52%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.24 (s, 3 H), 3.20 - 3.40 (m, 2 H), 3.50 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.65 (d, J = 1.5 Hz, 1 H), 9.51 (t, J =1.5 Hz, 1 H).

Ejemplo de referencia 63

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol

Por medio de un método similar al del Ejemplo de referencia 61, se obtuvo el compuesto del título a partir de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acetaldehído obtenido en el Ejemplo de referencia 62.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.37 - 2.57 (m, 2 H), 3.44 - 3.55 (m, 5 H), 6.66 (dd, J = 3.2, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1

H).

Ejemplo de referencia 64

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.49 (s, 3 H), 4.12 (q, J = 6.9 Hz, 2 H), 5.60 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.28 (d, J = 16.3 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H)

Ejemplo de referencia 65

3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoato de etilo

El (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 64 (5.09 g) se disolvió en un solvente mixto de tetrahidrofurano (25 ml) y etanol (25 ml), se añadió óxido de platino (500 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 16 h. El catalizador se eliminó por filtración, y el filtrado se

concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 75:25, v/v) para dar el compuesto del título (4.91 g, rendimiento del 96%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.12 - 1.19 (m, 3 H), 2.18 - 2.25 (m, 2 H), 2.30 (s, 3 H), 2.47 - 2.66 (m, 2 H), 3.41 - 3.45 (m, 3 H), 3.94 - 4.03 (m, 2 H), 6.66 - 6.70 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 66

3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol

A una solución de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoato de etilo obtenido en el Ejemplo de referencia 65 (4.11 g) en tetrahidrofurano (24 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de diisobutilalumino (solución toluénica 1.5 M, 20 ml) en pequeñas porciones con agitación. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, y se volvió a enfriar a 0°C en un baño helado. Se agregaron metanol y agua a la mezcla de reacción con agitación, la mezcla se filtró a través de celite, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (3.47 g, rendimiento del 96%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44 - 1.56 (m, 2 H), 2.20 - 2.40 (m, 5 H), 3.39 - 3.47 (m, 5 H), 6.66 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 2.1 Hz, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 67

ácido [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acético

[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acetaldehído obtenido en el Ejemplo de referencia 62 (501 mg) se disolvió en un solvente mixto de alcohol terbutílico (5.8 ml) y agua (1.2 ml). Se añadieron fosfato de sodio diácido (627 mg), clorito de sodio (236 mg) y 2-metil-2-buteno (611 mg), y la mezcla se agitó a temperatura ambiente durante 14 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (412 mg, rendimiento del 78%) en forma de cristales de color amarillo pálido.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.17 (s, 3 H), 3.01 - 3.16 (m, 2 H), 3.40 (s, 3 H), 6.75 (d, J = 3.0 Hz, 1 H), 7.04

(d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.5, 2.1 Hz, 1 H), 7.51 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 12.25 (br s, 1 H).

Ejemplo de referencia 68

ácido 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoico

Por medio de un método similar al del Ejemplo de referencia 65, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.09 (t, J = 7.8 Hz, 2 H), 2.20 (s, 3 H), 2.49 - 2.53 (m, 2 H), 3.37 (s, 3 H), 6.76 (d, J = 2.7 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.56 (d, J = 3.0 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 12.07 (br s, 1 H).

Ejemplo de referencia 69

(2E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]but-2-enoato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acetaldehído obtenido en el Ejemplo de referencia 62 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.18 - 1.29 (m, 3 H), 2.25 (s, 3 H), 2.96 - 3.17 (m, 2 H), 3.49 (s, 3 H), 4.07 -

4.17 (m, 2 H), 5.49 - 5.60 (m, 1 H), 6.65 (dd, J = 3.3, 0.8 Hz, 1 H), 6.71 - 6.82 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 70

ácido (2E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]but-2-enoico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]but-2-enoato de etilo obtenido en el Ejemplo de referencia 69.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.30 (s, 3 H), 3.37 - 3.52 (m, 5 H), 5.32 - 5.49 (m, 1 H), 5.88 - 5.98 (m, 1 H), 6.72 - 6.83 (m, 1 H), 6.96 - 7.07 (m, 1 H), 7.14 - 7.23 (m, 1 H), 7.51 - 7.65 (m, 1 H), 7.70 - 7.80 (m, 1 H), 12.11 (br s, 1 H).

Ejemplo de referencia 71

ácido 4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]butanoico

Por medio de un método similar al del Ejemplo de referencia 65, se obtuvo el compuesto del título a partir de ácido (2E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]but-2-enoico obtenido en el Ejemplo de referencia 70.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.34 - 1.47 (m, 2 H), 1.95 - 2.32 (m, 7 H), 3.37 (s, 3 H), 6.75 (d, J = 2.7 Hz, 1 H), 7.01 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.55 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 72

2-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}-1H-isoindol-1,3(2H)-diona

A una solución de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 (3.52 g) en tetrahidrofurano (25 ml) se añadieron cloruro de metansulfonilo (2.05 g) y trietilamina (1.94 g) con agitación a 0°C, y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se disolvió en N,N-dimetilformamida (15 ml). Se añadió ftalimida de potasio (2.07 g), y la mezcla se agitó a 50°C durante 16 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (3.23 g, rendimiento del 62%) en forma de cristales incoloros.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3 H), 3.41 (s, 3 H), 4.38 (d, J = 15.3 Hz, 1 H), 4.73 (d, J = 15.3 Hz, 1 H), 6.59 (dd, J = 3.4, 0.8 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 1 H), 6.89 (dd, J = 8.7, 1.9 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 1.7 Hz, 1 H), 7.55 - 7.65 (m, 4 H).

Ejemplo de referencia 73

2-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-1H-isoindol-1,3(2H)-diona

Por medio de un método similar al del Ejemplo de referencia 72, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol obtenido en el Ejemplo de referencia 63.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3 H), 2.50 - 2.84 (m, 2 H), 3.42 (s, 3 H), 3.50 - 3.75 (m, 2 H), 6.65 (dd, J = 3.3, 0.8 Hz, 1 H), 6.80 - 6.96 (m, 2 H), 7.19 (d, J = 3.2 Hz, 1 H), 7.57 (d, J = 1.7 Hz, 1 H), 7.68 (s, 4 H).

Ejemplo de referencia 74

2-{3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propil}-1H-isoindol-1,3(2H)-diona

Por medio de un método similar al del Ejemplo de referencia 72, se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenido en el Ejemplo de referencia 66.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55 - 1.73 (m, 2 H), 2.15 - 2.54 (m, 5 H), 3.42 - 3.56 (m, 5 H), 6.58 (d, J = 3.4

Hz, 1 H), 6.88 - 6.97 (m, 1 H), 7.06 - 7.14 (m, 2 H), 7.52 (d, J = 1.7 Hz, 1 H), 7.65 - 7.97 (m, 4 H).

Ejemplo de referencia 75

1-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanamina

A una solución de 2-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}-1H-isoindol-1,3(2H)-diona obtenida en el Ejemplo de referencia 72 (543 mg) en tetrahidrofurano (13 ml) se añadió una solución acuosa al 35% de hidracina (1.23 g) con agitación, y la mezcla se calentó a reflujo durante 16 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, y de concentrar, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (305 mg, rendimiento del 83%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (br s, 2 H), 2.35 (s, 3 H), 3.40 - 3.55 (m, 5 H), 6.68 (d, J = 2.3 Hz, 1 H), 6.97 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 76

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanamina

Por medio de un método similar al del Ejemplo de referencia 75, se obtuvo el compuesto del título a partir de 2-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-1H-isoindol-1,3(2H)-diona obtenida en el Ejemplo de referencia 73.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.12 - 1.32 (m, 2 H), 2.24 - 2.44 (m, 5 H), 2.60 (br s, 2 H), 3.46 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 77

3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-amina

Por medio de un método similar al del Ejemplo de referencia 75, se obtuvo el compuesto del título a partir de 2-{3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propil}-1H-isoindol-1,3(2H)-diona obtenida en el Ejemplo de referencia 74.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.07 - 1.23 (m, 2 H), 1.34 - 1.46 (m, 2 H), 2.15 - 2.36 (m, 5 H), 2.50 (br s, 2 H), 3.45 (s, 3 H), 6.67 (dd, J = 3.3, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.15 - 7.21 (m, 1 H),

7.65 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 78

3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanal

A una mezcla de celite® (4.00 g) en diclorometano (35 ml) se añadió dicromato de piridinio (4.00 g) con agitación, y la mezcla se agitó a temperatura ambiente durante 10 min. Se agregó 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenido en el Ejemplo de referencia 66 (2.70 g) a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se filtró a través de celite®, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (1.49 g, rendimiento del 56%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.35 (dd, J = 5.7, 1.9 Hz, 2 H), 2.52 - 2.61 (m, 2 H), 3.44 (s, 3 H), 6.69 (d, J = 3.4 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.66 (d, J = 1.9 Hz, 1 H), 9.53 (s, 1 H).

Ejemplo de referencia 79

1-(4-formil-1,3-dimetil-1H-pirazol-5-il)-1H-indol-5-carbonitrilo

Por medio de un método similar al del Ejemplo de

referencia 1, se obtuvo el compuesto del título a partir de 1H-indol-5-carbonitrilo y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.58 (s, 3 H), 6.90 (d, J = 3.3 Hz, 1 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.31 (d, J = 3.3 Hz, 1 H), 7.53 (dd, J = 8.7, 1.6 Hz, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 9.54 (s, 1 H).

Ejemplo de referencia 80

(2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1-(4-formil-1,3-dimetil-1H-pirazol-5-il)-1H-indol-5-carbonitrilo obtenido en el Ejemplo de referencia 79 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.19 - 1.25 (m, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 4.08 - 4.17 (m, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.90 (dd, J = 3.4, 0.8 Hz, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.21 - 7.28 (m, 2 H), 7.50 (dd, J = 8.5, 1.5 Hz, 1 H), 8.09 (d, J = 0.9 Hz, 1 H).

Ejemplo de referencia 81

ácido (2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de

(2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 80.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 3 H), 3.48 (s, 3 H), 5.38 (d, J = 16.2 Hz, 1 H), 6.92 - 7.02 (m, 2 H), 7.21 (d, J = 8.5 Hz, 1 H), 7.58 (dd, J = 8.7, 1.3 Hz, 1 H), 7.81 (d, J = 3.2 Hz, 1 H), 8.29 (s, 1 H).

Ejemplo de referencia 82

5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 6-fluoro-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.59 (s, 3 H), 6.76 - 6.82 (m, 2 H), 6.97 - 7.05 (m, 1 H), 7.17 (d, J = 3.4 Hz, 1 H), 7.63 (dd, J = 8.7, 5.3 Hz, 1 H), 9.54 (s, 1 H).

Ejemplo de referencia 83

ácido (2E)-3-[5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 2, se obtuvo el compuesto del título a partir de 5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 82 y ácido malónico.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.49 (s,

3 H), 5.33 - 5.42 (m, 1 H), 6.84 - 6.91 (m, 2 H), 7.01 - 7.11 (m, 2 H), 7.57 (d, J = 3.4 Hz, 1 H), 7.73 (dd, J = 8.5, 5.5 Hz, 1 H), 12.17 (br s, 1 H).

Ejemplo de referencia 84

5-(metoximetil)-2-metil-2,4-dihidro-3H-pirazol-3-ona

A una solución de 4-metoxiacetacetato de metilo (3.48 g) en tolueno (110 ml) se añadió gota a gota una solución de metilhidracina (1.10 g) en tolueno (35 ml) durante 20 min a 0°C, y la mezcla se agitó a 100°C durante 1.5 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró a presión reducida. El residuo se cristalizó en éter diisopropílico-hexano para dar el compuesto del título (3.20 g, rendimiento del 95%) en forma de cristales marrones.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.29 (s, 2 H), 3.31 (s, 3 H), 3.39 (s, 3 H), 4.17 (s, 2 H).

Ejemplo de referencia 85

5-cloro-3-(metoximetil)-1-metil-1H-pirazol-4-carbaldehído

Se añadió cloruro de fosforilo (201 g) gota a gota durante 30 min a N,N-dimetilformamida (31.9 g) enfriada a 0°C. La 5-(metoximetil)-2-metil-2,4-dihidro-3H-pirazol-3-ona obtenida en el Ejemplo de referencia 84 (31.0 g) se añadió a esta mezcla de reacción, y la mezcla se agitó con

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calentamiento a 80°C durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se vertió en agua helada, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10 - 50:50, v/v) para dar el compuesto del título (23.5 g, rendimiento del 57%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.48 (s, 3 H), 3.88 (s, 3 H), 4.69 (s, 2 H), 9.90 (s, 1 H).

Ejemplo de referencia 86

5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-fluoro-1H-indol y 5-cloro-3-(metoximetil)-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 85.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.55 (s, 3 H), 3.64 (s, 3 H), 4.78 (s, 2 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.97 - 7.05 (m, 2 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.33 - 7.40 (m, 1 H), 9.59 (s, 1 H).

Ejemplo de referencia 87

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 86 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.18 - 1.26 (m, 3 H), 3.50 (s, 3 H), 3.55 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.54 - 4.64 (m, 2 H), 5.76 (d, J = 16.2 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.88 - 7.04 (m, 2 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.31 (d, J = 16.2 Hz, 1 H), 7.36 (dd, J = 9.1, 2.4 Hz, 1 H).

Ejemplo de referencia 88

ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 87.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.34 (s, 3 H), 3.55 (s, 3 H), 4.47 - 4.59 (m, 2 H), 5.47 (d, J = 16.2 Hz, 1 H), 6.87 (d, J = 3.4 Hz, 1 H), 6.98 - 7.15 (m, 3 H), 7.52 (dd, J = 9.5, 2.2 Hz, 1 H), 7.69 (d, J = 3.2 Hz, 1 H), 12.22 (br s, 1 H).

Ejemplo de referencia 89

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilonitrilo

A una solución de (cianometil)fosfonato de dietilo (1.07 g) en tetrahidrofurano (22 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 263 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Una solución de 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (1.50 g) en tetrahidrofurano (8 ml) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a temperatura ambiente durante 4 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el compuesto del título (1.49 g, rendimiento del 92%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3 H), 3.54 (s, 3 H), 4.83 (d, J = 17.0 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.8, 2.0 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 90

(1Z,2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N'-hidroxiprop-2-enimidamida

A una solución de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilonitrilo obtenida en el Ejemplo de referencia 89 (321 mg) en sulfóxido de dimetilo (11 ml) se añadieron cloruro de hidroxilamonio (377 mg) y trietilamina (549 mg) con agitación, y la mezcla se agitó a 75°C durante 3 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 35:65, v/v) para dar el compuesto del título (159 mg, rendimiento del 44%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.44 (s, 3 H), 3.49 (s, 3 H), 4.42 (br s, 2 H), 5.73 (d, J = 17.0 Hz, 1 H), 6.34 (d, J = 17.0 Hz, 1 H), 6.73 (d, J = 2.7 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 2.7 Hz, 1 H), 7.20 (d, J = 9.1 Hz, 1 H), 7.67 (s, 1 H).

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Ejemplo de referencia 91

5-cloro-1-{4-[(2,2-dietoxietoxi)metil]-1,3-dimetil-1H-pirazol-5-il}-1H-indol

A una solución de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 (1.12 g) en N,N-dimetilformamida (8 ml) se añadió hidruro de sodio al 60% (en aceite, 195 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Se añadió 2-bromo-1,1-dietoxietano (1.20 g) a esta mezcla de reacción, y la mezcla se agitó a 80°C durante 72 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 75:25, v/v) para dar el compuesto del título (1.05 g, rendimiento del 66%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.14 (t, J = 7.0 Hz, 6 H), 2.35 (s, 3 H), 3.31 (d, J = 4.9 Hz, 2 H), 3.36 - 3.65 (m, 7 H), 4.08 - 4.26 (m, 2 H), 4.46 (t, J = 5.3 Hz, 1 H), 6.66 (d, J = 3.0 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.14 - 7.21 (m, 2 H), 7.65 (d, J = 1.9 Hz, 1 H).

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Ejemplo de referencia 92

{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metoxi}acetaldehído

A una solución de 5-cloro-1-{4-[(2,2-dietoxietoxi)metil]-1,3-dimetil-1H-pirazol-5-il}-1H-indol obtenida en el Ejemplo de referencia 91 (1.03 g) en tetrahidrofurano (5.3 ml) se añadió ácido clorhídrico 1 N (5.3 ml), y la mezcla se agitó a 50°C durante 2.5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v) para dar el compuesto del título (643 mg, rendimiento del 77%) en forma de un sólido amorfo de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.46 - 3.53 (m, 5 H), 3.89 (dd, J = 1.8, 0.8 Hz, 2 H), 6.69 (dd, J = 3.3, 0.8 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.16 - 7.22 (m, 2 H), 7.66 (d, J = 1.5 Hz, 1 H), 9.53 (t, J = 0.9 Hz, 1 H).

Ejemplo de referencia 93

ácido {[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metoxi}acético

Por medio de un método similar al del Ejemplo de

referencia 67, se obtuvo el compuesto del título a partir de {[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metoxi}acetaldehído obtenido en el Ejemplo de referencia 92.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.26 (s, 3 H), 3.39 - 3.45 (m, 5 H), 3.81 (s, 2 H), 6.76 (dd, J = 3.2, 0.8 Hz, 1 H), 7.07 - 7.13 (m, 1 H), 7.16 - 7.22 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.74 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 94

ácido (3E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-oxobut-3-enoico

5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (1.03 g) se disolvió en un solvente mixto de metanol (18 ml) y agua (18 ml), se añadieron ácido pirúvico (1.32 g) y carbonato de sodio (1.59 g), y la mezcla se calentó a reflujo durante 8 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (750 mg, rendimiento del 58%) en forma de cristales de color amarillo pálido.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.43 (s, 3 H), 3.52 (s, 3

H), 6.22 (d, J = 16.7 Hz, 1 H), 6.88 (d, J = 3.0 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.15 - 7.26 (m, 2 H), 7.70 (d, J = 3.4 Hz, 1 H), 7.81 (d, J = 1.9 Hz, 1 H), 13.92 (br s, 1 H).

Ejemplo de referencia 95

(3E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-oxobut-3-enoato de etilo

A una solución de ácido (3E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-oxobut-3-enoico obtenida en el Ejemplo de referencia 94 (545 mg) en etanol (10 ml) se añadió ácido clorhídrico (0.5 ml), y la mezcla se calentó a reflujo durante 18 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró a presión reducida. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (403 mg, rendimiento del 68%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 - 1.29 (m, 3 H), 2.50 (s, 3 H), 3.56 (s, 3 H), 4.18 - 4.28 (m, 2 H), 6.43 (d, J = 16.4 Hz, 1 H), 6.79 (dd, J = 3.3, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.41 - 7.50 (m, 1 H), 7.70 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 96

4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-hidroxibutanoato de etilo

(3E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-

pirazol-4-il]-2-oxobut-3-enoato de etilo obtenido en el Ejemplo de referencia 95 (403 mg) se disolvió en un solvente mixto de tetrahidrofurano (15 ml) y etanol (15 ml), se añadió paladio sobre carbón al 10% (42 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 16 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se disolvió en un solvente mixto de tetrahidrofurano (15 ml) y etanol (15 ml), se añadió borohidruro de sodio (41 mg), y la mezcla se agitó a 0°C durante 3 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (251 mg, rendimiento del 62%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.08 - 1.18 (m, 3 H), 1.48 - 1.78 (m, 2 H), 2.19 - 2.51 (m, 5 H), 2.65 (dd, J = 10.6, 5.2 Hz, 1 H), 3.41 - 3.47 (m, 3 H), 3.95 - 4.16 (m, 2 H), 6.65 - 6.69 (m, 1 H), 6.94 (dd, J = 8.8, 2.5 Hz, 1 H), 7.12 (dd, J = 5.0, 3.3 Hz, 1 H), 7.15 - 7.20 (m, 1 H), 7.65 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 97

2-cloro-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]butanoato de etilo

A una solución de 4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-hidroxibutanoato de etilo obtenida en el Ejemplo de referencia 96 (241 mg) en tetrahidrofurano (7 ml) se añadió cloruro de tionilo (229 mg), y la mezcla se calentó a reflujo durante 22 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró. El residuo se purificó por HPLC preparativa (herramienta: Gilson, Inc., sistema de purificación de alto rendimiento, columna: YMC Combiprep ODS-A, S-5 µm, 50 x 20 mm, solvente: SOLUCIÓN A; 0.1% de agua con contenido de ácido trifluoroacético, SOLUCIÓN B; 0.1% de acetonitrilo con contenido de ácido trifluoroacético, ciclo de gradiente: 0.00 min (SOLUCION A/SOLUCION B = 90/10), 1.00 min (SOLUCION A/SOLUCION B = 90/10), 4.20 min (SOLUCION A/SOLUCION B = 10/90), 5.40 min (SOLUCION A/SOLUCION B = 10/90), 5.50 min (SOLUCION A/SOLUCION B = 90/10), 5.60 min (SOLUCION A/SOLUCION B = 90/10), velocidad de flujo: 25 ml/min, método de detección: UV 220 nm) para dar el compuesto del título (93.7 mg, rendimiento del 37%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.13 - 1.23 (m, 3 H), 1.81 - 1.94 (m, 2 H), 2.30 (s, 3 H), 2.33 - 2.52 (m, 2 H), 3.46 (s, 3 H), 4.00 - 4.17 (m, 3 H), 6.68 (d, J = 3.4 Hz, 1

H), 6.92 (dd, J = 8.7, 1.9 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 98

metansulfonato de ciclopropilo

Se añadió (Bromometil)ciclopropano (3.00 g) a una solución acuosa saturada de sulfito de sodio (27 ml), y la mezcla se calentó a reflujo durante 24 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró a presión reducida. Se añadió etanol al residuo, y la mezcla se agitó a 50°C durante 30 min. La mezcla se filtró, y el filtrado se concentró. Se añadió tolueno al residuo, y la mezcla se concentró nuevamente a presión reducida. El residuo se secó para dar el compuesto del título (2.54 g, rendimiento del 72%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.12 - 0.19 (m, 2 H), 0.36 - 0.45 (m, 2 H), 0.86 - 0.99 (m, 1 H), 2.32 (d, J = 6.8 Hz, 2 H).

Ejemplo de referencia 99

4-metilpentan-1-sulfonato de sodio

Por medio de un método similar al del Ejemplo de referencia 98, se obtuvo el compuesto del título a partir de 1-bromo-4-metilpentano.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.85 (d, J = 6.6 Hz, 6 H), 1.11 - 1.26 (m, 2 H), 1.43 - 1.62 (m, 3 H), 2.31 - 2.41 (m, 2 H).

Ejemplo de referencia 100

1-ciclopropilmetansulfonamida

Ciclopropilmetansulfonato de sodio obtenido en el Ejemplo de referencia 98 (961 mg) se disolvió en un solvente mixto de N,N-dimetilformamida (0.5 ml) y tetrahidrofurano (12 ml), se añadió cloruro de tionilo (1.45 g), y la mezcla se calentó a reflujo durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se filtró, y el filtrado se concentró. El residuo se disolvió en tetrahidrofurano (12 ml), y la solución se añadió amoníaco acuoso al 35% (6 ml) a 0°C. La mezcla de reacción se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró para dar el compuesto del título (579 mg, rendimiento del 70%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.28 - 0.37 (m, 2 H), 0.51 - 0.64 (m, 2 H), 0.92 - 1.08 (m, 1 H), 3.14 - 3.29 (m, 2 H).

Ejemplo de referencia 101

4-metilpentan-1-sulfonamida

Por medio de un método similar al del Ejemplo de referencia 100, se obtuvo el compuesto del título a partir de 4-metilpentan-1-sulfonato de sodio obtenido en el Ejemplo de referencia 99.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.87 (d, J = 6.8 Hz, 6 H), 1.13 - 1.31 (m, 2 H), 1.46 - 1.75 (m, 3 H), 2.87 - 3.00 (m, 2 H).

Ejemplo de referencia 102

(morfolin-4-ilsulfonil)carbamato de bencilo

A una solución de alcohol bencílico (3.00 g) en acetonitrilo (200 ml) se añadió isocianato de clorosulfonilo (4.70 g) con agitación a 0°C, y la mezcla se agitó a 0°C durante 30 min. Se añadió piridina (6.58 g) a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se agregó morfolina (9.67 g) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (9.23 g, rendimiento del 99%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6): 3.15 - 3.21 (m, 4 H), 3.57 - 3.63 (m, 4 H), 5.15 (s, 2 H), 7.31 - 7.45 (m, 5 H), 11.50 (br s, 1 H).

Ejemplo de referencia 103

{[metil(pentil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de

alcohol bencílico, isocianato de clorosulfonilo y N-metilpentan-1-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.8 Hz, 3 H), 1.16 - 1.38 (m, 4 H), 1.48 - 1.61 (m, 2 H), 2.90 (s, 3 H), 3.17 - 3.26 (m, 2 H), 5.17 (s, 2 H), 7.32 - 7.39 (m, 5 H).

Ejemplo de referencia 104

[(butilamino)sulfonil]carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y butan-1-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.4 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.42 - 1.57 (m, 2 H), 2.98 - 3.09 (m, 2 H), 5.12 - 5.17 (m, 1 H), 5.18 (s, 2 H), 7.29 - 7.43 (m, 5 H), 7.50 (br s, 1 H).

Ejemplo de referencia 105

{[(1-propilbutil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y heptan-4-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 6 H), 1.19 - 1.51 (m, 8 H), 3.27 - 3.42 (m, 1 H), 4.73 - 4.91 (m, 1 H), 5.19 (s, 2 H), 7.33 - 7.46 (m, 5 H).

Ejemplo de referencia 106

{[(1-etilpropil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y pentan-3-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.4 Hz, 6 H), 1.35 - 1.59 (m, 4 H), 3.16 - 3.36 (m, 1 H), 4.87 (d, J = 7.3 Hz, 1 H), 5.19 (s, 2 H), 7.30 (br s, 1 H), 7.32 - 7.43 (m, 5 H).

Ejemplo de referencia 107

[(ciclohexilamino)sulfonil]carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y ciclohexilamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 - 1.37 (m, 6 H), 1.48 - 1.74 (m, 2 H), 1.77 - 1.94 (m, 2 H), 2.97 - 3.33 (m, 1 H), 4.97 (d, J = 6.8 Hz, 1 H), 5.20 (s, 2 H), 7.29 (br s, 1 H), 7.37 (s, 5 H).

Ejemplo de referencia 108

{[(ciclopropilmetil)amino]sulfonil}carbamato de bencilo

A una solución de alcohol bencílico (12.08 g) en acetonitrilo (250 ml) se añadió isocianato de clorosulfonilo

(9.75 ml) con agitación a 0°C, y la mezcla se agitó a 0°C durante 30 min. Piridina (17.9 ml) se añadió a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se agregó ciclopropilmetilamina (11.92 g) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 5 h. Se añadió ácido clorhídrico 1 N a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (21.22 g, rendimiento del 67%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.18 (m, 2 H), 0.45 - 0.54 (m, 2 H), 0.82 - 1.04 (m, 1 H), 2.90 (dd, J = 7.2, 5.8 Hz, 2 H), 5.19 (s, 2 H), 5.22 (br s, 1 H), 7.30 (br s, 1 H), 7.33 - 7.44 (m, 5 H).

Ejemplo de referencia 109

morfolin-4-sulfonamida

(Morfolin-4-ilsulfonil)carbamato de bencilo obtenido en el Ejemplo de referencia 102 (9.23 g) se disolvió en un solvente mixto de tetrahidrofurano (100 ml) y etanol (100 ml), se añadió paladio sobre carbón al 10% (923 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 4 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se

cristalizó en hexano-etanol para dar el compuesto del título (4.93 g, rendimiento del 97%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.13 - 3.20 (m, 4 H), 3.77 - 3.82 (m, 4 H), 4.43 (br s, 2 H).

Ejemplo de referencia 110

N-metil-N-pentilsulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[metil(pentil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 103.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.94 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.53 - 1.65 (m, 2 H), 2.80 (s, 3 H), 3.06 - 3.14 (m, 2 H), 4.59 (br s, 2 H).

Ejemplo de referencia 111

N-butilsulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de [(butilamino)sulfonil]carbamato de bencilo obtenido en el Ejemplo de referencia 104.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.3 Hz, 3 H), 1.31 - 1.47 (m, 2 H), 1.50 - 1.63 (m, 2 H), 3.07 - 3.19 (m, 2 H), 4.41 (br s, 1 H), 4.63 (br s, 2 H).

Ejemplo de referencia 112

N-(1-propilbutil)sulfamida

Por medio de un método similar al del Ejemplo de

referencia 109, se obtuvo el compuesto del título a partir de {[(1-propilbutil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 105.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.2 Hz, 6 H), 1.27 - 1.66 (m, 8 H), 3.29 - 3.50 (m, 1 H), 4.15 (br s, 1 H), 4.50 (br s, 2 H).

Ejemplo de referencia 113

N-(1-etilpropil)sulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(1-etilpropil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 106.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.4 Hz, 6 H), 1.26 - 1.78 (m, 4 H), 3.05 - 3.46 (m, 1 H), 4.23 (d, J = 8.1 Hz, 1 H), 4.55 (br s, 2 H).

Ejemplo de referencia 114

N-ciclohexilsulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de [(ciclohexilamino)sulfonil]carbamato de bencilo obtenido en el Ejemplo de referencia 107.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.06 - 1.49 (m, 6 H), 1.49 - 1.83 (m, 2 H), 1.93 - 2.14 (m, 2 H), 3.09 - 3.42 (m, 1 H), 4.51 (br s, 1 H), 4.74 (br s, 2 H).

Ejemplo de referencia 115

N-(ciclopropilmetil)sulfamida

{[(Ciclopropilmetil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 108 (20.30 g) se disolvió en un solvente mixto de tetrahidrofurano (150 ml) y etanol (150 ml), se añadió paladio sobre carbón al 10% (30.39 g), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 6 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (9.37 g, rendimiento del 87%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.17 - 0.31 (m, 2 H), 0.49 - 0.64 (m, 2 H), 0.94 - 1.18 (m, 1 H), 3.00 (dd, J = 7.2, 6.0 Hz, 2 H), 4.40 (br s, 1 H), 4.51 (br s, 2 H).

Ejemplo de referencia 116

N-({[(benciloxi)carbonil]amino}sulfonil)glicinato de etilo

A una solución de alcohol bencílico (2.01 g) en acetonitrilo (40 ml) se añadió isocianato de clorosulfonilo (1.70 ml) con agitación a 0°C, y la mezcla se agitó durante 30 min. Piridina (3.0 ml) se añadió a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se agregaron clorhidrato de glicinetiléster (3.90 g) y N,N-diisopropiletilamina (6.4 ml), y la mezcla se agitó a

temperatura ambiente durante 4 h. ácido clorhídrico 1 N se añadió a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (5.70 g, rendimiento del 96%) en forma de cristales incoloros tetrahidratados.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3 H), 3.96 (d, J = 5.7 Hz, 2 H), 4.21 (q, J = 6.9 Hz, 2 H), 5.21 (s, 2 H), 5.61 (t, J = 5.7 Hz, 1 H), 7.31 - 7.49 (m, 5 H).

Ejemplo de referencia 117

N-(aminosulfonil)glicinato de etilo

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de N-({[(benciloxi)carbonil]amino}sulfonil)glicinato de etilo obtenido en el Ejemplo de referencia 116.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 1.31 (t, J = 7.2 Hz, 3 H), 3.94 (d, J = 5.7 Hz, 2 H), 4.25 (q, J = 7.1 Hz, 2 H), 4.80 (br s, 2 H), 5.09 (br s, 1 H).

Ejemplo de referencia 118

(1,4-dioxa-8-azaespiro[4.5]dec-8-ilsulfonil)carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de

alcohol bencílico, isocianato de clorosulfonilo y 1,4-dioxa-8-azaespiro[4.5]decano.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.66 - 1.86 (m, 4 H), 3.50 (t, J = 5.8 Hz, 4 H), 3.97 (s, 4 H), 5.18 (s, 2 H), 7.17 (br s, 1 H), 7.30 - 7.44 (m, 5 H).

Ejemplo de referencia 119

{[(3-isopropoxipropil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y 3-isopropoxipropan-1-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.15 (d, J = 6.0 Hz, 6 H), 1.70 - 1.91 (m, 2 H), 3.04 - 3.34 (m, 2 H), 3.48 (t, J = 5.6 Hz, 2 H), 3.52 - 3.59 (m, 1 H), 5.20 (s, 2 H), 5.85 (t, J = 5.6 Hz, 1 H), 7.31 (br s, 1 H), 7.34 - 7.42 (m, 5 H).

Ejemplo de referencia 120

1,4-dioxa-8-azaespiro[4.5]decan-8-sulfonamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de (1,4-dioxa-8-azaespiro[4.5]dec-8-ilsulfonil)carbamato de bencilo obtenido en el Ejemplo de referencia 118.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.83 (t, J = 5.9 Hz, 4 H), 3.32 (t, J = 5.8 Hz, 4 H), 3.98 (s, 4 H), 4.38 (br s, 2 H).

Ejemplo de referencia 121

N-(3-isopropoxipropil)sulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(3-isopropoxipropil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 119.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16 (d, J = 6.0 Hz, 6 H), 1.57 - 1.98 (m, 2 H), 3.27 (t, J = 6.1 Hz, 2 H), 3.33 - 3.69 (m, 3 H), 4.54 (br s, 2 H), 5.15 (br s, 1 H).

Ejemplo de referencia 122

{[(ciclohexilmetil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y 1-ciclohexilmetanamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.78 - 0.98 (m, 2 H), 1.04 - 1.32 (m, 3 H), 1.32 - 1.53 (m, 1 H), 1.62 - 1.82 (m, 5 H), 2.70 - 2.94 (m, 2 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.20 (s, 2 H), 7.23 (br s, 1 H), 7.31 - 7.43 (m, 5 H).

Ejemplo de referencia 123

N-(ciclohexilmetil)sulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(ciclohexilmetil)amino]sulfonil}carbamato de bencilo

obtenido en el Ejemplo de referencia 122.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 1.05 (m, 2 H), 1.11 - 1.35 (m, 3 H), 1.42 - 1.55 (m, 1 H), 1.62 - 1.84 (m, 5 H), 2.90 - 3.03 (m, 2 H), 4.30 (br s, 1 H), 4.48 (br s, 2 H).

Ejemplo de referencia 124

{[(3-metilbutil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y 3-metilbutan-1-amina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (d, J = 6.6 Hz, 6 H), 1.30 - 1.47 (m, 2 H), 1.50 - 1.73 (m, 1 H), 2.95 - 3.13 (m, 2 H), 5.11 (br s, 1 H), 5.19 (s, 2 H), 7.38 - 7.56 (m, 6 H).

Ejemplo de referencia 125

N-(3-metilbutil)sulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(3-metilbutil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 124.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, J = 6.6 Hz, 6 H), 1.36 - 1.54 (m, 2 H), 1.59 - 1.75 (m, 1 H), 3.05 - 3.18 (m, 2 H), 4.32 (br s, 3 H).

Ejemplo de referencia 126

[(propilamino)sulfonil]carbamato de bencilo

Por medio de un método similar al del Ejemplo de

referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y propan-1-amina.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.81 (t, J = 7.3 Hz, 3 H), 1.12 - 1.56 (m, 2 H), 2.75 - 2.86 (m, 2 H), 5.14 (s, 2 H), 7.14 - 7.41 (m, 5 H), 7.76 (t, J = 5.9 Hz, 1 H), 11.20 (s, 1 H).

Ejemplo de referencia 127

N-propilsulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de [(propilamino)sulfonil]carbamato de bencilo obtenido en el Ejemplo de referencia 126.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.4 Hz, 3 H), 1.55 - 1.67 (m, 2 H), 3.09 (t, J = 7.2 Hz, 2 H), 4.47 (br s, 3 H).

Ejemplo de referencia 128

(2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 1 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.05 - 1.33 (m, 3 H),

2.47 (s, 3 H), 3.50 (s, 3 H), 3.98 - 4.22 (m, 2 H), 5.54 - 5.73 (m, 1 H), 6.80 (d, J = 2.7 Hz, 1 H), 6.95 - 7.04 (m, 1 H), 7.05 - 7.15 (m, 1 H), 7.16 - 7.30 (m, 3 H), 7.65 - 7.78 (m, 1 H).

Ejemplo de referencia 129

(2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

A una solución de (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 128 (5.00 g) en acetonitrilo (75 ml) se añadió N-clorosuccinimida (2.16 g) a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 2 h, y luego a 50°C durante 2 h. La mezcla de reacción se concentró a presión reducida, y el residuo obtenido se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40 - 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (4.50 g, rendimiento del 81%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.1 Hz, 3 H), 2.47 (s, 3 H), 3.50 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.71 (d, J = 16.2 Hz, 1 H), 6.96 - 7.01 (m, 1 H), 7.10 (s, 1 H), 7.27 (d, J = 16.2 Hz, 1 H), 7.29 - 7.33 (m, 2 H), 7.65 - 7.77 (m, 1 H).

Ejemplo de referencia 130

ácido (2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 129.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.38 (s, 3 H), 3.50 (s, 3 H), 5.44 (d, J = 16.2 Hz, 1 H), 7.04 (d, J = 16.2 Hz, 1 H), 7.08 - 7.13 (m, 1 H), 7.29 - 7.39 (m, 2 H), 7.61 - 7.77 (m, 1 H), 7.91 (s, 1 H), 12.20 (br s, 1 H).

Ejemplo de referencia 131

5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 3-cloro-1H-pirrolo[2,3-b]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.69 (s, 3 H), 7.28 - 7.34 (m, 2 H), 8.06 (dd, J = 8.0, 1.6 Hz, 1 H), 8.41 (dd, J = 4.9, 1.5 Hz, 1 H), 9.62 (s, 1 H).

Ejemplo de referencia 132

(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de

referencia 12, se obtuvo el compuesto del título a partir de 5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 131 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.14 (t, J = 7.1 Hz, 3 H), 2.39 (s, 3 H), 3.52 (s, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.41 (dd, J = 7.9, 4.7 Hz, 1 H), 8.09 (s, 1 H), 8.18 (dd, J = 8.0, 1.6 Hz, 1 H), 8.39 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo de referencia 133

ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 132.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.52 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 7.04 (d, J = 16.2 Hz, 1 H), 7.41 (dd, J = 8.1, 4.7 Hz, 1 H), 8.08 (s, 1 H), 8.17 (dd, J = 7.9, 1.5 Hz, 1 H), 8.39 (dd, J = 4.7, 1.5 Hz, 1 H), 12.22 (br s, 1 H).

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Ejemplo de referencia 134

1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 3-metil-1H-pirrolo[2,3-b]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.39 (d, J = 1.1 Hz, 3 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.98 - 7.11 (m, 1 H), 7.21 (dd, J = 7.9, 4.7 Hz, 1 H), 7.97 (dd, J = 7.8, 1.6 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 9.58 (s, 1 H).

Ejemplo de referencia 135

(2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 134 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 3 H), 2.39 (d, J = 1.1 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.76 (d, J = 16.4 Hz, 1 H), 6.96 (d, J = 1.1 Hz, 1 H), 7.19 (dd, J = 7.8, 4.8 Hz, 1 H), 7.30 (d, J = 16.2 Hz, 1 H), 7.96 (dd, J = 7.8, 1.6 Hz, 1 H), 8.33 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo de referencia 136

ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 135.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 6 H), 3.47 (s, 3 H), 5.54 (d, J = 16.2 Hz, 1 H), 7.01 (d, J = 16.4 Hz, 1 H), 7.26 (dd, J = 7.9, 4.7 Hz, 1 H), 7.46 (s, 1 H), 8.13 (dd, J = 7.9, 1.5 Hz, 1 H), 8.26 (dd, J = 4.7, 1.5 Hz, 1 H), 12.19 (br s, 1 H).

Ejemplo de referencia 137

5-(1H-indol-3-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una mezcla de ácido [1-(ter-butoxicarbonil)-1H-indol-3-il]borónico (2.01 g), 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (2.44 g), una solución acuosa 2.0 M de carbonato de sodio (8.0 ml) y 1.2-dimetoxietano (16 ml) se añadió tetraquis(trifenilfosfina)paladio (0) (0.45 g), y la mezcla de reacción se calentó a reflujo bajo una atmósfera de nitrógeno durante 12 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se

lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 95:5 - 80:20, v/v) para dar una mezcla (2.86 g), en forma de un sólido marrón, de 3-(4-formil-1,3-dimetil-1H-pirazol-5-il)-1H-indol-1-carboxilato de ter-butilo y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído, y el compuesto del título (0.44 g, rendimiento del 24%) en forma de un sólido de color marrón pálido.

La mezcla obtenida (2.86 g) de 3-(4-formil-1,3-dimetil-1H-pirazol-5-il)-1H-indol-1-carboxilato de ter-butilo y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído se disolvió en una solución de cloruro de hidrógeno 4 M-acetato de etilo (45 ml), y la mezcla se agitó a temperatura ambiente durante 3.5 h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50 - 0:100, v/v) para dar el compuesto del título (1.01 g, rendimiento del 54%) en forma de un sólido de color marrón pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 3.76 (s, 3 H), 7.03 - 7.73 (m, 5 H), 8.65 (br s, 1 H), 9.66 (s, 1 H).

Ejemplo de referencia 138

1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-carbaldehído

A una solución de 5-(1H-indol-3-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 137 (1.42 g) en N,N-dimetilformamida (30 ml) se añadió hidruro de sodio al 60% (en aceite, 285 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Se agregó yoduro de metilo (0.58 ml) a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se neutralizó con ácido clorhídrico 1 N, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10 - 65:35, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.15 g, rendimiento del 77%) en forma de cristales de color marrón pálido.

^{1}H-NMR (300 MHz, $CDCl_3$)δ: 2.56 (s, 3 H), 3.76 (s, 3 H), 3.92 (s, 3 H), 7.07 - 7.57 (m, 5 H), 9.65 (s, 1 H).

Ejemplo de referencia 139

(2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de

referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 138 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.2 Hz, 3 H), 2.49 (s, 3 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 4.15 (q, J = 7.0 Hz, 2 H), 6.04 (d, J = 16.2 Hz, 1 H), 7.07 - 7.66 (m, 6 H).

Ejemplo de referencia 140

ácido (2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 139.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.36 (s, 3 H), 3.63 (s, 3 H), 3.92 (s, 3 H), 5.88 (d, J = 16.2 Hz, 1 H), 7.05 - 7.16 (m, 1 H), 7.20 - 7.36 (m, 3 H), 7.59 (d, J = 8.9 Hz, 1 H), 7.67 (s, 1 H), 11.91 (br s, 1 H).

Ejemplo de referencia 141 1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 39, se obtuvo el compuesto del título a partir de 3-metil-1H-indazol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 2.67 (s, 3

H), 3.71 (s, 3 H), 6.87 - 7.88 (m, 4 H), 9.58 (s, 1 H).

Ejemplo de referencia 142

(2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 141 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 2.67 (s, 3 H), 3.57 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.72 (d, J = 16.4 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 1 H), 7.21 - 7.35 (m, 2 H), 7.37 - 7.48 (m, 1 H), 7.77 (d, J = 7.9 Hz, 1 H).

Ejemplo de referencia 143

ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 142.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.39 (s, 3 H), 2.62 (s, 3 H), 3.51 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 1 H), 7.27 - 7.37 (m, 1 H), 7.44 - 7.57 (m, 1 H), 7.93 (d, J = 8.1 Hz, 1 H), 12.17

(br s, 1 H).

Ejemplo de referencia 144

(2E)-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

A una solución de 1H-pirrolo[2,3-b]piridin-6-ol (5.27 g) en acetona (300 ml) se añadieron ácido dimetilsulfúrico (4.10 ml) y carbonato de potasio (5.50 g), y la mezcla se agitó a temperatura ambiente durante 13 h. La mezcla de reacción se filtró a través de celite®, y el filtrado se concentró. El residuo obtenido se disolvió en N,N-dimetilformamida (80 ml), se añadieron 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (7.47 g) e hidruro de sodio al 60% (en aceite, 2.36 g) con agitación, y la mezcla se agitó a 80°C durante 15 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10 - 75:25, v/v) para dar un sólido marrón (7.53 g).

A una solución del sólido marrón obtenido (7.53 g) en etanol (60 ml) se añadieron (dietoxifosforil)acetato de etilo (9.37 g) y etóxido de sodio (3.79 g), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la

mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10 - 65:35, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.36 g, rendimiento del 14%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.64 (s, 3 H), 3.83 (s, 3 H), 4.15 (q, J = 7.1 Hz, 2 H), 5.77 (d, J = 16.2 Hz, 1 H), 6.54 - 6.76 (m, 2 H), 6.98 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 16.2 Hz, 1 H), 7.86 (d, J = 8.5 Hz, 1 H).

Ejemplo de referencia 145

ácido (2E)-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 144.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.56 (s, 3 H), 3.74 (s, 3 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.50 - 6.84 (m, 2 H), 7.12 (d, J = 16.2 Hz, 1 H), 7.43 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 12.15 (br s, 1 H).

Ejemplo de referencia 146

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de ter-butilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 y (dietoxifosforil)acetato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 9 H), 2.45 (s, 3 H), 3.49 (s, 3 H), 5.61 (d, J = 16.4 Hz, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.17 (d, J = 16.2 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 147

trans-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]ciclopropanecarboxilato de ter-butilo

A una solución de yoduro de trimetilsulfoxonio (4.71 g) en sulfóxido de dimetilo (20 ml) se añadió hidruro de sodio al 60% (en aceite, 856 mg) con agitación a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 1.5 h. Una solución de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de ter-butilo obtenido en el Ejemplo de referencia 146 (3.97 g) en sulfóxido de dimetilo (60 ml) se añadió a esta mezcla de reacción con agitación, y la mezcla se agitó a temperatura

ambiente durante 48 h. Una solución acuosa saturada de cloruro de amonio y agua se añadieron a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró, y el filtrado se concentró. El residuo obtenido se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 100:0 - 60:40, v/v) para dar el compuesto del título (2.21 g, rendimiento del 54%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.36 - 0.65 (m, 1 H), 0.99 - 1.22 (m, 2 H), 1.26 (s, 5 H), 1.33 (s, 4 H), 1.86 - 2.00 (m, 1 H), 2.32 (s, 3 H), 3.47 (s, 1.5 H), 3.49 (s, 1.5 H), 6.53 - 6.72 (m, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.07 (dd, J = 11.0, 3.4 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 148

ácido trans-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]ciclopropanecarboxílico

Trans-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]ciclopropancarboxilato de ter-butilo obtenido en el Ejemplo de referencia 147 (2.15 g) se disolvió en una solución de cloruro de hidrógeno 4 M-acetato de etilo (10 ml), y la mezcla se agitó a temperatura ambiente durante 3 h, y luego a 50°C durante 12 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se diluyó con acetato

de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró, y el filtrado se concentró. El residuo obtenido se cristalizó en hexano-acetato de etilo para dar el compuesto del título (0.52 g, rendimiento del 43%) en forma de cristales incoloros (un solvato con 0.05 moles de acetato de etilo/mol).

^{1}H-NMR (300 MHz, DMSO-d_6): 0.40 - 0.60 (m, 1 H), 0.71 - 0.87 (m, 0.5 H), 0.88 - 1.03 (m, 0.5 H), 1.11 - 1.24 (m, 0.5 H), 1.25 - 1.38 (m, 0.5 H), 1.80 - 1.97 (m, 1 H), 2.22 (s, 3 H), 3.38 (s, 1.5 H), 3.38 (s, 1.5 H), 6.76 (dd, J = 2.3, 1.1 Hz, 1 H), 7.04 (t, J = 9.3 Hz, 1 H), 7.13 - 7.25 (m, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.74 (t, J = 1.9 Hz, 1 H), 12.09 (br s, 1 H).

Ejemplo de referencia 149

5-ciclopropil-2-metil-2,4-dihidro-3H-pirazol-3-ona

A una solución de 3-ciclopropil-3-oxopropionoato de metilo (39.8 g) en tolueno (150 ml) se añadió metilhidracina (13.0 g), y la mezcla se calentó a reflujo durante 4 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró a presión reducida. El residuo se cristalizó en éter dietílico para dar el compuesto del título (37.9 g, rendimiento del 98%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.74 - 0.82 (m, 2 H), 0.92 - 1.01 (m, 2 H), 1.71 - 1.83 (m, 1 H), 3.05 (s, 2 H), 3.26 (s, 3 H).

Ejemplo de referencia 150

5-cloro-3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído

Cloruro de fosforilo (165 g) se añadió gota a gota durante 25 min a N,N-dimetilformamida (19.0 g) enfriada a 0°C. Se agregó 5-ciclopropil-2-metil-2,4-dihidro-3H-pirazol-3-ona obtenida en el Ejemplo de referencia 149 (29.7 g) a esta mezcla de reacción, y la mezcla se agitó con calentamiento a 100°C durante 2 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se vertió en agua helada, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 85:15, v/v) para dar el compuesto del título (39.1 g, rendimiento del 98%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 1.03 (m, 4 H), 2.39 - 2.51 (m, 1 H), 3.77 (s, 3 H), 9.91 (s, 1 H).

Ejemplo de referencia 151

[(etilamino)sulfonil]carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y etanamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.13 - 1.20 (m, 3 H),

3.05 - 3.16 (m, 2 H), 5.17 - 5.21 (m, 2 H), 7.33 - 7.39 (m, 5 H), 7.64 (br s, 1 H).

Ejemplo de referencia 152

N-etilsulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de [(etilamino)sulfonil]carbamato de bencilo obtenido en el Ejemplo de referencia 151.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.03 - 1.10 (m, 3 H), 2.84 - 2.95 (m, 2 H), 6.37 - 6.49 (m, 3 H).

Ejemplo de referencia 153

3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-fluoro-1H-indol y 5-cloro-3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 150.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 - 1.11 (m, 4 H), 2.50 - 2.61 (m, 1 H), 3.53 (s, 3 H), 6.77 (d, J = 3.4 Hz, 1 H), 7.00 - 7.04 (m, 2 H), 7.22 (d, J = 3.2 Hz, 1 H), 7.33 - 7.38 (m, 1 H), 9.57 (s, 1 H).

Ejemplo de referencia 154

(2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de

referencia 12, se obtuvo el compuesto del título a partir de 3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 153 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 - 1.07 (m, 4 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.94 - 2.06 (m, 1 H), 3.47 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.79 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.88 - 7.03 (m, 2 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.33 - 7.43 (m, 2 H).

Ejemplo de referencia 155

ácido (2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 154.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 - 1.02 (m, 4 H), 1.99 - 2.12 (m, 1 H), 3.46 (s, 3 H), 5.49 (d, J = 16.3 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.99 - 7.11 (m, 2 H), 7.15 - 7.22 (m, 1 H), 7.52 (dd, J = 9.5, 1.9 Hz, 1 H), 7.67 (d, J = 3.0 Hz, 1 H), 12.15 (br s, 1 H).

Ejemplo de referencia 156

(2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

A una solución de (2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 27 (31.9 g) en diclorometano (150 ml) se añadió gota a gota tribromuro de boro (solución de diclorometano 1 M, 154 ml) con agitación a -78°C, y la mezcla se agitó a -78°C durante 3 h. La mezcla de reacción se neutralizó con etanol (100 ml), y se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (18.9 g, rendimiento del 76%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.41 (s, 3 H), 3.48 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.32 (d, J = 2.1 Hz, 1 H), 6.69 - 6.73 (m, 1 H), 6.83 (dd, J = 8.6, 2.2 Hz, 1 H), 6.94 (d, J = 3.2 Hz, 1 H), 7.19 (s, 1 H), 7.30 (d, J = 16.4 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H).

Ejemplo de referencia 157

(2E)-3-{1,3-dimetil-5-[6-(2-oxopropoxi)-1H-indol-1-il]-1H-pirazol-4-il}acrilato de etilo

A una solución de (2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 156 (2.02 g) en acetona (10 ml) se añadieron cloroacetona (689 mg), carbonato de potasio (1.28 g) y yoduro de sodio (1.28 g), y la mezcla se agitó a 50°C durante 16 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (2.26 g, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.18 - 1.25 (m, 3 H), 2.27 (s, 3 H), 2.47 (s, 3 H), 3.48 - 3.52 (m, 3 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.49 (s, 2 H), 5.55 - 5.68 (m, 1 H), 6.42 (d, J = 1.7 Hz, 1 H), 6.73 (d, J = 3.2 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 7.00 (d, J = 3.4 Hz, 1 H), 7.25 - 7.34 (m, 1 H), 7.58 - 7.64 (m, 1 H).

Ejemplo de referencia 158

(2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

A una solución de (2E)-3-[5-(6-hidroxi-1H-indol-1-

il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 156 (1.08 g) en N,N-dimetilformamida (5 ml) se añadieron éter bromoetilmetílico (553 mg), carbonato de potasio (688 mg) y yoduro de sodio (995 mg), y la mezcla se agitó a 80°C durante 16 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.26 g, rendimiento del 99%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16 - 1.25 (m, 3 H), 2.46 (s, 3 H), 3.43 (s, 3 H), 3.48 - 3.52 (m, 3 H), 3.70 - 3.77 (m, 2 H), 4.03 - 4.17 (m, 4 H), 5.55 - 5.68 (m, 1 H), 6.41 - 6.48 (m, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.89 - 6.98 (m, 2 H), 7.28 - 7.35 (m, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 159

ácido (2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de

referencia 158.

^{1}H-NMR (300 MHz DMSO-d_6): 2.38 (s, 3 H), 3.27 (s, 3 H), 3.49 (s, 3 H), 3.61 (t, J = 4.5 Hz, 2 H), 3.92 - 4.11 (m, 2 H), 5.38 - 5.48 (m, 1 H), 6.50 (d, J = 1.7 Hz, 1 H), 6.76 (d, J = 3.2 Hz, 1 H), 6.84 (dd, J = 8.7, 2.1 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.39 (d, J = 3.4 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 12.15 (br s, 1 H).

Ejemplo de referencia 160

(2E)-3-{5-[6-(ciclopropilmetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 157, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 156 y bromometilciclopropano.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.29 - 0.36 (m, 2 H), 0.58 - 0.66 (m, 2 H), 1.17 - 1.29 (m, 4 H), 2.47 (s, 3 H), 3.49 (s, 3 H), 3.73 (d, J = 6.8 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.41 (d, J = 2.1 Hz, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.31 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 161

ácido (2E)-3-{5-[6-(ciclopropilmetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-{5-[6-(ciclopropilmetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 160.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.24 - 0.32 (m, 2 H), 0.47 - 0.56 (m, 2 H), 1.12 - 1.21 (m, 1 H), 2.38 (s, 3 H), 3.48 (s, 3 H), 3.66 - 3.80 (m, 2 H), 5.42 (d, J = 16.2 Hz, 1 H), 6.45 (d, J = 1.7 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.84 (dd, J = 8.7, 2.3 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.37 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 12.13 (br s, 1 H).

Ejemplo de referencia 162

(2E)-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

A una solución de (2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 156 (1.54 g) en tetrahidrofurano (20 ml) se añadieron isopropanol (426 mg) y tributilfosfina (1.91 g), 1,1'-azodicarbonildipiperidina (2.38 g) se añadió con agitación, y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión

reducida, éter diisopropílico se añadió al residuo, y el material insoluble se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el compuesto del título (1.66 g, rendimiento del 96%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.19 - 1.24 (m, 3 H), 1.29 (dd, J = 6.0, 3.6 Hz, 6 H), 2.46 (s, 3 H), 3.51 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.42 - 4.52 (m, 1 H), 5.66 (d, J = 16.2 Hz, 1 H), 6.46 (d, J = 2.1 Hz, 1 H), 6.68 - 6.71 (m, 1 H), 6.86 (dd, J = 8.6, 2.2 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.32 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H).

Ejemplo de referencia 163

ácido (2E)-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 162.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.20 (dd, J = 9.5, 5.9 Hz, 6 H), 2.38 (s, 3 H), 3.49 (s, 3 H), 4.46 - 4.56 (m, 1 H), 5.41 - 5.49 (m, 1 H), 6.47 (d, J = 1.7 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.81 (dd, J = 8.7, 2.1 Hz, 1 H), 7.08 (d, J = 16.2 Hz, 1 H), 7.40 (d, J = 3.2 Hz, 1 H), 7.57 (d, J = 8.5 Hz,

1 H), 12.19 (br s, 1 H).

Ejemplo de referencia 164

{[(aliloxi)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y clorhidrato de O-alilhidroxilamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.47 (d, J = 6.4 Hz, 2 H), 5.22 (s, 2 H), 5.27 - 5.39 (m, 2 H), 5.85 - 6.00 (m, 1 H), 7.31 - 7.42 (m, 5 H), 7.50 (br s, 1 H), 7.83 (s, 1 H).

Ejemplo de referencia 165

N-propoxisulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(aliloxi)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 164.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.4 Hz, 3 H), 1.60 - 1.74 (m, 2 H), 3.96 (t, J = 6.8 Hz, 2 H), 5.17 (br s, 2 H).

Ejemplo de referencia 166

(2E)-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 162, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-

il]acrilato de etilo obtenido en el Ejemplo de referencia 156 y etanol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.1 Hz, 3 H), 1.39 (t, J = 7.0 Hz, 3 H), 2.46 (s, 3 H), 3.50 (s, 3 H), 3.97 (q, J = 7.0 Hz, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 5.64 (d, J = 16.4 Hz, 1 H), 6.43 (d, J = 1.7 Hz, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.87 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.4 Hz, 1 H), 7.32 (d, J = 16.2 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 167

ácido (2E)-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 166.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.28 (t, J = 7.0 Hz, 3 H), 2.38 (s, 3 H), 3.49 (s, 3 H), 3.84 - 4.02 (m, 2 H), 5.38 - 5.47 (m, 1 H), 6.46 (s, 1 H), 6.75 (d, J = 3.2 Hz, 1 H), 6.82 (dd, J = 8.7, 2.1 Hz, 1 H), 7.09 (d, J = 16.2 Hz, 1 H), 7.38 (d, J = 3.2 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 12.14 (br s, 1 H).

Ejemplo de referencia 168

(2E)-3-{5-[6-(2-ter-butoxi-1-metil-2-oxoetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

Por medio de un método similar al del Ejemplo de

referencia 158, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 156 y 2-bromopropionoato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 6.6 Hz, 3 H), 1.35 (d, J = 3.8 Hz, 9 H), 1.53 - 1.60 (m, 3 H), 2.45 (d, J = 3.4 Hz, 3 H), 3.44 - 3.50 (m, 3 H), 4.07 - 4.17 (m, 2 H), 4.49 - 4.59 (m, 1 H), 5.61 (dd, J = 16.3, 8.0 Hz, 1 H), 6.40 (dd, J = 8.5, 2.1 Hz, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.84 - 6.92 (m, 1 H), 6.97 (d, J = 3.4 Hz, 1 H), 7.24 - 7.35 (m, 1 H), 7.57 (d, J = 8.3 Hz, 1 H).

Ejemplo de referencia 169

ácido 2-[(1-{4-[(1E)-3-etoxi-3-oxoprop-1-en-1-il]-1,3-dimetil-1H-pirazol-5-il}-1H-indol-6-il)oxi]propanoico

Una solución de (2E)-3-{5-[6-(2-ter-butoxi-1-metil-2-oxoetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 168 (2.51 g) en ácido trifluoroacético (20 ml) se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (1.81 g, rendimiento del 83%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.13 (t, J = 7.1 Hz, 3 H), 1.44 (dd, J = 6.8, 1.5 Hz, 3 H), 2.39 (s, 3 H), 3.46 (d, J = 7.9 Hz, 3 H), 3.99 - 4.09 (m, 2 H), 4.71 - 4.86 (m, 1 H), 5.49 (dd, J = 20.5, 16.2 Hz, 1 H), 6.45 (dd, J = 8.9, 1.8 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.83 (dd, J = 8.6, 2.2 Hz, 1 H), 7.15 (dd, J = 16.3, 6.7 Hz, 1 H), 7.40 (d, J = 3.4 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 12.95 (br s, 1 H).

Ejemplo de referencia 170

(2E)-3-{5-[6-(2-hidroxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

A una solución de ácido 2-[(1-{4-[(1E)-3-etoxi-3-oxoprop-1-en-1-il]-1,3-dimetil-1H-pirazol-5-il}-1H-indol-6-il)oxi]propanoico obtenida en el Ejemplo de referencia 169 (201 mg) y N,N-dimetilformamida (0.1 ml) en tetrahidrofurano (5 ml) se añadió gota a gota cloruro de oxalilo (96.3 mg), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, y tetrahidrofurano (5 ml) y agua (0.5 ml) se añadieron al residuo. Se añadió borohidruro de sodio (28.7 mg), y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de

etilo 35:65, v/v) para dar el compuesto del título (97.3 mg, rendimiento del 50%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.18 - 1.26 (m, 6 H), 2.47 (s, 3 H), 3.52 (s, 3 H), 3.63 - 3.76 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.38 - 4.47 (m, 1 H), 5.66 (dd, J = 16.3, 1.5 Hz, 1 H), 6.52 (d, J = 1.9 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 6.99 (d, J = 3.4 Hz, 1 H), 7.31 (dd, J = 16.3, 2.7 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 171

(2E)-3-{5-[6-(2-metoxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo

A una solución de (2E)-3-{5-[6-(2-hidroxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 170 (656 mg) en N,N-dimetilformamida (2 ml) se añadió hidruro de sodio al 60% (en aceite, 102 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Se agregó yoduro de metilo (0.16 ml) a esta mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 48 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 65:35, v/v) para dar el compuesto del título (496 mg, rendimiento del 73%) en

forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 - 1.30 (m, 6 H), 2.46 (s, 3 H), 3.38 (d, J = 1.5 Hz, 3 H), 3.42 - 3.59 (m, 5 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.41 - 4.52 (m, 1 H), 5.57 - 5.69 (m, 1 H), 6.50 - 6.54 (m, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.95 - 6.99 (m, 1 H), 7.28 - 7.36 (m, 1 H), 7.53 - 7.60 (m, 1 H).

Ejemplo de referencia 172

ácido (2E)-3-{5-[6-(2-metoxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-{5-[6-(2-metoxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 171.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.15 (dd, J = 11.1, 6.2 Hz, 3 H), 2.38 (s, 3 H), 3.24 (d, J = 7.0 Hz, 3 H), 3.37 - 3.46 (m, 2 H), 3.49 (s, 3 H), 4.47 - 4.57 (m, 1 H), 5.44 (dd, J = 16.2, 4.3 Hz, 1 H), 6.53 (s, 1 H), 6.75 (d, J = 3.2 Hz, 1 H), 6.83 (dd, J = 8.7, 2.1 Hz, 1 H), 7.05 - 7.13 (m, 1 H), 7.41 (dd, J = 3.4, 2.1 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 12.17 (br s, 1 H).

Ejemplo de referencia 173

1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-metil-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3 H), 2.55 (s, 3 H), 3.57 (s, 3 H), 6.72 (d, J = 3.4 Hz, 1 H), 6.98 - 7.02 (m, 1 H), 7.08 - 7.13 (m, 1 H), 7.15 (d, J = 3.0 Hz, 1 H), 7.49 (s, 1 H), 9.51 (s, 1 H).

Ejemplo de referencia 174

(2E)-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 173 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.44 - 2.49 (m, 6 H), 3.49 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.89 (d, J = 8.3 Hz, 1 H), 7.03 - 7.09 (m, 2 H), 7.30 (d, J = 16.4 Hz, 1 H), 7.50 (s, 1 H).

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Ejemplo de referencia 175

ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 174.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.35 - 2.42 (m, 6 H), 3.47 (s, 3 H), 5.41 (d, J = 16.4 Hz, 1 H), 6.76 (d, J = 3.2 Hz, 1 H), 6.90 (1 H, d, J = 8.3 Hz), 7.01 - 7.10 (m, 2 H), 7.47 - 7.52 (m, 2 H), 12.15 (br s, 1 H).

Ejemplo de referencia 176

(piperidin-1-ilsulfonil)carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y piperidina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 - 1.69 (m, 6 H), 3.27 - 3.35 (m, 4 H), 5.17 (s, 2 H), 7.37 (s, 5 H).

Ejemplo de referencia 177

piperidin-1-sulfonamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de (piperidin-1-ilsulfonil)carbamato de bencilo obtenido en el Ejemplo de referencia 176.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.47 - 1.58 (m, 2 H),

1.63 - 1.73 (m, 4 H), 3.11 - 3.16 (m, 4 H), 4.79 (br s, 2 H).

Ejemplo de referencia 178

(E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

A una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (3.46 g) en N,N-dimetilformamida (73 ml) se añadió hidruro de sodio al 60% (en aceite, 876 mg) con agitación a 0°C, y la mezcla se agitó a 0°C durante 1 h. 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (2.0 g) se añadió a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa saturada de cloruro de amonio (30 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 55:45, v/v) para dar un aceite incoloro. Se añadió ácido trifluoroacético (15 ml) a este aceite incoloro, y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el

residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (2.52 g, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3 H), 3.53 (s, 3 H), 4.48 (s, 2 H), 5.88 (d, J = 15.5 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.09 - 7.17 (m, 2 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 179

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

A una solución de (E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 178 (2.18 g) en un solvente mixto de tetrahidrofurano (31 ml) y etanol (31 ml) se añadió paladio sobre carbón al 10% (218 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 5 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.65 g, rendimiento del 75%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.71 - 2.82 (m, 2 H), 2.87 - 2.97 (m, 2 H), 3.47 (s, 3 H), 4.43 (br s, 2 H), 6.70 (d, J = 2.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H),

7.11 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 180

(E)-2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 24 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.44 (s, 3 H), 3.55 (s, 3 H), 4.46 (br s, 2 H), 5.87 (d, J = 15.6 Hz, 1 H), 6.80 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.15 (d, J = 15.6 Hz, 1 H), 7.22 (dd, J = 8.5, 1.7 Hz, 1 H), 7.63 (d, J = 8.5 Hz, 1 H).

Ejemplo de referencia 181

2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 180.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.22 (s, 3 H), 2.44 - 2.56 (m, 1 H), 2.60 - 2.72 (m, 1 H), 2.75 - 2.92 (m, 2 H), 3.37 (s, 3 H), 6.77 (s, 2 H), 6.80 - 6.83 (m, 1 H), 7.04 -

7.07 (m, 1 H), 7.20 (dd, J = 8.5, 1.9 Hz, 1 H), 7.57 (d, J = 3.4 Hz, 1 H), 7.71 (d, J = 8.5 Hz, 1 H).

Ejemplo de referencia 182

5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una solución de 5-cloro-1H-pirrolo[2,3-b]piridina (2.91 g) en N,N-dimetilformamida (25 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 970 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (2.93 g) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 80°C durante 30 min. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v) para dar el compuesto del título (1.55 g, rendimiento del 30%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.67 (s, 3 H), 6.74 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H), 9.60 (s, 1 H).

Ejemplo de referencia 183

(E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 182 y {[(difenilfosforil)metil]sulfonil}carbamato de terbutilo.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.36 (s, 3 H), 3.49 (s, 3 H), 6.09 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 15.9 Hz, 1 H), 6.85 - 6.91 (m, 3 H), 7.81 (d, J = 3.4 Hz, 1 H), 8.28 - 8.33 (m, 2 H).

Ejemplo de referencia 184

2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 183.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.21 (s, 3 H), 2.53 - 2.60 (m, 2 H), 2.86 - 2.94 (m, 2 H), 3.41 (s, 3 H), 6.74 (s, 2 H), 6.80 (d, J = 3.8 Hz, 1 H), 7.80 (d, J = 3.8 Hz, 1 H), 8.27 (q, J = 2.3 Hz, 2 H).

Ejemplo de referencia 185

(E)-2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 20 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 3.54 (s, 3 H), 4.49 (s, 2 H), 5.87 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.2 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.96 - 7.04 (m, 1 H), 7.10 - 7.18 (m, 2 H), 7.36 (dd, J = 9.1, 2.4 Hz, 1 H).

Ejemplo de referencia 186

2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 185.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.22 (s, 3 H), 2.55 - 2.71 (m, 2 H), 2.75 - 2.94 (m, 2 H), 3.37 (s, 3 H), 6.74 - 6.79 (m, 3 H), 7.01 - 7.07 (m, 2 H), 7.45 - 7.51 (m, 1 H), 7.60 (d, J = 3.4 Hz, 1 H).

Ejemplo de referencia 187

(E)-2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 11 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3 H), 3.58 (s, 3 H), 4.71 (s, 2 H), 6.07 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.12 (d, J = 15.6 Hz, 1 H), 7.17 - 7.23 (m, 2 H), 8.03 (dd, J = 7.9, 1.5 Hz, 1 H), 8.33 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo de referencia 188

2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 187.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3 H), 2.73 - 3.24 (m, 4 H), 3.46 (s, 3 H), 4.99 (s, 2 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.22 (dd, J = 7.9, 4.9 Hz, 1 H), 8.04 (dd, J = 7.8, 1.6 Hz, 1 H), 8.31 (dd, J = 4.7,

1.5 Hz, 1 H).

Ejemplo de referencia 189

(E)-2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 58 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.48 (s, 3 H), 3.71 (s, 3 H), 6.08 (d, J = 15.9 Hz, 1 H), 6.49 (d, J = 2.3 Hz, 1 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.81 - 6.89 (m, 4 H), 7.36 (d, J = 3.4 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 190

2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 189.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3 H), 2.71 - 2.84 (m, 2 H), 2.86 - 2.97 (m, 2 H), 3.49 (s, 3 H), 3.77 (s, 3 H), 4.52 (s, 2 H), 6.43 (d, J = 2.1 Hz, 1 H), 6.64 - 6.67 (m, 1 H), 6.85 (dd, J = 8.7, 2.3 Hz, 1 H), 6.95 (d, J = 3.2 Hz, 1 H), 7.54 (d, J = 8.7 Hz, 1 H).

Ejemplo de referencia 191

5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-carbaldehído

A una solución de 5-cloro-1H-pirrolo[2,3-b]piridina (1.22 g) en N,N-dimetilformamida (25 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 340 mg) con agitación, y la mezcla se agitó a 0°C durante 20 min. 5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-carbaldehído (1.51 g) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 100°C durante 3.5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 80:20, v/v) para dar el compuesto del título (1.71 g, rendimiento del 73%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.81 (s, 3 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 9.87 (s, 1 H).

Ejemplo de referencia 192

(E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etilensulfonamida

A una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (2.46 g) en N,N-dimetilformamida (50 ml) se añadió hidruro de sodio al 60% (en aceite, 645 mg) con agitación a 0°C, y la mezcla se agitó a 0°C durante 1 h. 5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 191 (1.71 g) se añadió a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa saturada de cloruro de amonio (50 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, ácido trifluoroacético (52 ml) se añadió al residuo, y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 65:35, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto

del título (1.51 g, rendimiento del 72%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.66 (s, 3 H), 5.86 (d, J = 15.8 Hz, 1 H), 6.89 - 7.08 (m, 4 H), 7.91 (d, J = 3.8 Hz, 1 H), 8.32 - 8.38 (m, 2 H).

Ejemplo de referencia 193

2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etansulfonamida

A una solución de (E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 192 (1.36 g) en un solvente mixto de tetrahidrofurano (30 ml) y etanol (30 ml) se añadió paladio sobre carbón al 10% (136 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 8 h. El catalizador se eliminó por filtración, y el filtrado se concentró. A una solución de este residuo en un solvente mixto de tetrahidrofurano (30 ml) y etanol (30 ml) se añadió paladio sobre carbón al 10% (136 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 24 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.22 g, rendimiento del 90%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.67 - 2.75 (m, 2 H),

2.84 - 2.96 (m, 2 H), 3.61 (s, 3 H), 6.82 - 6.89 (m, 3 H), 7.92 (d, J = 3.8 Hz, 1 H), 8.32 (s, 2 H).

Ejemplo de referencia 194

(E)-2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 41 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.46 (s, 3 H), 3.55 (s, 3 H), 4.43 (s, 2 H), 5.88 (d, J = 15.6 Hz,1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.14 (d, J = 15.6 Hz, 1 H), 7.23 - 7.27 (m, 2 H), 7.50 (d, J = 8.5 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H).

Ejemplo de referencia 195

2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etilensulfonamida obtenida en el Ejemplo de referencia 194.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.24 (s, 3 H), 2.42 - 2.54 (m, 1 H), 2.60 - 2.73 (m, 1 H), 2.77 - 2.95 (m, 2 H), 3.38 (s, 3 H), 6.76 (s, 2 H), 6.94 (d, J = 3.0 Hz, 1 H), 7.32

(s, 1 H), 7.49 (d, J = 8.3 Hz, 1 H), 7.80 (d, J = 3.4 Hz, 1 H), 7.93 (d, J = 8.3 Hz, 1 H).

Ejemplo de referencia 196

sulfamato de butilo

Se añadió ácido fórmico (930 mg) a isocianato de clorosulfonilo (2.86 g) enfriado a 0°C en un baño helado, y la mezcla se agitó vigorosamente durante 5 min. Se agregó acetonitrilo (10 ml) a la mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h, y luego a temperatura ambiente durante 7 h. Una solución de butanol (1.00 g) y piridina (1.60 g) en acetonitrilo (9 ml) se añadió a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 24 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró para dar el compuesto del título (2.09 g, rendimiento del 99%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 - 0.99 (m, 3 H), 1.38 - 1.52 (m, 2 H), 1.67 - 1.79 (m, 2 H), 4.22 (t, J = 6.5 Hz, 2 H), 4.98 (br s, 2 H).

Ejemplo de referencia 197

N-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}sulfamida

A una solución de 5-(5-cloro-1H-indol-1-il)-1,3-

dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 37 (321 mg) en etanol (5.8 ml) se añadió sulfamida (946 mg), y la mezcla se calentó a reflujo durante 24 h. Se añadió borohidruro de sodio (48.8 mg) a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 35:65, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (100 mg, rendimiento del 24%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 3.51 (s, 3 H), 3.85 - 4.00 (m, 2 H), 4.04 - 4.15 (m, 3 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.15 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 198

5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-cloro-6-metoxi-1H-indol y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3 H), 3.59 (s, 3 H), 3.85 (s, 3 H), 6.55 (s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.70 (s, 1 H), 9.55 (s, 1 H).

Ejemplo de referencia 199

(E)-2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 198 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3 H), 3.55 (s, 3 H), 3.83 (s, 3 H), 4.49 (s, 2 H), 5.92 (d, J = 15.6 Hz, 1 H), 6.44 (s, 1 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.98 (d, J = 3.2 Hz, 1 H), 7.17 (d, J = 15.6 Hz, 1 H), 7.70 (s, 1 H).

Ejemplo de referencia 200

2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 199.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.23 (s, 3 H), 2.54 - 2.70 (m, 2 H), 2.78 - 2.93 (m, 2 H), 3.39 (s, 3 H), 3.80 (s,

3 H), 6.64 (s, 1 H), 6.68 (d, J = 3.4 Hz, 1 H), 6.77 (s, 2 H), 7.41 (d, J = 3.4 Hz, 1 H), 7.75 (s, 1 H).

Ejemplo de referencia 201

1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-carbaldehído

A una solución de 5-(trifluorometil)-1H-pirrolo[2,3-b]piridina (8.08 g) en N,N-dimetilformamida (80 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 1.89 g) con agitación, y la mezcla se agitó a 0°C durante 30 min. 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (6.25 g) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 80°C durante 8 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (8.40 g, rendimiento del 69%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 3.68 (s, 3 H), 6.89 (d, J = 3.8 Hz, 1 H), 7.46 (d, J = 3.6 Hz, 1 H), 8.30 (d, J = 1.5 Hz, 1 H), 8.62 (d, J = 1.3 Hz, 1 H), 9.63 (s, 1 H).

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Ejemplo de referencia 202

(2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 201 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.58 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.71 (d, J = 16.3 Hz, 1 H), 6.88 (d, J = 3.8 Hz, 1 H), 7.23 - 7.30 (m, 1 H), 7.35 (d, J = 3.8 Hz, 1 H), 8.31 (d, J = 1.9 Hz, 1 H), 8.62 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 203

ácido (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 202.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.39 (s, 3 H), 3.51 (s, 3 H), 5.48 (d, J = 16.3 Hz, 1 H), 7.04 (d, J = 3.4 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.97 (d, J = 3.4 Hz, 1 H), 8.65 (d, J = 4.5 Hz, 2 H), 12.21 (br s, 1 H).

Ejemplo de referencia 204

1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

A una solución de 5-metil-1H-pirrolo[2,3-b]piridina (1.70 g) en N,N-dimetilformamida (30 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 561 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído (1.85 g) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 80°C durante 6 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.42 g, rendimiento del 48%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.46 (s, 3 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 7.25 - 7.29 (m, 1 H), 7.80 - 7.83 (m, 1 H), 8.19 (d, J = 2.1 Hz, 1 H), 9.57 (s, 1 H).

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Ejemplo de referencia 205

(2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

A una solución de (dietoxifosforil)acetato de etilo (1.38 g) en tetrahidrofurano (46 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 269 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Una solución de 1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 204 (1.42 g) en tetrahidrofurano (10 ml) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 0°C durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (1.61 g, rendimiento del 89%) en forma de cristales de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.44 - 2.47 (m, 6 H), 3.58 (s, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 5.69 (d, J = 16.3 Hz, 1 H), 6.68 (d, J = 3.4 Hz, 1 H), 7.15 (d, J = 3.8 Hz, 1 H), 7.30 (d, J = 16.3 Hz, 1 H), 7.81 (d, J = 1.5 Hz, 1 H), 8.18 (d, J = 1.5 Hz, 1 H).

Ejemplo de referencia 206

ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

A una solución de (2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 205 (1.59 g) en un solvente mixto de tetrahidrofurano (25 ml) y etanol (25 ml), se añadió una solución acuosa 1 N de hidróxido de sodio (9.8 ml), y la mezcla se agitó con calentamiento a 60°C durante 3 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró. Una solución acuosa (20 ml) del residuo se neutralizó con una solución acuosa (15 ml) de sulfato de potasio ácido (1.33 g), y los cristales precipitados se recogieron por filtración. Los cristales se disolvieron en acetato de etilo, y la solución se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (1.14 g, rendimiento del 79%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 3 H), 2.41 (s, 3 H), 3.48 (s, 3 H), 5.47 (d, J = 16.3 Hz, 1 H), 6.79 (d, J = 3.8 Hz, 1 H), 7.06 (d, J = 16.3 Hz, 1 H), 7.65 (d, J = 3.4 Hz, 1 H), 7.95 (s, 1 H), 8.12 (d, J = 1.9 Hz, 1 H), 12.14 (br s, 1 H).

Ejemplo de referencia 207

(E)-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etilensulfonamida

Una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (8.92 g) en N,N-dimetilformamida (180 ml) se añadió hidruro de sodio al 60% (en aceite, 2.33 g) con agitación a 0°C, y la mezcla se agitó a 0°C durante 1 h. 1,3-Dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 201 (5.79 g) se añadió a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa saturada de cloruro de amonio (100 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, se añadió ácido trifluoroacético (50 ml) al residuo, y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto

del título (6.36 g, rendimiento del 88%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.38 (s, 3 H), 3.50 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 15.9 Hz, 1 H), 6.86 (s, 2 H), 7.06 (d, J = 3.8 Hz, 1 H), 7.95 (d, J = 3.8 Hz, 1 H), 8.60 (s, 1 H), 8.65 (s, 1 H).

Ejemplo de referencia 208

2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida

A una solución de (E)-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etilensulfonamida obtenida en el Ejemplo de referencia 207 (6.31 g) en un solvente mixto de tetrahidrofurano (80 ml) y etanol (80 ml) se añadió paladio sobre carbón al 10% (631 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 8 h. El catalizador se eliminó por filtración, y el filtrado se concentró. A una solución de este residuo en un solvente mixto de tetrahidrofurano (80 ml) y etanol (80 ml) se añadió paladio sobre carbón al 10% (631 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 5 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se cristalizó en hexano-etanol para dar el compuesto del título (6.11 g, rendimiento del 96%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.22 (s, 3 H), 2.53 - 2.63 (m, 2 H), 2.92 (t, J = 8.3 Hz, 2 H), 3.43 (s, 3 H), 6.74 (s, 2 H), 6.98 (d, J = 3.4 Hz, 1 H), 7.93 (d, J = 3.4 Hz, 1 H), 8.60 (s, 1 H), 8.65 (s, 1 H).

Ejemplo de referencia 209

(E)-2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 204 y {[(difenilfosforil)metil]sulfonil}carbamato de terbutilo.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.36 (s, 3 H), 2.41 (s, 3 H), 3.47 (s, 3 H), 6.12 (d, J = 15.6 Hz, 1 H), 6.76 - 6.89 (m, 4 H), 7.63 (d, J = 3.6 Hz, 1 H), 7.95 (d, J = 1.1 Hz, 1 H), 8.13 (d, J = 1.5 Hz, 1 H).

Ejemplo de referencia 210

2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 209.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.20 (s, 3 H), 2.40 (s, 3 H), 2.53 - 2.62 (m, 2 H), 2.85 - 2.93 (m, 2 H), 3.39 (s, 3 H), 6.71 (d, J = 3.6 Hz, 1 H), 6.75 (s, 2 H), 7.63 (d, J = 3.8 Hz, 1 H), 7.89 - 7.93 (m, 1 H), 8.11 (d, J = 2.1 Hz, 1 H).

Ejemplo de referencia 211

3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propanoato de etilo

Por medio de un método similar al del Ejemplo de referencia 65, se obtuvo el compuesto del título a partir de (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 202.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16 (t, J = 7.1 Hz, 3 H), 2.26 - 2.35 (m, 5 H), 2.54 - 2.63 (m, 2 H), 3.51 (s, 3 H), 3.99 (q, J = 7.0 Hz, 2 H), 6.82 (d, J = 3.6 Hz, 1 H), 7.37 (d, J = 3.6 Hz, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 212

3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propan-1-ol

Por medio de un método similar al del Ejemplo de referencia 66, se obtuvo el compuesto del título a partir de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propanoato de etilo obtenida

en el Ejemplo de referencia 211.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 - 1.65 (m, 2 H), 2.29 - 2.40 (m, 5 H), 3.43 - 3.52 (m, 5 H), 6.81 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.27 (d, J = 1.7 Hz, 1 H), 8.60 (d, J = 1.7 Hz, 1 H).

Ejemplo de referencia 213

5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

1,3-Dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 11 (1.38 g) se disolvió en metanol (100 ml), se añadió paladio sobre carbón al 10% (530 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 78 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo) para dar el compuesto del título (0.85 g, rendimiento del 61%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3 H), 3.28 (t, J = 8.6 Hz, 2 H), 3.73 (s, 3 H), 4.04 (t, J = 8.6 Hz, 2 H), 6.67 (dd, J = 6.9, 5.5 Hz, 1 H), 7.40 (d, J = 6.9 Hz, 1 H), 7.89 (d, J = 5.5 Hz, 1 H), 9.78 (s, 1 H).

Ejemplo de referencia 214

(2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 213 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 - 1.32 (m, 3 H), 2.38 (s, 3 H), 3.23 - 3.35 (m, 2 H), 3.66 (s, 3 H), 3.75 - 3.95 (m, 2 H), 4.15 - 4.21 (m, 2 H), 5.96 (d, J = 16.2 Hz, 1 H), 6.65 (dd, J = 7.2, 5.3 Hz, 1 H), 7.39 (dd, J = 7.2, 1.5 Hz, 1 H), 7.45 (d, J = 16.2 Hz, 1 H), 7.90 (dd, J = 5.3, 1.5 Hz, 1 H).

Ejemplo de referencia 215

ácido (2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 214.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.27 (s, 3 H), 3.26 (t, J = 8.5 Hz, 2 H), 3.56 (s, 3 H), 3.79 - 3.95 (m, 2 H), 5.80 (d, J = 16.1 Hz, 1 H), 6.68 (dd, J = 7.2, 4.5 Hz, 1 H), 7.24

(d, J = 16.1 Hz, 1 H), 7.50 (dd, J = 7.2, 1.5 Hz, 1 H), 7.76 (d, J = 4.5 Hz, 1 H), 12.08 (s, 1 H).

Ejemplo de referencia 216

3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[2,3-b]piridina y 5-cloro-3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 150.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 - 1.08 (m, 4 H), 2.45 - 2.55 (m, 1 H), 3.63 (s, 3 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.22 (dd, J = 7.8, 4.8 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.02 (dd, J = 7.8, 1.5 Hz, 1 H), 8.36 (dd, J = 4.8, 1.5 Hz, 1 H), 9.66 (s, 1 H).

Ejemplo de referencia 217

(2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 216 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.00 (d, J = 7.2 Hz, 4 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.91 - 2.05 (m, 1 H), 3.55 (s, 3

H), 4.13 (q, J = 7.1 Hz, 2 H), 5.92 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.15 - 7.24 (m, 2 H), 7.40 (d, J = 16.1 Hz, 1 H), 8.02 (dd, J = 7.8, 1.7 Hz, 1 H), 8.35 (dd, J = 4.5, 1.7 Hz, 1 H).

Ejemplo de referencia 218

ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 217.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.85 - 0.99 (m, 4 H), 2.00 - 2.10 (m, 1 H), 3.47 (s, 3 H), 5.59 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 16.2 Hz, 1 H), 7.28 (dd, J = 7.9, 4.7 Hz, 1 H), 7.72 (d, J = 3.6 Hz, 1 H), 8.17 (dd, J = 7.9, 1.6 Hz, 1 H), 8.28 (dd, J = 4.7, 1.6 Hz, 1 H), 12.14 (s, 1 H).

Ejemplo de referencia 219

3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 213, se obtuvo el compuesto del título a partir de 3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 - 1.05 (m, 4 H), 2.03 - 2.31 (m, 1 H), 3.27 (t, J = 8.5 Hz, 2 H), 3.68 (s, 3 H), 3.94 - 4.10 (m, 2 H), 6.66 (dd, J = 7.2, 5.1 Hz, 1 H), 7.35 - 7.42 (m, 1 H), 7.88 (d, J = 5.1 Hz, 1 H), 9.91 (s, 1 H).

Ejemplo de referencia 220

(2E)-3-[3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 219 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 - 0.96 (m, 4 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.87 - 1.96 (m, 1 H), 3.23 - 3.32 (m, 2 H), 3.62 (s, 3 H), 3.78 - 3.95 (m, 2 H), 4.18 (q, J = 7.1 Hz, 2 H), 6.18 (d, J = 16.1 Hz, 1 H), 6.64 (dd, J = 7.2, 5.3 Hz, 1 H), 7.38 (dd, J = 7.2, 1.5 Hz, 1 H), 7.54 (d, J = 16.1 Hz, 1 H), 7.90 (d, J = 5.3 Hz, 1 H).

Ejemplo de referencia 221

ácido (2E)-3-[3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de

referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 220.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.75 - 0.83 (m, 2 H), 0.85 - 0.94 (m, 2 H), 1.90 - 1.99 (m, 1 H), 3.25 (t, J = 8.3 Hz, 2 H), 3.54 (s, 3 H), 3.78 - 3.93 (m, 2 H), 5.98 (d, J = 16.3 Hz, 1 H), 6.68 (dd, J = 7.2, 5.3 Hz, 1 H), 7.34 (d, J = 16.3 Hz, 1 H), 7.45 - 7.53 (m, 1 H), 7.74 - 7.77 (m, 1 H), 12.08 (s, 1 H).

Ejemplo de referencia 222

1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[3,2-c]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 3.59 (s, 3 H), 6.93 (dd, J = 3.4, 0.8 Hz, 1 H), 7.05 (d, J = 5.7 Hz, 1 H), 7.24 (d, J = 3.4 Hz, 1 H), 8.44 (d, J = 5.7 Hz, 1 H), 9.06 (d, J = 0.8 Hz, 1 H), 9.56 (s, 1 H).

Ejemplo de referencia 223

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de

referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 222 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J = 7.2 Hz, 3 H), 2.47 (s, 3 H), 3.51 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.60 (d, J = 16.2 Hz, 1 H), 6.92 (dd, J = 3.4, 0.9 Hz, 1 H), 6.97 (d, J = 5.8 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.26 (d, J = 16.2 Hz, 1 H), 8.40 (d, J = 5.8 Hz, 1 H), 9.05 (d, J = 0.9 Hz, 1 H).

Ejemplo de referencia 224

ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 223.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 3.50 (s, 3 H), 5.37 (d, J = 16.2 Hz, 1 H), 7.02 - 7.08 (m, 2 H), 7.11 (d, J = 5.8 Hz, 1 H), 7.71 (d, J = 3.4 Hz, 1 H), 8.30 (d, J = 5.8 Hz, 1 H), 9.01 (s, 1 H), 12.19 (s, 1 H).

Ejemplo de referencia 225

1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[2,3-c]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3 H), 3.62 (s, 3 H), 6.84 (d, J = 3.0 Hz, 1 H), 7.34 (d, J = 3.0 Hz, 1 H), 7.64 (d, J = 5.5 Hz, 1 H), 8.43 (d, J = 5.5 Hz, 1 H), 8.53 (s, 1 H), 9.59 (s, 1 H).

Ejemplo de referencia 226

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 225 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (t, J = 7.2 Hz, 3 H), 2.48 (s, 3 H), 3.54 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.63 (d, J = 16.4 Hz, 1 H), 6.84 (dd, J = 3.3, 0.9 Hz, 1 H), 7.24 (s, 1 H), 7.27 (d, J = 16.4 Hz, 1 H), 7.64 (dd, J = 5.5, 0.9 Hz, 1 H), 8.41 (d, J = 5.5 Hz, 1 H), 8.45 (s, 1 H).

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Ejemplo de referencia 227

ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 226.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.39 (s, 3 H), 3.53 (s, 3 H), 5.36 (d, J = 16.2 Hz, 1 H), 6.95 (dd, J = 3.3, 0.8 Hz, 1 H), 7.06 (d, J = 16.2 Hz, 1 H), 7.74 (dd, J = 5.4, 0.8 Hz, 1 H), 7.85 (d, J = 3.3 Hz, 1 H), 8.31 (d, J = 5.4 Hz, 1 H), 8.41 (s, 1 H), 12.19 (s, 1 H).

Ejemplo de referencia 228

1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[2,3-b]piridina y 5-cloro-1-metil-3-(trifluorometil)-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3 H), 6.80 (d, J = 3.9 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.32 (d, J = 3.9 Hz, 1 H), 8.01 - 8.05 (m, 1 H), 8.32 - 8.35 (m, 1 H), 9.83 (s, 1 H).

Ejemplo de referencia 229

(2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 228 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, J = 7.2 Hz, 3 H), 3.70 (s, 3 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.59 (d, J = 16.2 Hz, 1 H), 6.83 (d, J = 3.8 Hz, 1 H), 7.19 (d, J = 3.8 Hz, 1 H), 7.25 (dd, J = 8.1, 4.5 Hz, 1 H), 7.39 (d, J = 16.2 Hz, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 8.36 (d, J = 4.5 Hz, 1 H).

Ejemplo de referencia 230

ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 229.

^{1}H-NMR (300 MHz, DMSO-d_6): 3.66 (s, 3 H), 5.23 (d, J = 16.5 Hz, 1 H), 6.95 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 16.5 Hz, 1 H), 7.32 (dd, J = 8.0, 4.5 Hz, 1 H), 7.80 (d, J = 3.8 Hz, 1 H), 8.18 - 8.23 (m, 1 H), 8.28 - 8.32 (m, 1 H), 12.56 (s, 1 H).

Ejemplo de referencia 231

3-(1-naftil)tiofen-2-carbaldehído

A una mezcla de ácido 1-naftilborónico (1.67 g), 3-bromotiofen-2-carbaldehído (1.81 g), una solución acuosa 2.0 M de carbonato de sodio (10.0 ml) y 1.2-dimetoxietano (30 ml) se añadió tetraquis(trifenilfosfina)paladio (0) (0.43 g), y la mezcla de reacción se calentó a reflujo bajo una atmósfera de nitrógeno durante 5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 95:5, v/v) para dar el compuesto del título (2.28 g, rendimiento del 98%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, J = 4.9 Hz, 1 H), 7.45 - 7.49 (m, 4 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.83 (dd, J = 4.9, 1.5 Hz, 1 H), 7.91 - 7.98 (m, 2 H), 9.60 (s, 1 H).

Ejemplo de referencia 232

(2E)-3-[3-(1-naftil)-2-tienil]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 3-(1-naftil)tiofen-2-carbaldehído obtenido en el Ejemplo de referencia 231 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (d, J = 7.1 Hz, 3 H), 4.13 (q, J = 7.1 Hz, 2 H), 6.26 (d, J = 15.6 Hz, 1 H), 7.14 (d, J = 5.1 Hz, 1 H), 7.35 (dd, J = 7.0, 1.1 Hz, 1 H), 7.40 - 7.58 (m, 5 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.86 - 7.96 (m, 2 H).

Ejemplo de referencia 233

ácido (2E)-3-[3-(1-naftil)-2-tienil]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[3-(1-naftil)-2-tienil]acrilato de etilo obtenido en el Ejemplo de referencia 232.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 6.18 (d, J = 15.5 Hz, 1 H), 7.18 - 7.27 (m, 2 H), 7.41 (d, J = 6.1 Hz, 1 H), 7.47 - 7.68 (m, 4 H), 7.89 (d, J = 5.3 Hz, 1 H), 8.00 - 8.08 (m, 2 H), 12.33 (s, 1 H).

Ejemplo de referencia 234

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

A una solución de (dietoxifosforil)acetato de etilo (2.54 g) en tetrahidrofurano (20 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 459 mg) con agitación, y la mezcla se agitó a 0°C durante 30 min. Una solución de 5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 182 (2.03 g) en tetrahidrofurano (25

ml) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 0°C durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (2.54 g, rendimiento del 99%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.69 (d, J = 16.3 Hz, 1 H), 6.73 (d, J = 3.8 Hz, 1 H), 7.23 - 7.30 (m, 2 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H).

Ejemplo de referencia 235

ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

A una solución de (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 234 (2.50 g) en un solvente mixto de tetrahidrofurano (15 ml) y etanol (15 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (15 ml), y la mezcla se agitó con calentamiento a 60°C durante 2 h. La mezcla de reacción se dejó enfriar hasta

temperatura ambiente, se neutralizó con una solución acuosa (80 ml) de sulfato de potasio ácido (2.1 g), y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (2.18 g, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.37 (s, 3 H), 3.49 (s, 3 H), 5.46 (d, J = 16.3 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.83 (d, J = 3.6 Hz, 1 H), 8.29 - 8.33 (m, 2 H), 12.17 (s, 1 H).

Ejemplo de referencia 236

5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-bromo-1H-pirrolo[2,3-b]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.67 (s, 3 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.33 (d, J = 3.6 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H), 8.38 (d, J = 2.1 Hz, 1 H), 9.60 (s, 1 H).

Ejemplo de referencia 237

(2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 236 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 3 H), 2.45 (s, 3 H), 3.57 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.69 (d, J = 16.5 Hz, 1 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.22 (d, J = 3.6 Hz, 1 H), 7.28 (d, J = 16.5 Hz, 1 H), 8.16 (d, J = 2.3 Hz, 1 H), 8.37 (d, J = 2.3 Hz, 1 H).

Ejemplo de referencia 238

ácido (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 237.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3 H), 3.49 (s, 3 H), 5.46 (d, J = 16.3 Hz, 1 H), 6.87 (d, J = 3.4 Hz, 1 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.81 (d, J = 3.4 Hz, 1 H), 8.36 (d, J = 2.3 Hz, 1 H), 8.44 (d, J = 2.3 Hz, 1 H), 12.17 (s, 1

H).

Ejemplo de referencia 239

metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo

A una solución de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol obtenido en el Ejemplo de referencia 63 (630 mg) en tetrahidrofurano (10 ml) se añadieron trietilamina (442 mg) y cloruro de metansulfonilo (393 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró para dar el compuesto del título (797 mg, rendimiento del 99%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.58 - 2.75 (m, 2 H), 2.77 (s, 3 H), 3.46 (s, 3 H), 4.04 (t, J = 6.6 Hz, 2 H), 6.69 (d, J = 3.2 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo de referencia 240

4-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-3-oxopiperazin-1-carboxilato de ter-butilo

A una solución de 3-oxopiperazin-1-carboxilato de ter-butilo (466 mg) en N,N-dimetilformamida (5 ml), que se

enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 120 mg) con agitación, y la mezcla se agitó a temperatura ambiente durante 15 min. Una solución de metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo obtenida en el Ejemplo de referencia 239 (642 mg) en N,N-dimetilformamida (5 ml) se añadió a esta mezcla de reacción, y la mezcla de reacción se agitó a 60°C durante 12 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 10:90, v/v) para dar el compuesto del título (486 mg, rendimiento del 59%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44 (s, 9 H), 2.32 (s, 3 H), 2.40 - 2.53 (m, 2 H), 2.96 - 3.05 (m, 2 H), 3.18 - 3.28 (m, 2 H), 3.40 - 3.50 (m, 5 H), 3.96 (s, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 2.1 Hz, 1 H).

Ejemplo de referencia 241

2-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etoxi}-1H-isoindol-1,3(2H)-diona

A una solución de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol obtenido en el Ejemplo de referencia 63 (2.06 g) en tetrahidrofurano (50 ml) se añadieron N-hidroxiftalimida (1.29 g) y trifenilfosfina (2.23 g), y luego se añade azodicarboxilato de dietilo (solución toluénica al 40%, 5.57 g), y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró a presión reducida, acetato de etilo se añadió al residuo, y el material insoluble se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (2.97 g, rendimiento del 96%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3 H), 2.64 - 2.85 (m, 2 H), 3.47 (s, 3 H), 4.02 (t, J = 7.6 Hz, 2 H), 6.61 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.09 - 7.17 (m, 2 H), 7.54 (d, J = 1.9 Hz, 1 H), 7.72 - 7.80 (m, 4 H).

Ejemplo de referencia 242

1-{4-[2-(aminooxi)etil]-1,3-dimetil-1H-pirazol-5-il}-5-cloro-1H-indol

A una solución de 2-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etoxi}-1H-isoindol-1,3(2H)-diona

obtenida en el Ejemplo de referencia 241 (1.26 g) en tetrahidrofurano (20 ml) se añadió una solución acuosa al 35% de hidracina (2.91 g), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró para dar el compuesto del título (919 mg, rendimiento del 99%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3 H), 2.40 - 2.60 (m, 2 H), 3.44 (s, 3 H), 3.51 (t, J = 6.6 Hz, 2 H), 5.04 (s, 2 H), 6.64 - 6.69 (m, 1 H), 6.94 - 6.99 (m, 1 H), 7.12 - 7.22 (m, 2 H), 7.63 - 7.67 (m, 1 H).

Ejemplo de referencia 243

1,1-dióxido de (4R)-5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-4-isopropil-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona

A una solución de 1,1-dióxido de (4R)-4-isopropil-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona obtenida en el Ejemplo de referencia 273 (800 mg) en N,N-dimetilformamida (6 ml) se añadió hidruro de sodio al 60% (en aceite, 103 mg) con agitación a 0°C, y la mezcla se agitó a temperatura ambiente durante 10 min. Una solución de metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo obtenida en el Ejemplo de referencia 239 (783 mg) en N,N-

dimetilformamida (6 ml) se añadió a esta mezcla de reacción, y la mezcla de reacción se agitó a 100°C durante 5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v) para dar el compuesto del título (740 mg, rendimiento del 59%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.58 (dd, J = 17.6, 7.0 Hz, 3 H), 0.79 (dd, J = 7.0, 2.7 Hz, 3 H), 1.61 - 1.82 (m, 1 H), 2.30 (s, 3 H), 2.50 - 2.88 (m, 3 H), 3.08 - 3.32 (m, 1 H), 3.41 (d, J = 3.0 Hz, 1 H), 3.51 (d, J = 3.0 Hz, 3 H), 3.78 (s, 3 H), 4.53 - 4.66 (m, 2 H), 6.67 - 6.70 (m, 1 H), 6.83 (d, J = 8.3 Hz, 2 H), 6.89 - 6.93 (m, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.14 - 7.22 (m, 1 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.66 (s, 1 H).

Ejemplo de referencia 244

5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído

A una solución de 5-cloro-1H-pirrolo[2,3-b]piridina (1.30 g) en N,N-dimetilformamida (25 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 380 mg) con agitación, y la mezcla se agitó a 0°C

durante 20 min. 5-cloro-3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 150 (1.47 g) se añadió a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 100°C durante 4 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el compuesto del título (1.69 g, rendimiento del 70%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.00 - 1.08 (m, 4 H), 2.40 - 2.52 (m, 1 H), 3.61 (s, 3 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 3.6 Hz, 1 H), 7.99 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H), 9.68 (s, 1 H).

Ejemplo de referencia 245

(E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etilensulfonamida

A una solución de {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo (2.64 g) en N,N-dimetilformamida (20 ml) se añadió hidruro de sodio al 60% (en aceite, 676 mg) con agitación a 0°C, y la mezcla se agitó a 0°C durante 1 h. 5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-

carbaldehído obtenido en el Ejemplo de referencia 244 (1.68 g) se añadió a la mezcla de reacción a 0°C, y la mezcla se agitó a temperatura ambiente durante 1.5 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar cristales incoloros. Se añadió ácido trifluoroacético (20 ml) a los cristales incoloros, y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (1.49 g, rendimiento del 74%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.01 (d, J = 7.6 Hz, 4 H), 1.88 - 1.96 (m, 1 H), 3.55 (s, 3 H), 4.48 (s, 2 H), 6.34 (d, J = 15.5 Hz, 1 H), 6.74 (d, J = 3.8 Hz, 1 H), 7.20 - 7.26 (m, 2 H), 8.01 (d, J = 2.3 Hz, 1 H), 8.29 (d, J = 2.3 Hz, 1 H).

Ejemplo de referencia 246

2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida

A una solución de (E)-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 245 (935 mg) en un solvente mixto de tetrahidrofurano (25 ml) y etanol (25 ml) se añadió paladio sobre carbón al 10% (200 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 3 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 30:70, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (758 mg, rendimiento del 80%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 - 1.00 (m, 4 H), 1.78 - 1.89 (m, 1 H), 2.78 - 2.90 (m, 1 H), 2.95 - 3.25 (m, 2 H), 3.30 - 3.40 (m, 1 H), 3.42 (s, 3 H), 4.83 (s, 2 H), 6.69 (d, J = 3.4 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 8.00 (d, J = 2.3 Hz, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Ejemplo de referencia 247

1,1-dióxido de 5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona

Por medio de un método similar al del Ejemplo de

referencia 243, se obtuvo el compuesto del título a partir de metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo obtenido en el Ejemplo de referencia 239 y 1,1-dióxido de 2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona obtenido en el Ejemplo de referencia 269.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3 H), 2.44 - 2.63 (m, 2 H), 3.02 (t, J = 6.8 Hz, 2 H), 3.19 - 3.34 (m, 2 H), 3.47 (s, 3 H), 3.79 (s, 3 H), 4.59 (s, 2 H), 6.62 (d, J = 3.2 Hz, 1 H), 6.86 (d, J = 8.3 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.2 Hz, 1 H), 7.11 (dd, J = 8.7, 1.7 Hz, 1 H), 7.33 (d, J = 8.3 Hz, 2 H), 7.66 (s, 1 H).

Ejemplo de referencia 248

1-bencil-5-cloro-3-metil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 85, se obtuvo el compuesto del título a partir de 2-bencil-5-metil-2,4-dihidro-3H-pirazol-3-ona.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3 H), 5.30 (s, 2 H), 7.23 - 7.38 (m, 5 H), 9.87 (s, 1 H).

Ejemplo de referencia 249

1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[2,3-b]piridina y 1-bencil-5-cloro-3-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3 H), 5.16 (s, 2 H), 6.66 (d, J = 3.8 Hz, 1 H), 6.85 - 6.92 (m, 2 H), 7.04 (d, J = 3.8 Hz, 1 H), 7.15 - 7.27 (m, 4 H), 7.98 - 8.01 (m, 1 H), 8.35 (d, J = 4.9 Hz, 1 H), 9.55 (s, 1 H).

Ejemplo de referencia 250

(2E)-3-[1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 249 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J = 7.1 Hz, 3 H), 2.47 (s, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.95 (d, J = 15.0 Hz, 1 H), 5.15 (d, J = 15.0 Hz, 1 H), 5.68 (d, J = 16.2 Hz, 1 H), 6.64 (d, J = 3.6 Hz, 1 H), 6.82 - 6.95 (m, 3 H), 7.12 - 7.36 (m, 5 H), 7.97 - 8.00 (m, 1 H), 8.33 (dd, J = 4.9, 1.5 Hz, 1 H).

Ejemplo de referencia 251

ácido (2E)-3-[1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-

1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 250.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.38 (s, 3 H), 4.83 (d, J = 15.6 Hz, 1 H), 5.06 (d, J = 15.6 Hz, 1 H), 5.47 (d, J = 16.3 Hz, 1 H), 6.83 (d, J = 3.4 Hz, 1 H), 6.93 (dd, J = 5.7, 4.2 Hz, 2 H), 7.05 (d, J = 16.3 Hz, 1 H), 7.16 - 7.22 (m, 3 H), 7.26 (dd, J = 8.0, 4.5 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 8.14 (dd, J = 8.0, 1.5 Hz, 1 H), 8.22 - 8.31 (m, 1 H), 12.15 (s, 1 H).

Ejemplo de referencia 252

3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

A 1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 249 (2.32 g) se añadió ácido trifluoroacético (35 ml), y la mezcla se calentó a reflujo durante 150 h. La mezcla de reacción se concentró a presión reducida, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 55:45, v/v) para dar el compuesto del título (880 mg, rendimiento del 53%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.52 (s, 3 H), 6.68 (d, J

= 3.8 Hz, 1 H), 7.22 (dd, J = 7.6, 4.9 Hz, 1 H), 7.98 - 8.14 (m, 2 H), 8.36 (d, J = 3.8 Hz, 1 H), 9.88 (s, 1 H).

Ejemplo de referencia 253

(2E)-3-[3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

A una solución de 3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 252 (473 mg) en tolueno (20 ml) se añadió (trifenilfosforaniliden)acetato de etilo (1.16 g), y la mezcla se calentó a reflujo durante 15 h. La mezcla de reacción se concentró a presión reducida, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 10:90, v/v) para dar el compuesto del título (589 mg, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.32 (s, 3 H), 4.14 (q, J = 7.2 Hz, 2 H), 5.56 - 5.62 (m, 1 H), 6.70 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 7.8, 4.6 Hz, 1 H), 7.37 (d, J = 3.4 Hz, 1 H), 7.41 - 7.49 (m, 1 H), 8.03 (dd, J = 7.8, 1.5 Hz, 1 H), 8.35 (dd, J = 4.6, 1.5 Hz, 1 H), 12.00 (s, 1 H).

Ejemplo de referencia 254

ácido (2E)-3-[3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

A una solución de (2E)-3-[3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

obtenido en el Ejemplo de referencia 253 (1.75 g) en un solvente mixto de tetrahidrofurano (12 ml) y etanol (12 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (18 ml), y la mezcla se agitó con calentamiento a 80°C durante 4 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, se neutralizó con una solución acuosa (50 ml) de sulfato de potasio ácido (2.5 g), y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (1.10 g, rendimiento del 69%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.46 (s, 3 H), 5.34 (d, J = 16.2 Hz, 1 H), 6.73 (d, J = 3.6 Hz, 1 H), 7.16 - 7.28 (m, 2 H), 7.60 (d, J = 3.6 Hz, 1 H), 8.09 (dd, J = 7.8, 1.6 Hz, 1 H), 8.22 (dd, J = 4.7, 1.5 Hz, 1 H), 12.00 (s, 1 H), 13.23 (s, 1 H).

Ejemplo de referencia 255

ácido (2E)-3-[1-(ter-butoxicarbonil)-5-metil-3-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

A una solución de ácido (2E)-3-[3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 254 (715 mg) en un solvente mixto de tetrahidrofurano (10 ml) y agua (5 ml) se añadieron carbonato de sodio (284 mg) y dicarbonato de di-ter-butilo

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(6.24 g), y la mezcla se agitó a temperatura ambiente durante 72 h. La mezcla de reacción se neutralizó con sulfato de potasio ácido (0.73 g), y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v) para dar el compuesto del título (549 mg, rendimiento del 56%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.60 (s, 9 H), 2.69 (s, 3 H), 5.11 (d, J = 16.2 Hz, 1 H), 6.80 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 7.8, 4.6 Hz, 1 H), 7.33 (d, J = 16.2 Hz, 1 H), 7.68 (d, J = 3.6 Hz, 1 H), 8.13 (dd, J = 7.8, 1.5 Hz, 1 H), 8.24 (dd, J = 4.6, 1.5 Hz, 1 H), 12.28 (s, 1 H).

Ejemplo de referencia 256

1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 9, se obtuvo el compuesto del título a partir de 1-bencil-2-butil-4-cloro-1H-imidazol-5-carbaldehído y ácido 1-naftilborónico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.3 Hz, 3 H), 1.35 - 1.48 (m, 2 H), 1.70 - 1.84 (m, 2 H), 2.75 - 2.81 (m, 2 H), 5.72 (s, 2 H), 7.15 (d, J = 7.0 Hz, 2 H), 7.29 - 7.40 (m, 3 H), 7.49 - 7.60 (m, 4 H), 7.87 - 7.95 (m, 2 H), 8.09 - 8.15

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(m, 1 H), 9.50 (s, 1 H).

Ejemplo de referencia 257

(2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-carbaldehído obtenido en el Ejemplo de referencia 256 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.4 Hz, 3 H), 1.11 (t, J = 7.0 Hz, 3 H), 1.34 - 1.46 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.73 - 2.79 (m, 2 H), 4.01 (q, J = 7.0 Hz, 2 H), 5.34 (s, 2 H), 5.56 (d, J = 16.3 Hz, 1 H), 7.11 (d, J = 6.8 Hz, 2 H), 7.30 - 7.56 (m, 8 H), 7.85 - 7.93 (m, 3 H).

Ejemplo de referencia 258

ácido (2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]acrilato de etilo obtenido en el Ejemplo de referencia 257.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.83 (t, J = 7.4 Hz, 3 H), 1.28 - 1.42 (m, 2 H), 1.58 - 1.69 (m, 2 H), 2.77 (t, J = 7.6 Hz, 2 H), 5.39 (d, J = 16.3 Hz, 1 H), 5.51 (s, 2 H), 7.11 (d, J = 7.2 Hz, 2 H), 7.28 (d, J = 16.3 Hz, 1 H), 7.34 (d, J =

7.6 Hz, 1 H), 7.39 - 7.64 (m, 6 H), 7.81 (d, J = 8.3 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 2 H), 12.02 (s, 1 H).

Ejemplo de referencia 259

N-({[(benciloxi)carbonil]amino}sulfonil)-alaninato de etilo

A una solución de alcohol bencílico (2.25 g) en acetonitrilo (40 ml) se añadió isocianato de clorosulfonilo (1.90 ml) con agitación a 0°C, y la mezcla se agitó durante 30 min. Piridina (3.35 ml) se añadió a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se añadieron clorhidrato de éster etílico de β-alanina (4.79 g) y N,N-diisopropiletilamina (7.13 ml), y la mezcla se agitó a temperatura ambiente durante 3 h. ácido clorhídrico 1 N se añadió a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (6.55 g, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, J = 7.2 Hz, 3 H), 2.59 (t, J = 6.1 Hz, 2 H), 3.24 - 3.45 (m, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.20 (s, 2 H), 5.76 (t, J = 6.2 Hz, 1 H), 7.30 - 7.38 (m, 5 H), 7.40 (br s, 1 H).

Ejemplo de referencia 260

N-(aminosulfonil)-β-alaninato de etilo

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de N-({[(benciloxi)carbonil]amino}sulfonil)-β-alaninato de etilo obtenida en el Ejemplo de referencia 259.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3 H), 2.65 (t, J = 5.9 Hz, 2 H), 3.28 - 3.54 (m, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.61 (br s, 2 H), 5.05 (t, J = 5.7 Hz, 1 H).

Ejemplo de referencia 261

5-(difluorometil)-2-metil-2,4-dihidro-3H-pirazol-3-ona

Por medio de un método similar al del Ejemplo de referencia 84, se obtuvo el compuesto del título a partir de 4.4-difluoro-3-oxobutanoato de etilo y metilhidracina.

^{1}H-NMR (300 MHz, DMSO-d_6): 3.54 (s, 3 H), 5.55 (s, 1 H), 6.70 (t, J = 54.8 Hz, 1 H), 11.35 (s, 1 H).

Ejemplo de referencia 262

5-cloro-3-(difluorometil)-1-metil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 85, se obtuvo el compuesto del título a partir de 5-(difluorometil)-2-metil-2,4-dihidro-3H-pirazol-3-ona obtenida en el Ejemplo de referencia 261.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.93 (s, 3 H), 6.90 (t, J

= 53.6 Hz, 1 H), 9.96 (s, 1 H).

Ejemplo de referencia 263

3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 1H-pirrolo[2,3-b]piridina y 5-cloro-3-(difluorometil)-1-metil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 262.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.81 (s, 3 H), 6.77 - 7.16 (m, 2 H), 7.24 (dd, J = 8.0, 4.7 Hz, 1 H), 7.34 (d, J = 3.8 Hz, 1 H), 8.03 (dd, J = 8.0, 1.5 Hz, 1 H), 8.35 (dd, J = 4.7, 1.5 Hz, 1 H), 9.79 (s, 1 H).

Ejemplo de referencia 264

(2E)-3-[3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 263 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, J = 7.2 Hz, 3 H), 3.67 (s, 3 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.86 (d, J = 16.3 Hz, 1 H), 6.58 - 6.93 (m, 2 H), 7.20 - 7.29 (m, 2 H), 7.37 (d, J = 16.3 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.36 (dd,

J = 4.9, 1.5 Hz, 1 H).

Ejemplo de referencia 265

ácido (2E)-3-[3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 264.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.62 (s, 3 H), 5.42 (d, J = 16.3 Hz, 1 H), 6.94 (d, J = 3.6 Hz, 1 H), 7.06 - 7.42 (m, 3 H), 7.81 (d, J = 3.6 Hz, 1 H), 8.20 (dd, J = 8.0, 1.5 Hz, 1 H), 8.30 (dd, J = 4.5, 1.5 Hz, 1 H), 12.41 (s, 1 H).

Ejemplo de referencia 266

N-{[(ter-butoxicarbonil)amino]sulfonil}glicinato de etilo

A una solución de alcohol ter-butílico (10 g) en acetonitrilo (200 ml), que se enfrió a 0°C en un baño helado, se añadió gota a gota isocianato de clorosulfonilo (22.9 g), y la mezcla se agitó a 0°C durante 1 h. Piridina (33 ml) se añadió a la mezcla de reacción a 0°C, y la mezcla de reacción luego se agitó a 0°C durante 45 min para dar una solución de N-clorosulfonilcarbamato de ter-butilo en acetonitrilo. A una suspensión de clorhidrato de glicinetiléster (56.5 g) en acetonitrilo (200 ml), que se enfrió a 0°C en un baño helado,

se añadió trietilamina (57 ml), y la mezcla se agitó a 0°C durante 20 min. El precipitado objetivo se eliminó por filtración, y se lavó con una pequeña cantidad de acetonitrilo. El filtrado obtenido se añadió a la solución antes mencionada de N-clorosulfonilcarbamato de ter-butilo en acetonitrilo, que se enfrió a 0°C en un baño helado, y la mezcla se agitó a temperatura ambiente durante 14 h. La mezcla de reacción se concentró a presión reducida, se añadió ácido clorhídrico 1 M (260 ml) al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se suspendió en diclorometano (100 ml) calentado antes, y el material insoluble se recogió por filtración y se secó para dar el compuesto del título (30.3 g, rendimiento del 80%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.1 Hz, 3 H), 1.50 (s, 9 H), 3.95 (s, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 5.63 (br s, 1 H).

Ejemplo de referencia 267

N-{[(ter-butoxicarbonil)(4-metoxibencil)amino]sulfonil}glicinato de etilo

A una solución de N-{[(ter-butoxicarbonil)amino]sulfonil}glicinato de etilo obtenida en el Ejemplo de referencia 266 (20.0 g), trifenilfosfina (18.6

g) y alcohol 4-metoxibencílico (9.79 g) en tetrahidrofurano (100 ml) se añadieron azodicarboxilato de dietilo (31.6 g) y tetrahidrofurano (20 ml) bajo una atmósfera de nitrógeno a 0°C, y la mezcla se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró a presión reducida, se añadió una solución acuosa saturada de carbonato de sodio ácido al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 75:25, v/v), y se cristalizó en hexano-éter isopropílico para dar el compuesto del título (17.7 g, rendimiento del 62%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, J = 7.1 Hz, 3 H), 1.54 (s, 9 H), 3.55 (d, J = 5.4 Hz, 2 H), 3.80 (s, 3 H), 4.14 (q, J = 7.1 Hz, 2 H), 4.76 (s, 2 H), 5.70 (t, J = 5.4 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H).

Ejemplo de referencia 268

N-{[(4-metoxibencil)amino]sulfonil}glicinato de etilo

A N-{[(ter-butoxicarbonil)(4-metoxibencil)amino]sulfonil}glicinato de etilo obtenido en el Ejemplo de referencia 267 (10.0 g) se añadió una solución de cloruro de hidrógeno 4 M-acetato de etilo (100 ml) a 0°C, y

la mezcla se agitó a 0°C durante 1 h, y luego a temperatura ambiente durante 3.5 h. La mezcla de reacción se concentró a presión reducida, el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 80:20 - 60:40, v/v) para dar el compuesto del título (6.48 g, rendimiento del 86%) en forma de un sólido objetivo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3 H), 3.79 (d, J = 5.1 Hz, 2 H), 3.80 (s, 3 H), 4.17 - 4.25 (m, 4 H), 4.52 (t, J = 5.9 Hz, 1 H), 4.82 (t, J = 5.6 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.7 Hz, 2 H).

Ejemplo de referencia 269

1,1-dióxido de 2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona

A una solución de N-{[(4-metoxibencil)amino]sulfonil}glicinato de etilo obtenida en el Ejemplo de referencia 268 (6.21 g) en metanol (60 ml) se añadieron metóxido de sodio (aproximadamente solución metanólica al 28%: 11.9 g) y metanol (40 ml), y la mezcla se agitó a temperatura ambiente durante 6 h. Se añadió ácido clorhídrico 1 M (70 ml) a la mezcla de reacción a 0°C, y la mezcla de reacción se concentró a presión reducida. Se agregó agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de

sílice (hexano-acetato de etilo 70:30 - 60:40, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (3.76 g, rendimiento del 71%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.79 (s, 3 H), 4.02 (d, J = 7.2 Hz, 2 H), 4.68 (s, 2 H), 4.83 (br s, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.4 Hz, 2 H).

Ejemplo de referencia 270

N-{[(ter-butoxicarbonil)amino]sulfonil}-D-valinato de metilo

Por medio de un método similar al del Ejemplo de referencia 266, se obtuvo el compuesto del título a partir de clorhidrato de éster metílico de D-valina, alcohol ter-butílico e isocianato de clorosulfonilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.49 (s, 9 H), 2.09 - 2.19 (m, 1 H), 3.75 (s, 3 H), 4.03 (dd, J = 9.3, 4.8 Hz, 1 H), 5.63 (d, J = 9.3 Hz, 1 H).

Ejemplo de referencia 271

N-{[(ter-butoxicarbonil)(4-metoxibencil)amino]sulfonil}-D-valinato de metilo

Por medio de un método similar al del Ejemplo de referencia 267, se obtuvo el compuesto del título a partir de N-{[(ter-butoxicarbonil)amino]sulfonil}-D-valinato de metilo obtenido en el Ejemplo de referencia 270 y 4-metoxialcohol

bencílico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.82 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 1.53 (s, 9 H), 1.97 - 2.04 (m, 1 H), 3.58 (dd, J = 8.7, 4.8 Hz, 1 H), 3.62 (s, 3 H), 3.80 (s, 3 H), 4.64 (d, J = 15.3 Hz, 1 H), 4.81 (d, J = 15.3 Hz, 1 H), 5.78 (d, J = 8.7 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 9.0 Hz, 2 H).

Ejemplo de referencia 272

N-{[(4-metoxibencil)amino]sulfonil}-D-valinato de metilo

Por medio de un método similar al del Ejemplo de referencia 268, se obtuvo el compuesto del título a partir de N-{[(ter-butoxicarbonil)(4-metoxibencil)amino]sulfonil}-D-valinato de metilo obtenido en el Ejemplo de referencia 271.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.91 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.6 Hz, 3 H), 2.06 - 2.16 (m, 1 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 3.84 (dd, J = 9.9, 4.8 Hz, 1 H), 4.08 - 4.15 (m, 2 H), 4.32 (t, J = 6.0 Hz, 1 H), 4.97 (d, J = 9.9 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.4 Hz, 2 H).

Ejemplo de referencia 273

1,1-dióxido de (4R)-4-isopropil-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona

Por medio de un método similar al del Ejemplo de referencia 269, se obtuvo el compuesto del título a partir de N-{[(4-metoxibencil)amino]sulfonil}-D-valinato de metilo

obtenido en el Ejemplo de referencia 272.

^{1}H-NMR (300 MHz, $CDCl_3$) δ:0.92 (d, J = 6.9 Hz, 3 H), 1.04 (d, J = 6.9 Hz, 3 H), 2.30 - 2.40 (m, 1 H), 3.79 (s, 3 H), 4.07 (dd, J = 6.9, 3.6 Hz, 1 H), 4.64 (d, J = 15.0 Hz, 1 H), 4.69 (d, J = 15.0 Hz, 1 H), 4.75 (d, J = 6.9 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H).

Ejemplo de referencia 274

2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-carboxilato de metilo

A una solución de 4-bromo-2,5-dimetil-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-carboxilato de metilo (827 mg) en tolueno (22 ml) se añadieron ácido 1-naftalenborónico (785 mg) y carbonato de potasio (1.89 g) bajo una atmósfera de argón, y la mezcla se agitó a temperatura ambiente durante 30 min. Se agregaron tris(dibencilidenacetona)dipaladio (0) (52 mg) y 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (93 mg) a esta mezcla de reacción, y la mezcla se agitó a 100°C durante 18 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10, v/v) para dar el compuesto del título (902 mg,

rendimiento del 96%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.00 (s, 9 H), 0.90 - 0.97 (m, 2 H), 1.98 (s, 3 H), 2.67 (s, 3 H), 3.23 (s, 3 H), 3.53 - 3.60 (m, 2 H), 5.09 - 5.38 (m, 2 H), 7.22 - 7.48 (m, 5 H), 7.74 - 7.85 (m, 2 H).

Ejemplo de referencia 275

2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-carbaldehído

A una solución de 2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-carboxilato de metilo obtenido en el Ejemplo de referencia 274 (1.22 g) en éter dietílico (30 ml) se añadió hidruro de diisobutilalumino (solución toluénica 1.5 M, 4.9 ml) agitada a 0°C, y la mezcla se agitó a temperatura ambiente durante 2 h. Metanol y agua se añadieron a esta mezcla de reacción, la mezcla se filtró a través de celite(, y el filtrado se concentró. El residuo se disolvió en diclorometano (10 ml), la solución se añadió a una mezcla de dicromato de piridinio (1.34 g) y celite® (1.34 g) en diclorometano (30 ml) con agitación, y la mezcla se agitó a temperatura ambiente durante 7 h. La mezcla de reacción se filtró a través de celite®, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 85:15, v/v) para dar el compuesto del título (214 mg, rendimiento del 19%) en forma de un aceite de color amarillo pálido.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.00 (s, 9 H), 0.91 - 0.98 (m, 2 H), 2.03 (s, 3 H), 2.70 (s, 3 H), 3.55 - 3.61 (m, 2 H), 5.22 - 5.31 (m, 2 H), 7.32 - 7.51 (m, 4 H), 7.65 (d, J = 8.3 Hz, 1 H), 7.80 - 7.88 (m, 2 H), 9.40 (s, 1 H).

Ejemplo de referencia 276

(2E)-3-(2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-il)acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-carbaldehído obtenido en el Ejemplo de referencia 275 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.00 (s, 9 H), 0.90 - 0.97 (m, 2 H), 1.09 (t, J = 7.0 Hz, 3 H), 1.94 (s, 3 H), 2.47 (s, 3 H), 3.52 - 3.59 (m, 2 H), 3.93 - 4.02 (m, 2 H), 5.08 (d, J = 15.9 Hz, 1 H), 5.18 - 5.30 (m, 2 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.39 - 7.61 (m, 4 H), 7.80 - 7.88 (m, 2 H).

Ejemplo de referencia 277

ácido (2E)-3-(2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-il)acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-(2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-il)acrilato de etilo obtenido en el Ejemplo de referencia 276.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.00 (s, 9 H), 0.85 - 0.93 (m, 2 H), 1.92 (s, 3 H), 2.43 (s, 3 H), 3.58 (t, J = 7.8 Hz, 2 H), 4.86 (d, J = 15.9 Hz, 1 H), 5.27 - 5.38 (m, 2 H), 7.28 - 7.61 (m, 6 H), 7.91 - 8.00 (m, 2 H).

Ejemplo de referencia 278

{[(2-isopropoxietil)amino]sulfonil}carbamato de bencilo

Por medio de un método similar al del Ejemplo de referencia 102, se obtuvo el compuesto del título a partir de alcohol bencílico, isocianato de clorosulfonilo y 2-isopropoxietanamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.13 (d, J = 6.4 Hz, 6 H), 3.24 (q, J = 4.9 Hz, 2 H), 3.47 - 3.60 (m, 3 H), 5.19 (s, 2 H), 5.49 (br s, 1 H), 7.32 - 7.41 (m, 5 H).

Ejemplo de referencia 279

N-(2-isopropoxietil)sulfamida

Por medio de un método similar al del Ejemplo de referencia 109, se obtuvo el compuesto del título a partir de {[(2-isopropoxietil)amino]sulfonil}carbamato de bencilo obtenido en el Ejemplo de referencia 278.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 (d, J = 6.2 Hz, 6 H), 3.31 (q, J = 5.3 Hz, 2 H), 3.53 - 3.67 (m, 3 H), 4.80 (br s, 3 H).

Ejemplo de referencia 280

5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

A una mezcla de 5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 236 (1.52 g), ácido ciclopropilborónico (818 mg), carbonato de potasio (3.94 g) y tolueno (50 ml) se agitó a temperatura ambiente durante 30 min bajo una atmósfera de argón. Tris(dibencilidenacetona)dipaladio (0) (109 mg) y 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (195 mg) se añadieron a esta mezcla de reacción a temperatura ambiente, y la mezcla de reacción se agitó a 100°C durante 18 h bajo argón. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el compuesto del título (1.31 g, rendimiento del 99%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.71 - 0.78 (m, 2 H), 1.00 - 1.08 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.54 (s, 3 H), 3.68 (s, 3 H), 6.68 (d, J = 3.8 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 7.65 (d, J = 2.3 Hz, 1 H), 8.21 (d, J = 1.9 Hz, 1 H),

9.57 (s, 1 H).

Ejemplo de referencia 281

(E)-2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo de referencia 178, se obtuvo el compuesto del título a partir de 5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 280 y {[(difenilfosforil)metil]sulfonil}carbamato de ter-butilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.72 - 0.79 (m, 2 H), 0.95 - 1.03 (m, 2 H), 2.02 - 2.13 (m, 1 H), 2.36 (s, 3 H), 3.47 (s, 3 H), 6.12 (d, J = 15.6 Hz, 1 H), 6.76 - 6.83 (m, 2 H), 6.87 (s, 2 H), 7.62 (d, J = 3.8 Hz, 1 H), 7.77 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H).

Ejemplo de referencia 282

2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo de referencia 179, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 281.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.71 - 0.78 (m, 2 H), 0.95 - 1.02 (m, 2 H), 2.01 - 2.12 (m, 1 H), 2.20 (s, 3 H),

2.56 (dd, J = 7.5, 3.2 Hz, 2 H), 2.85 - 2.94 (m, 2 H), 3.39 (s, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 6.76 (s, 2 H), 7.62 (d, J = 3.6 Hz, 1 H), 7.73 (d, J = 2.1 Hz, 1 H), 8.13 (d, J = 2.1 Hz, 1 H).

Ejemplo de referencia 283

5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído

Por medio de un método similar al del Ejemplo de referencia 1, se obtuvo el compuesto del título a partir de 5-fluoro-1H-pirrolo[2,3-b]piridina y 5-cloro-1,3-dimetil-1H-pirazol-4-carbaldehído.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.55 (s, 3 H), 3.68 (s, 3 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.38 (d, J = 3.8 Hz, 1 H), 7.72 (dd, J = 8.5, 2.6 Hz, 1 H), 8.23 (dd, J = 2.4, 1.7 Hz, 1 H), 9.60 (s, 1 H).

Ejemplo de referencia 284

(2E)-3-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo

Por medio de un método similar al del Ejemplo de referencia 12, se obtuvo el compuesto del título a partir de 5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenido en el Ejemplo de referencia 283 y (dietoxifosforil)acetato de etilo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.2 Hz, 3 H), 2.46 (s, 3 H), 3.58 (s, 3 H), 4.14 (q, J = 7.0 Hz, 2 H), 5.70

(d, J = 16.2 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.25 - 7.31 (m, 2 H), 7.72 (dd, J = 8.5, 2.6 Hz, 1 H), 8.22 (dd, J = 2.5, 1.6 Hz, 1 H).

Ejemplo de referencia 285

ácido (2E)-3-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

Por medio de un método similar al del Ejemplo de referencia 13, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilato de etilo obtenido en el Ejemplo de referencia 284.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.37 (s, 3 H), 3.50 (s, 3 H), 5.47 (d, J = 16.2 Hz, 1 H), 6.90 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.2 Hz, 1 H), 7.84 (d, J = 3.6 Hz, 1 H), 8.09 (dd, J = 9.1, 2.7 Hz, 1 H), 8.29 (dd, J = 2.5, 1.6 Hz, 1 H), 12.20 (br s, 1 H).

Ejemplo de referencia 286

[(pentilamino)sulfonil]carbamato de bencilo

A una solución de alcohol bencílico (3.06 g) en diclorometano (150 ml) se añadió isocianato de clorosulfonilo (2.55 ml) con agitación a 0°C, y la mezcla se agitó a 0°C durante 30 min. Se añadió piridina (8.0 ml) a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se agregó 1-pentilamina (16.0 ml), y la mezcla se agitó durante la noche a temperatura ambiente. Se agregó ácido clorhídrico 1 N

a la mezcla de reacción, y la mezcla se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N, una solución acuosa saturada de carbonato de sodio ácido y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (8.18 g, rendimiento del 96%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.92 (m, 3 H), 1.25 - 1.34 (m, 4 H), 1.46 - 1.63 (m, 2 H), 2.98 - 3.07 (m, 2 H), 5.07 (s, 1 H), 5.19 (s, 2 H), 7.28 - 7.42 (m, 5 H).

Ejemplo de referencia 287

N-pentilsulfamida

El [(pentilamino)sulfonil]carbamato de bencilo obtenido en el Ejemplo de referencia 286 (5.83 g) se disolvió en un solvente mixto de tetrahidrofurano (50 ml) y etanol (50 ml), se añadió paladio sobre carbón al 10% (3.11 g), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 4 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se cristalizó en éter diisopropílico-acetato de etilo para dar el compuesto del título (3.15 g, rendimiento del 98%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.95 (m, 3 H), 1.30 - 1.40 (m, 4 H), 1.52 - 1.63 (m, 2 H), 3.10 - 3.16 (m, 2

H), 4.51 (br s, 3 H).

Ejemplo de referencia 288

ácido 3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico

Por medio de un método similar al del Ejemplo de referencia 65, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 206.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3 H), 2.29 - 2.36 (m, 2 H), 2.45 (s, 3 H), 2.53 - 2.72 (m, 2 H), 3.45 (s, 3 H), 6.63 (d, J = 3.6 Hz, 1 H), 7.15 (d, J = 3.6 Hz, 1 H), 7.82 (d, J = 1.1 Hz, 1 H), 8.14 (d, J = 2.1 Hz, 1 H).

Ejemplo de referencia 289

3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propan-1-ol

A una solución de ácido 3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 288 (410 mg) y N,N-dimetilformamida (0.1 ml) en tetrahidrofurano (13 ml) se añadió gota a gota cloruro de oxalilo (261.8 mg), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, tetrahidrofurano (13 ml) y metanol (13 ml) se añadieron al residuo. La mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua a

la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró. Se agregó tetrahidrofurano (13 ml) se añadió al residuo, que se enfrió a 0°C en un baño helado, se añadió hidruro de diisobutilalumino (solución toluénica 1.5 M, 13 ml) en pequeñas porciones con agitación. La mezcla de reacción se agitó a temperatura ambiente durante 2 h, y se volvió a enfriar a 0°C en un baño helado. Metanol y agua se añadieron a la mezcla de reacción con agitación, la mezcla se filtró a través de celite®, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo-metanol 95:5, v/v) para dar el compuesto del título (291 mg, rendimiento del 74%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54 - 1.72 (m, 2 H), 2.29 (s, 3 H), 2.33 - 2.40 (m, 2 H), 2.44 (s, 3 H), 3.42 - 3.53 (m, 5 H), 6.61 (d, J = 3.6 Hz, 1 H), 7.14 (d, J = 3.6 Hz, 1 H), 7.79 (d, J = 1.3 Hz, 1 H), 8.16 (d, J = 2.1 Hz, 1 H).

Ejemplo 1

(2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Una mezcla de ácido (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 2 (400 mg), anhídrido 2-metil-6-nitrobenzoico (586

mg), pentan-1-sulfonamida (240 mg), trietilamina (465 mg), 4-dimetilaminopiridina (175 mg) y acetonitrilo (8 ml) se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró a presión reducida, a solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v) para dar el compuesto del título (579 mg, rendimiento del 98%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.1 Hz, 3 H), 1.25 - 1.40 (m, 4 H), 1.72 - 1.76 (m, 2 H), 2.44 (s, 3 H), 3.28 - 3.34 (m, 2 H), 3.54 (s, 3 H), 5.23 (d, J = 15.6 Hz, 1 H), 6.83 (d, J = 3.2 Hz, 1 H), 6.94 - 7.01 (m, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.23 - 7.27 (m, 2 H), 7.40 (s, 1 H), 7.48 (d, J = 15.6 Hz, 1 H), 7.73 - 7.75 (m, 1 H).

Ejemplo 2

3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)propanamida

(2E)-3-[5-(1H-Indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 1 (233 mg) se disolvió en un solvente mixto de tetrahidrofurano (10 ml) y metanol (10 ml), se añadió paladio sobre carbón al 10% (25 mg), y la mezcla se agitó bajo 1 átomo de atmósfera

de hidrógeno a temperatura ambiente durante 6 h. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 55:45, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (174 mg, rendimiento del 74%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.92 (m, 3 H), 1.25 - 1.40 (m, 4 H), 1.65 - 1.75 (m, 2 H), 2.01 - 2.15 (m, 2 H), 2.30 (s, 3 H), 2.62 (t, J = 7.6 Hz, 2 H), 3.23 - 3.30 (m, 2 H), 3.47 (s, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.96 - 7.02 (m, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.20 - 7.27 (m, 2 H), 7.39 (s, 1 H), 7.70 - 7.73 (m, 1 H).

Ejemplo 3

(2E)-3-[5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 5 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H), 1.22 - 1.43 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.46 (s, 3 H), 3.31 - 3.36 (m, 2 H), 3.57 (s, 3 H), 5.45 (d, J = 15.9 Hz, 1 H), 7.14 (d, J = 8.3 Hz, 1 H), 7.29 - 7.33 (m, 1 H), 7.44 - 7.51 (m, 2 H), 7.64 (s, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 8.32

(d, J = 1.5 Hz, 1 H).

Ejemplo 4

(2E)-3-[5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(2H-indazol-2-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 6 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.0 Hz, 3 H), 1.23 - 1.42 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 - 3.37 (m, 2 H), 3.69 (s, 3 H), 5.70 (d, J = 15.9 Hz, 1 H), 7.18 - 7.24 (m, 1 H), 7.42 - 7.45 (m, 1 H), 7.49 (d, J = 15.9 Hz, 1 H), 7.73 - 7.78 (m, 2 H), 7.90 (s, 1 H), 8.13 (s, 1 H).

Ejemplo 5

(2E)-3-[5-(1H-bencimidazol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1H-bencimidazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 8 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.81 (t, J = 7.1 Hz, 3 H), 1.18 - 1.36 (m, 4 H), 1.58 - 1.67 (m, 2 H), 2.49 (s, 3 H), 3.30 - 3.36 (m, 2 H), 3.55 (s, 3 H), 5.67 (d, J = 16.0 Hz, 1 H), 7.12 (d, J = 7.5 Hz, 1 H), 7.26 - 7.40 (m, 2 H), 7.50 (d,

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J = 8.1 Hz, 1 H), 7.65 (d, J = 16.0 Hz, 1 H), 7.76 (s, 1 H), 10.30 (s, 1 H).

Ejemplo 6

(2E)-3-[5-(1-benzotien-3-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1-benzotien-3-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 10 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.90 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.68 - 1.79 (m, 2 H), 2.47 (s, 3 H), 3.31 - 3.37 (m, 2 H), 3.64 (s, 3 H), 5.75 (d, J = 15.8 Hz, 1 H), 7.35 - 7.50 (m, 3 H), 7.50 - 7.58 (m, 2 H), 7.68 (s, 1 H), 7.96 - 7.99 (m, 1 H).

Ejemplo 7

{(2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

A una solución de (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 1 (445 mg) en metanol (4 ml) se añadió una solución acuosa (1 ml) de hidrógeno-carbonato de potasio (108 mg), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, y el residuo se cristalizó en éter dietílico-metanol para dar

el compuesto del título (483 mg, rendimiento del 99%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.82 (m, 3 H), 1.15 - 1.23 (m, 4 H), 1.37 - 1.47 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.41 (s, 3 H), 5.57 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz, 1 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.95 - 6.99 (m, 1 H), 7.14 - 7.22 (m, 2 H), 7.51 (d, J = 3.4 Hz, 1 H), 7.68 - 7.71 (m, 1 H).

Ejemplo 8

{(2E)-3-[5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 3.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.76 - 0.84 (m, 3 H), 1.15 - 1.24 (m, 4 H), 1.35 - 1.47 (m, 2 H), 2.36 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.44 (s, 3 H), 5.58 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 7.22 (dd, J = 8.5, 0.9 Hz, 1 H), 7.29 - 7.35 (m, 1 H), 7.45 - 7.50 (m, 1 H), 7.95 (d, J = 8.1 Hz, 1 H), 8.55 (d, J = 0.9 Hz, 1 H).

Ejemplo 9

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Una mezcla de ácido (2E)-3-[1,3-dimetil-5-(1H-

pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenida en el Ejemplo de referencia 13 (473 mg), anhídrido 2-metil-6-nitrobenzoico (689 mg), pentan-1-sulfonamida (269 mg), trietilamina (525 mg), 4-dimetilaminopiridina (206 mg) y acetonitrilo (8 ml) se agitó a temperatura ambiente durante 72 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (590 mg, rendimiento del 85%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.92 (m, 3 H), 1.23 - 1.44 (m, 4 H), 1.71 - 1.83 (m, 2 H), 2.29 (s, 3 H), 3.37 - 3.43 (m, 2 H), 3.56 (s, 3 H), 5.57 (d, J = 15.7 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.34 (d, J = 15.7 Hz, 1 H), 8.05 (dd, J = 7.8, 1.5 Hz, 1 H), 8.32 (dd, J = 4.7, 1.5 Hz, 1 H), 8.88 (s, 1 H).

La recristalización de los cristales crudos obtenidos en las mismas condiciones que en el Ejemplo 9 en hexano-éter diisopropílico-etanol dio cristales incoloros. Punto de fusión 149-163°C

La recristalización de los cristales crudos

obtenidos en las mismas condiciones que en el Ejemplo 9 en H_2O-95% de etanol (etanol-H_2O 95:5, v/v) dio cristales incoloros. Punto de fusión 194-197°C

Ejemplo 10

(2E)-3-[1,3-dimetil-5-(1-naftil)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1-naftil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 15 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 3 H), 1.23 - 1.34 (m, 4 H), 1.67 - 1.75 (m, 2 H), 2.49 (s, 3 H), 3.26 - 3.31 (m, 2 H), 3.51 (s, 3 H), 5.60 (d, J = 15.5 Hz, 1 H), 7.31 - 7.65 (m, 7 H), 7.97 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H).

Ejemplo 11

{(2E)-3-[1,3-dimetil-5-(1-naftil)-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1-naftil)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 10.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.75 - 0.82 (m, 3 H), 1.12 - 1.23 (m, 4 H), 1.35 - 1.48 (m, 2 H), 2.37 (s, 3 H), 2.78 - 2.85 (m, 2 H), 3.40 (s, 3 H), 5.70 (d, J = 16.1 Hz, 1

H), 6.77 (d, J = 16.1 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.48 - 7.63 (m, 3 H), 7.64 - 7.73 (m, 1 H), 8.07 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.0 Hz, 1 H).

Ejemplo 12

(2E)-3-[1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 17 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, J = 7.2 Hz, 3 H), 1.15 - 1.36 (m, 4 H), 1.52 - 1.62 (m, 2 H), 2.40 (s, 3 H), 2.56 (s, 3 H), 3.28 - 3.33 (m, 2 H), 3.46 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.89 (d, J = 3.4 Hz, 1 H), 6.97 - 7.15 (m, 3 H), 7.55 (d, J = 3.4 Hz, 1 H), 11.59 (s, 1 H).

Ejemplo 13

{(2E)-3-[1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(4-metil-1H-indol-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 12.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.82 (m, 3 H),

1.15 - 1.25 (m, 4 H), 1.38 - 1.52 (m, 2 H), 2.33 (s, 3 H), 2.55 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.39 (s, 3 H), 5.58 (d, J = 16.2 Hz, 1 H), 6.74 - 6.85 (m, 3 H), 6.97 (d, J = 7.2 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 7.48 (d, J = 3.2 Hz, 1 H).

Ejemplo 14

(2E)-3-[5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 19 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.92 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.34 (m, 2 H), 3.52 (s, 3 H), 5.35 (d, J = 15.5 Hz, 1 H), 6.89 (d, J = 8.0 Hz, 1 H), 6.95 (d, J = 3.4 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.16 - 7.21 (m, 1 H), 7.25 - 7.29 (m, 1 H), 7.46 (d, J = 15.5 Hz, 1 H), 7.74 (s, 1 H).

Ejemplo 15

{(2E)-3-[5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(4-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 14.

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^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.76 - 0.84 (m, 3 H), 1.16 - 1.25 (m, 4 H), 1.38 - 1.47 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.42 (s, 3 H), 5.54 (d, J = 16.2 Hz, 1 H), 6.74 (d, J = 16.2 Hz, 1 H), 6.85 (dd, J = 3.4, 0.9 Hz, 1 H), 6.99 (d, J = 7.9 Hz, 1 H), 7.16 - 7.24 (m, 1 H), 7.24 - 7.29 (m, 1 H), 7.68 (d, J = 3.4 Hz, 1 H).

Ejemplo 16

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.84 (m, 3 H), 1.18 - 1.35 (m, 4 H), 1.51 - 1.63 (m, 2 H), 2.39 (s, 3 H), 3.27 - 3.37 (m, 2 H), 3.47 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.86 (d, J = 3.4 Hz, 1 H), 7.00 - 7.11 (m, 3 H), 7.49 - 7.54 (m, 1 H), 7.66 (d, J = 3.4 Hz, 1 H), 11.60 (s, 1 H).

Ejemplo 17

{(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-

(pentilsulfonil)acrilamida obtenida en el Ejemplo 16.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.83 (m, 3 H), 1.17 - 1.25 (m, 4 H), 1.37 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.41 (s, 3 H), 5.56 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.95 - 7.07 (m, 2 H), 7.48 (dd, J = 9.6, 1.9 Hz, 1 H), 7.61 (d, J = 3.4 Hz, 1 H).

Ejemplo 18

(2E)-3-[5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 23 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.89 (m, 3 H), 1.21 - 1.38 (m, 4 H), 1.65 - 1.78 (m, 2 H), 2.42 (s, 3 H), 3.30 - 3.35 (m, 2 H), 3.53 (s, 3 H), 3.88 (s, 3 H), 5.24 (d, J = 15.7 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.84 - 6.93 (m, 2 H), 7.04 (d, J = 3.4 Hz, 1 H), 7.17 (s, 1 H), 7.48 (d, J = 15.7 Hz, 1 H), 7.68 (s, 1 H).

Ejemplo 19

{(2E)-3-[5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se

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obtuvo el compuesto del título a partir de (2E)-3-[5-(5-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 18.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.83 (m, 3 H), 1.18 - 1.22 (m, 4 H), 1.40 - 1.48 (m, 2 H), 2.33 (s, 3 H), 2.84 - 2.89 (m, 2 H), 3.41 (s, 3 H), 3.79 (s, 3 H), 5.58 (d, J = 16.3 Hz, 1 H), 6.69 - 6.89 (m, 4 H), 7.20 (d, J = 2.3 Hz, 1 H), 7.45 (d, J = 3.4 Hz, 1 H).

Ejemplo 20

(2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 25 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.91 (m, 3 H), 1.24 - 1.39 (m, 4 H), 1.68 - 1.78 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.34 (m, 2 H), 3.53 (s, 3 H), 5.33 (d, J = 15.9 Hz, 1 H), 6.81 (d, J = 3.0 Hz, 1 H), 6.97 (d, J = 1.7 Hz, 1 H), 7.06 (d, J = 3.0 Hz, 1 H), 7.23 (dd, J = 8.4, 1.7 Hz, 1 H), 7.45 (d, J = 15.9 Hz, 1 H), 7.47 (s, 1 H), 7.65 (d, J = 8.4 Hz, 1 H).

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Ejemplo 21

(2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 28 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.89 (m, 3 H), 1.27 - 1.38 (m, 4 H), 1.67 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 - 3.35 (m, 2 H), 3.47 (s, 3 H), 5.01 (s, 2 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.47 (d, J = 2.3 Hz, 1 H), 6.72 - 6.75 (m, 1 H), 6.94 (d, J = 3.2 Hz, 1 H), 6.99 (dd, J = 8.7, 2.3 Hz, 1 H), 7.29 - 7.51 (m, 7 H), 7.60 (d, J = 8.7 Hz, 1 H).

Ejemplo 22

(2E)-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

A una solución de (2E)-3-{5-[6-(benciloxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 21 (300 mg) en diclorometano (4 ml) se añadió gota a gota tribromuro de boro (solución de diclorometano 1 M, 1.2 ml) con agitación a -78°C, y la mezcla se agitó a -78°C durante 20 min. La mezcla de reacción se neutralizó con metanol (2 ml), y se concentró a presión reducida, se añadió agua, y la mezcla se extrajo

con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (233 mg, rendimiento del 93%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H), 1.24 - 1.43 (m, 4 H), 1.70 - 1.81 (m, 2 H), 2.35 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.51 (s, 3 H), 5.36 - 5.43 (m, 1 H), 6.15 - 6.31 (m, 2 H), 6.73 (d, J = 3.6 Hz, 1 H), 6.83 (dd, J = 8.5, 2.1 Hz, 1 H), 6.92 - 6.93 (m, 1 H), 7.43 (d, J = 15.5 Hz, 1 H), 7.55 (d, J = 8.5 Hz, 1 H), 8.02 (s, 1 H).

Ejemplo 23

(2E)-3-[1,3-dimetil-5-(2-naftil)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(2-naftil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 30 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.0 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.69 - 1.83 (m, 2 H), 2.45 (s, 3 H), 3.32 - 3.41 (m, 2 H), 3.72 (s, 3 H), 5.87 (d, J = 15.5 Hz, 1 H), 7.37 (dd, J = 8.3, 1.9 Hz, 1 H), 7.56 - 7.67 (m, 4 H), 7.79 (s, 1 H), 7.87 - 7.96 (m, 2 H), 8.00 (d, J = 8.7 Hz, 1 H).

Ejemplo 24

(2E)-3-[1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(quinolin-8-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 33 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.1 Hz, 3 H), 1.23 - 1.44 (m, 4 H), 1.70 - 1.85 (m, 2 H), 2.28 (s, 3 H), 3.43 - 3.49 (m, 2 H), 3.53 (s, 3 H), 5.72 (d, J = 15.6 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 7.52 (dd, J = 8.3, 4.1 Hz, 1 H), 7.62 - 7.76 (m, 2 H), 8.03 (dd, J = 7.6, 2.0 Hz, 1 H), 8.31 (dd, J = 8.3, 1.6 Hz, 1 H), 8.78 - 8.87 (m, 1 H), 8.92 (dd, J = 4.1, 1.6 Hz, 1 H).

Ejemplo 25

(2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 36 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.91 (m, 3 H), 1.27 - 1.40 (m, 4 H), 1.69 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.32 - 3.39 (m, 2 H), 3.53 (s, 3 H), 5.36 (d, J = 15.9 Hz, 1

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H), 6.73 - 6.81 (m, 2 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.38 - 7.58 (m, 3 H).

Ejemplo 26

{(2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5,6-difluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 25.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 - 0.83 (m, 3 H), 1.14 - 1.25 (m, 4 H), 1.38 - 1.50 (m, 2 H), 2.33 (s, 3 H), 2.82 - 2.90 (m, 2 H), 3.43 (s, 3 H), 5.52 (d, J = 16.3 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 6.82 (d, J = 3.0 Hz, 1 H), 7.09 (dd, J = 10.8, 7.0 Hz, 1 H), 7.61 (d, J = 3.0 Hz, 1 H), 7.72 (dd, J = 10.8, 8.0 Hz, 1H).

Ejemplo 27

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Una mezcla de 4-dimetilaminopiridina (643 mg), clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (875 mg) y acetonitrilo (10 ml) se agitó a temperatura ambiente durante 10 min. Pentan-1-sulfonamida (541 mg) y ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38

(1.11 g) se añadieron sucesivamente a la mezcla de reacción, y la mezcla se agitó a temperatura ambiente durante 15 h. Se añadió ácido clorhídrico 1 M se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50 - 40:60, v/v) para dar el compuesto del título (927 mg, rendimiento del 59%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.93 (m, 3 H), 1.27 - 1.41 (m, 4 H), 1.67 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.27 - 3.36 (m, 2 H), 3.53 (s, 3 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.78 (dd, J = 3.3, 0.8 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz, 1 H), 7.39 (br s, 1 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H).

Ejemplo 28

{(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de sodio

A una solución de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 27 (173 mg) en metanol (1 ml) se añadió una solución acuosa (0.5 ml) de carbonato de sodio ácido (35 mg), y la mezcla se agitó a temperatura ambiente

durante 6 h. La mezcla de reacción se concentró a presión reducida, y el residuo se cristalizó en éter dietílico-metanol para dar el compuesto del título (174 mg, rendimiento del 95%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.83 (m, 3 H), 1.15 - 1.23 (m, 4 H), 1.39 - 1.49 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.87 (m, 2 H), 3.41 (s, 3 H), 5.56 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz, 1 H), 6.81 (dd, J = 3.2, 0.8 Hz, 1 H), 7.01 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.62 (d, J = 3.2 Hz, 1 H), 7.77 (d, J = 1.9 Hz, 1 H).

Ejemplo 29

(2E)-3-[5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 40 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3 H), 1.27 - 1.37 (m, 4 H), 1.68 - 1.75 (m, 2 H), 2.44 (s, 3 H), 3.31 - 3.35 (m, 2 H), 3.58 (s, 3 H), 5.64 (d, J = 15.6 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 7.36 - 7.45 (m, 2 H), 7.50 - 7.56 (m, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 8.19 (br s, 1 H).

Ejemplo 30

(2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 42 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.66 - 0.90 (m, 3 H), 1.17 - 1.38 (m, 4 H), 1.42 - 1.68 (m, 2 H), 2.41 (s, 3 H), 3.25 - 3.30 (m, 2 H), 3.49 (s, 3 H), 5.82 - 6.15 (m, 1 H), 6.93 - 7.14 (m, 2 H), 7.29 - 7.40 (m, 1 H), 7.52 (dd, J = 8.7, 1.5 Hz, 1 H), 7.85 (d, J = 3.4 Hz, 1 H), 7.96 (d, J = 8.3 Hz, 1 H), 11.58 (s, 1 H).

Ejemplo 31

((2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}prop-2-enoil)(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 30.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.61 - 0.95 (m, 3 H), 1.19 - 1.29 (m, 4 H), 1.32 - 1.51 (m, 2 H), 2.36 (s, 3 H), 2.69 - 2.98 (m, 2 H), 3.22 - 3.33 (m, 2 H), 3.43 (s, 1 H),

5.51 (d, J = 15.9 Hz, 1 H), 6.75 (d, J = 16.3 Hz, 1 H), 6.98 (d, J = 3.4 Hz, 1 H), 7.28 (s, 1 H), 7.49 (d, J = 8.3 Hz, 1 H), 7.81 (d, J = 3.0 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 1 H).

Ejemplo 32

3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)propanamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 45 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 - 0.95 (m, 3 H), 1.32 - 1.45 (m, 4 H), 1.50 - 1.62 (m, 1 H), 1.64 - 1.80 (m, 1 H), 1.99 - 2.13 (m, 1 H), 2.26 (s, 3 H), 2.31 - 2.38 (m, 1 H), 2.54 - 2.66 (m, 1 H), 2.86 - 3.00 (m, 1 H), 3.03 - 3.16 (m, 1 H), 3.23 - 3.37 (m, 4 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 3.8 Hz, 1 H), 7.29 (dd, J = 7.9, 4.9 Hz, 1 H), 8.11 (dd, J = 7.9, 1.4 Hz, 1 H), 8.43 (dd, J = 4.9, 1.4 Hz, 1 H), 12.12 (s, 1 H).

Ejemplo 33

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Una mezcla de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 (300 mg), anhídrido 2-metil-6-

nitrobenzoico (440 mg), 4-metilbencensulfonamida (184 mg), trietilamina (329 mg), 4-dimetilaminopiridina (138 mg) y acetonitrilo (8 ml) se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en éter diisopropílico-metanol para dar el compuesto del título (420 mg, rendimiento del 91%) en forma de cristales incoloros. Punto de fusión 236.9-238.3°C.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.35 (s, 3 H), 2.35 (s, 3 H), 3.47 (s, 3 H), 6.04 (d, J = 16.1 Hz, 1 H), 6.86 (d, J = 3.4 Hz, 1 H), 6.93 (d, J = 16.1 Hz, 1 H), 7.27 (dd, J = 8.0, 4.6 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.67 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 2 H), 8.15 (dd, J = 8.0, 1.5 Hz, 1 H), 8.25 (dd, J = 4.6, 1.5 Hz, 1 H), 12.01 (s, 1 H).

Ejemplo 34

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-2-metil-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-2-metilacrílico obtenido en el Ejemplo de referencia 48 y

pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.28 - 1.45 (m, 4 H), 1.75 - 1.84 (m, 2 H), 2.30 (s, 3 H), 3.40 - 3.50 (m, 2 H), 3.67 (s, 3 H), 6.69 (d, J = 3.8 Hz, 1 H), 7.09 (d, J = 3.8 Hz, 1 H), 7.16 - 7.23 (m, 2 H), 7.77 (s, 1 H), 8.00 (dd, J = 8.0, 1.5 Hz, 1 H), 8.37 (dd, J = 4.5, 1.5 Hz, 1 H).

Ejemplo 35

(2E)-2-metil-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-2-metil-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 53 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.1 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.68 - 1.83 (m, 2 H), 2.12 (s, 3 H), 3.39 - 3.46 (m, 2 H), 3.66 (s, 3 H), 6.74 - 6.76 (m, 1 H), 6.81 (s, 1 H), 7.16 - 7.23 (m, 2 H), 7.89 (s, 1 H), 8.01 (d, J = 7.9 Hz, 1 H), 8.05 - 8.18 (m, 1 H), 8.28 - 8.34 (m, 1 H).

Ejemplo 36

(2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-

(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 57 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.92 (m, 3 H), 1.28 - 1.44 (m, 4 H), 1.69 - 1.84 (m, 2 H), 2.37 (s, 3 H), 3.16 - 3.28 (m, 2 H), 3.29 - 3.40 (m, 2 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 3.80 - 3.89 (m, 2 H), 5.73 (d, J = 2.3 Hz, 1 H), 5.84 (d, J = 15.5 Hz, 1 H), 6.33 (dd, J = 8.0, 2.3 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 15.5 Hz, 1 H), 7.63 - 7.71 (m, 1 H).

Ejemplo 37

{(2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-2,3-dihidro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 36.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.80 - 0.87 (m, 3 H), 1.16 - 1.30 (m, 4 H), 1.45 - 1.55 (m, 2 H), 2.25 (s, 3 H), 2.85 - 2.95 (m, 2 H), 3.10 - 3.17 (m, 2 H), 3.55 (s, 3 H), 3.59 (s, 3 H), 3.70 - 3.80 (m, 1 H), 3.81 - 3.92 (m, 1 H), 5.58 (d, J = 2.3 Hz, 1 H), 5.86 (d, J = 16.2 Hz, 1 H), 6.25 (dd, J = 8.0, 2.3 Hz, 1 H), 6.94 (d, J = 16.2 Hz, 1 H), 7.05 (d, J = 8.0 Hz, 1 H).

Ejemplo 38

(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 60 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.91 (m, 3 H), 1.26 - 1.40 (m, 4 H), 1.67 - 1.82 (m, 2 H), 2.44 (s, 3 H), 3.28 - 3.37 (m, 2 H), 3.55 (s, 3 H), 3.77 (s, 3 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.40 (d, J = 2.3 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.3 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.33 (s, 1 H), 7.50 (d, J = 15.6 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H).

Ejemplo 39

{(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 38.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.76 - 0.86 (m, 3 H), 1.15 - 1.26 (m, 4 H), 1.40 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.79 - 2.91 (m, 2 H), 3.42 (s, 3 H), 3.69 (s, 3 H), 5.60 (d,

J = 16.2 Hz, 1 H), 6.44 (d, J = 2.1 Hz, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.74 - 6.86 (m, 2 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Ejemplo 40

3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)propanamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido 3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 46 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 - 0.94 (m, 3 H), 1.32 - 1.47 (m, 4 H), 1.49 - 1.59 (m, 1 H), 1.60 - 1.75 (m, 1 H), 2.17 (s, 3 H), 2.17 - 2.28 (m, 1 H), 2.37 - 2.47 (m, 1 H), 2.59 - 2.70 (m, 1 H), 2.82 - 3.03 (m, 2 H), 3.17 - 3.35 (m, 3 H), 3.55 (s, 3 H), 3.76 - 3.98 (m, 2 H), 6.69 (dd, J = 7.2, 5.5 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.94 (dd, J = 5.5, 1.5 Hz, 1 H), 12.27 (s, 1 H).

Ejemplo 41

N-[({2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etil}amino)carbonil]pentan-1-sulfonamida

Acido 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 45 (302 mg), azidofosfato de difenilo (438 mg) y trietilamina (165 mg) se disolvieron en N,N-dimetilformamida

(5 ml), y la solución se agitó a temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se disolvió en tolueno (8 ml). La solución se calentó a reflujo durante 2 h, 1,8-diazabiciclo[5.4.0]undec-7-eno (330 mg) y pentan-1-sulfonamida (165 mg) se añadieron a la mezcla de reacción, y la mezcla luego se calentó a reflujo durante 4 h. La mezcla de reacción se concentró a presión reducida, y el residuo se sometió a cromatografía en gel de sílice (acetato de etilo-metanol 95:5, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (196 mg, rendimiento del 42%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.1 Hz, 3 H), 1.28 - 1.48 (m, 4 H), 1.65 - 1.80 (m, 2 H), 2.31 (s, 3 H), 2.32 - 2.43 (m, 1 H), 2.58 - 2.72 (m, 1 H), 3.09 - 3.20 (m, 1 H), 3.23 - 3.30 (m, 2 H), 3.33 - 3.48 (m, 4 H), 5.92 (s, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.19 (d, J = 3.8 Hz, 1 H), 7.27 (dd, J = 7.9, 4.7 Hz, 1 H), 7.79 (s, 1 H), 8.07 (dd, J = 7.9, 1.5 Hz, 1 H), 8.40 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo 42

N-[({2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etil}amino)carbonil]butan-1-sulfonamida

Por medio de un método similar al del Ejemplo 41,

se obtuvo el compuesto del título a partir de ácido 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 45 y butan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.3 Hz, 3 H), 1.37 - 1.50 (m, 2 H), 1.65 - 1.80 (m, 2 H), 2.31 (s, 3 H), 2.32 - 2.40 (m, 1 H), 2.61 - 2.71 (m, 1 H), 3.07 - 3.22 (m, 1 H), 3.22 - 3.29 (m, 2 H), 3.35 - 3.47 (m, 4 H), 5.89 (s, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 7.26 (dd, J = 7.8, 4.8 Hz, 1 H), 7.91 (s, 1 H), 8.07 (dd, J = 7.8, 1.5 Hz, 1 H), 8.40 (dd, J = 4.8, 1.5 Hz, 1 H).

Ejemplo 43

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(fenilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y bencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3 H), 3.47 (s, 3 H), 5.39 (d, J = 15.9 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 1.9 Hz, 1 H), 7.36 (d, J = 15.5 Hz, 1 H), 7.44 - 7.66 (m, 4 H), 7.90 - 7.98 (m, 2 H), 8.21 (br s, 1 H).

Ejemplo 44

{(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(fenilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(fenilsulfonil)acrilamida obtenida en el Ejemplo 43.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.32 (s, 3 H), 3.39 (s, 3 H), 5.52 (d, J = 15.9 Hz, 1 H), 6.70 (d, J = 16.3 Hz, 1 H), 6.80 (d, J = 3.4 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.34 (m, 3 H), 7.59 (d, J = 3.4 Hz, 1 H), 7.64 - 7.70 (m, 2 H), 7.75 (d, J = 1.9 Hz, 1 H).

Ejemplo 45

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 2.41 (s, 3 H), 3.47 (s, 3 H), 5.40 (d, J = 15.6 Hz, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.84 (d, J = 8.9 Hz, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 7.16 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.30 (m, 2 H),

7.35 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 1.9 Hz, 1 H), 7.82 (d, J = 8.3 Hz, 2 H), 8.34 (br s, 1 H).

Ejemplo 46

{(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}[(4-metilfenil)sulfonil]azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida obtenida en el Ejemplo 45.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.27 (s, 3 H), 2.31 (s, 3 H), 3.40 (s, 3 H), 5.51 (d, J = 16.3 Hz, 1 H), 6.68 (d, J = 16.3 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.98 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.50 - 7.61 (m, 3 H), 7.75 (d, J = 1.9 Hz, 1 H).

Ejemplo 47

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-clorofenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 2-clorobencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.51 (s, 3 H), 5.40 (d, J = 15.8 Hz, 1H), 6.75 (dd, J = 3.2, 0.8 Hz, 1

H), 6.86 (d, J = 8.9 Hz, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.30 - 7.57 (m, 4 H), 7.68 (d, J = 1.7 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H).

Ejemplo 48

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(3-clorofenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 3-clorobencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 3.47 (s, 3 H), 5.36 (d, J = 15.8 Hz, 1 H), 6.73 (d, J = 3.2 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.17 (dd, J = 8.7, 2.1 Hz, 1 H), 7.37 (d, J = 15.6 Hz, 1 H), 7.43 (d, J = 7.9 Hz, 1 H), 7.53 - 7.59 (m, 1 H), 7.63 (d, J = 1.9 Hz, 1 H), 7.82 - 7.88 (m, 1 H), 7.91 - 7.96 (m, 1 H).

Ejemplo 49

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-clorofenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-clorobencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3 H), 3.48 (s, 3 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.71 - 6.75 (m, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 7.43 - 7.49 (m, 2 H), 7.64 (d, J = 1.9 Hz, 1 H), 7.86 - 7.93 (m, 2 H), 8.19 (br s, 1 H).

Ejemplo 50

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2,4-diclorofenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 2,4-diclorobencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3 H), 3.48 (s, 3 H), 6.71 (s, 1 H), 6.87 (d, J = 8.9 Hz, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.14 - 7.45 (m, 5 H), 7.64 (d, J = 1.1 Hz, 1 H), 7.91 - 8.06 (m, 1 H).

Ejemplo 51

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[3-(trifluorometil)fenil]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 3-

(trifluorometil)bencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.48 (s, 3 H), 5.31 (d, J = 15.6 Hz, 1 H), 6.74 (dd, J = 3.3, 0.8 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.8, 2.0 Hz, 1 H), 7.38 (d, J = 15.6 Hz, 1 H), 7.62 - 7.70 (m, 2 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.18 - 8.24 (m, 2 H).

Ejemplo 52

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[4-(trifluorometil)fenil]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-(trifluorometil)bencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3 H), 3.48 (s, 3 H), 5.29 (d, J = 15.8 Hz, 1 H), 6.74 (dd, J = 3.2, 0.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 2.1 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 2 H), 8.09 (d, J = 8.3 Hz, 2 H).

Ejemplo 53

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metoxifenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se

obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-metoxibencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H), 6.86 (d, J = 8.9 Hz, 1 H), 6.90 - 6.96 (m, 2 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.36 (d, J = 15.6 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 7.84 - 7.90 (m, 2 H).

Ejemplo 54

(2E)-N-[(4-butilfenil)sulfonil]-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-butilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.95 (m, 3 H), 1.24 - 1.43 (m, 2 H), 1.53 - 1.66 (m, 2 H), 2.37 (s, 3 H), 2.61 - 2.70 (m, 2 H), 3.48 (s, 3 H), 5.38 (d, J = 15.6 Hz, 1 H), 6.73 (dd, J = 3.2, 0.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.05 (d, J = 3.2 Hz, 1 H), 7.17 (dd, J = 8.7, 1.9 Hz, 1 H), 7.25 - 7.31 (m, 2 H), 7.36 (d, J = 15.6 Hz, 1 H), 7.64 (d, J = 1.5 Hz, 1 H), 7.80 - 7.88 (m, 2 H).

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Ejemplo 55

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(2-furilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y furan-2-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3 H), 3.50 (s, 3 H), 5.50 (d, J = 15.8 Hz, 1 H), 6.48 (dd, J = 3.5, 1.8 Hz, 1 H), 6.75 - 6.79 (m, 1 H), 6.88 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.40 (d, J = 15.6 Hz, 1 H), 7.51 (d, J = 0.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Ejemplo 56

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(2-tienilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y tiofen-2-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.39 (s, 3 H), 3.48 (s, 3 H), 5.41 (d, J = 15.6 Hz, 1 H), 6.73 - 6.76 (m, 1 H), 6.87 (d, J = 8.7 Hz, 1 H), 7.02 - 7.09 (m, 2 H), 7.18 (dd, J = 8.8, 2.0 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.62 (dd, J = 5.1,

1.3 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H), 7.75 (dd, J = 3.8, 1.3 Hz, 1 H).

Ejemplo 57

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(2,3-dihidro-1-benzofuran-5-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 2,3-dihidro-1-benzofuran-5-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.24 (t, J = 8.8 Hz, 2 H), 3.49 (s, 3 H), 4.66 (t, J = 8.8 Hz, 2 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.73 - 6.89 (m, 3 H), 7.06 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.8, 2.0 Hz, 1 H), 7.36 (d, J = 15.8 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 7.72 (dd, J = 8.6, 2.2 Hz, 1 H), 7.81 (d, J = 1.9 Hz, 1 H).

Ejemplo 58

(2E)-N-(bencilsulfonil)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 1-fenilmetansulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3 H), 3.47 - 3.52 (m, 3 H), 4.49 (br s, 2 H), 5.31 (d, J = 15.3 Hz, 1 H), 6.71 (d, J = 2.1 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 3.2 Hz, 1 H), 7.15 - 7.49 (m, 7 H), 7.65 (s, 1 H).

Ejemplo 59

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(ciclopropilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y ciclopropansulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.01 - 1.09 (m, 2 H), 1.25 - 1.33 (m, 2 H), 2.43 (s, 3 H), 2.72 - 2.84 (m, 1 H), 3.52 (s, 3 H), 5.42 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Ejemplo 60

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(ciclopropilmetil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 1-

ciclopropilmetansulfonamida obtenida en el Ejemplo de referencia 100.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.28 (d, J = 4.5 Hz, 2 H), 0.55 - 0.68 (m, 2 H), 1.01 (d, J = 8.0 Hz, 1 H), 2.44 (s, 3 H), 3.22 (dd, J = 7.2, 1.9 Hz, 2 H), 3.53 (s, 3 H), 5.32 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.46 (d, J = 15.9 Hz, 1 H), 7.71 (s, 1 H).

Ejemplo 61

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilpentil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 4-metilpentan-1-sulfonamida obtenida en el Ejemplo de referencia 101.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (d, J = 6.6 Hz, 6 H), 1.18 - 1.29 (m, 2 H), 1.45 - 1.58 (m, 1 H), 1.66 - 1.80 (m, 2 H), 2.44 (s, 3 H), 3.30 (dd, J = 8.7, 7.2 Hz, 2 H), 3.52 (s, 3 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.78 (dd, J = 3.3, 0.8 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H).

Ejemplo 62

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida

Una mezcla de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 (353 mg), anhídrido 2-metil-6-nitrobenzoico (462 mg), N-pentilsulfamida obtenida en el Ejemplo de referencia 287 (195 mg), trietilamina (339 mg), 4-dimetilaminopiridina (137 mg) y acetonitrilo (11 ml) se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (299 mg, rendimiento del 58%) en forma de cristales incoloros. Punto de fusión 184.3-184.4°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.78 - 0.94 (m, 3 H), 1.19 - 1.35 (m, 4 H), 1.49 (d, J = 6.4 Hz, 2 H), 2.42 (s, 3 H), 2.90 (q, J = 6.6 Hz, 2 H), 3.52 (s, 3 H), 5.11 - 5.21 (m, 1 H), 5.31 (d, J = 15.5 Hz, 1 H), 6.74 - 6.96 (m, 2 H), 7.06 - 7.29 (m, 2 H), 7.40 (d, J = 15.9 Hz, 1 H), 7.69 (s, 1 H),

8.12 (br s, 1 H).

Ejemplo 63

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(2-isopropoxietil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(2-isopropoxietil)sulfamida obtenida en el Ejemplo de referencia 279.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10 (d, J = 6.1 Hz, 6 H), 2.43 (s, 3 H), 3.13 (t, J = 4.9 Hz, 2 H), 3.42 - 3.57 (m, 6 H), 5.26 (d, J = 15.9 Hz, 1 H), 5.44 (br s, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.42 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H).

Ejemplo 64

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[metil(pentil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-metil-N-pentilsulfamida obtenida en el Ejemplo de referencia 110.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.79 - 0.92 (m, 3 H), 1.19 - 1.40 (m, 4 H), 1.47 - 1.60 (m, 2 H), 2.42 (s, 3 H), 2.87 (s, 3 H), 3.20 (t, J = 7.4 Hz, 2 H), 3.50 (s, 3 H), 5.41 (d, J = 15.5 Hz, 1 H), 6.76 (d, J = 2.7 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.38 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H), 8.13 (br s, 1 H).

Ejemplo 65

(pentilsulfonil)carbamato de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilo

A una solución de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 (358 mg) en N,N-dimetilformamida (13 ml) se añadió N,N'-carbonildiimidazol (252 mg), y la mezcla se agitó a 50°C durante 1 h. Pentan-1-sulfonamida (294 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (336 mg) y 4-dimetilaminopiridina (206 mg) se añadieron a esta mezcla de reacción, y la mezcla se agitó a 50°C durante 4 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 60:40, v/v), y se cristalizó en hexano-acetato de etilo

para dar el compuesto del título (233 mg, rendimiento del 38%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.94 (m, 3 H), 1.25 - 1.46 (m, 4 H), 1.72 - 1.85 (m, 2 H), 2.35 (s, 3 H), 3.25 - 3.33 (m, 2 H), 3.50 (s, 3 H), 4.78 - 4.95 (m, 2 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 66

(pentilsulfonil)carbamato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo

Por medio de un método similar al del Ejemplo 65, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol obtenido en el Ejemplo de referencia 63 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.0 Hz, 3 H), 1.23 - 1.47 (m, 4 H), 1.70- 1.82 (m, 2 H), 2.29 (s, 3 H), 2.51 - 2.69 (m, 2 H), 3.22 - 3.31 (m, 2 H), 3.49 (s, 3 H), 3.92 - 4.17 (m, 2 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.18 - 7.27 (m, 1 H), 7.69 (d, J = 2.3 Hz, 1 H).

Ejemplo 67

(pentilsulfonil)carbamato de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propilo

Por medio de un método similar al del Ejemplo 65,

se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenida en el Ejemplo de referencia 66 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.94 (m, 3 H), 1.28 - 1.47 (m, 4 H), 1.56 - 1.70 (m, 2 H), 1.73 - 1.86 (m, 2 H), 2.20 - 2.42 (m, 5 H), 3.25 - 3.33 (m, 2 H), 3.47 (s, 3 H), 3.93 - 4.03 (m, 2 H), 6.69 - 6.72 (m, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m, 1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Ejemplo 68

(fenilsulfonil)carbamato de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilo

Por medio de un método similar al del Ejemplo 65, se obtuvo el compuesto del título a partir de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 y bencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.24 (s, 3 H), 3.49 (s, 3 H), 4.65 - 4.83 (m, 2 H), 6.66 (d, J = 2.8 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.15 (dd, J = 8.8, 2.0 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 7.60 - 7.68 (m, 2 H), 7.91 - 7.98 (m, 2 H).

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Ejemplo 69

[(4-metilfenil)sulfonil]carbamato de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilo

Por medio de un método similar al del Ejemplo 65, se obtuvo el compuesto del título a partir de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.25 (s, 3 H), 2.44 (s, 3 H), 3.49 (s, 3 H), 4.64 - 4.81 (m, 2 H), 6.66 (d, J = 2.6 Hz, 1 H), 6.86 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.15 (dd, J = 8.7, 1.9 Hz, 1 H), 7.29 (d, J = 8.3 Hz, 2 H), 7.65 (d, J = 1.7 Hz, 1 H), 7.82 (d, J = 8.5 Hz, 2 H).

Ejemplo 70

[(4-metoxifenil)sulfonil]carbamato de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilo

Por medio de un método similar al del Ejemplo 65, se obtuvo el compuesto del título a partir de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 y 4-metoxibencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.26 (s, 3 H), 3.49 (s, 3 H), 3.87 (s, 3 H), 4.65 - 4.83 (m, 2 H), 6.64 - 6.69 (m, 1 H), 6.84 - 7.02 (m, 3 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.16 (dd, J = 8.7, 1.9 Hz, 1 H), 7.65 (d, J = 1.9 Hz, 1 H), 7.83 - 7.90 (m, 2 H).

Ejemplo 71

{[(2-isopropoxietil)amino]sulfonil}carbamato de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilo

A una solución de [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanol obtenido en el Ejemplo de referencia 61 (355 mg) en acetonitrilo (13 ml) se añadió isocianato de clorosulfonilo (191 mg) con agitación a 0°C, y la mezcla se agitó a 0°C durante 30 min. Se añadió piridina (306 mg) a esta mezcla de reacción, y la mezcla se agitó a 0°C durante 1 h. Se añadió éter 2-aminoetilisopropílico (797 mg), y la mezcla se agitó a temperatura ambiente durante 17 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v) para dar el compuesto del título (141 mg, rendimiento del 23%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.09 (dd, J = 6.0, 0.9 Hz, 6 H), 2.36 (s, 3 H), 3.17 (br s, 2 H), 3.44 - 3.56 (m, 6 H), 4.77 - 4.92 (m, 2 H), 5.35 (br s, 1 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.15 - 7.23 (m, 2 H), 7.67 (d, J = 1.5 Hz, 1 H).

Ejemplo 72

{[(2-isopropoxietil)amino]sulfonil}carbamato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanol obtenido en el Ejemplo de referencia 63, isocianato de clorosulfonilo y éter 2-aminoetilisopropílico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10 (d, J = 6.2 Hz, 6 H), 2.31 (s, 3 H), 2.50 - 2.68(m, 2 H), 3.08 - 3.18 (m, 2 H), 3.45 - 3.58 (m, 6 H), 3.93 - 4.17 (m, 2 H), 5.34 (br s, 1 H), 6.71 (dd, J = 3.2, 0.8 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 1 H), 7.14 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.9, 2.1 Hz, 1 H), 7.69 (d, J = 1.5 Hz, 1 H).

Ejemplo 73

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenido en el Ejemplo de referencia 66, isocianato de clorosulfonilo y éter 2-aminoetilisopropílico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.12 (dd, J = 6.1, 1.0 Hz, 6 H), 1.52 - 1.68 (m, 2 H), 2.19 - 2.41 (m, 5 H), 3.17 (br s,

2 H), 3.44 - 3.62 (m, 6 H), 3.90 - 4.04 (m, 2 H), 5.34 (br s, 1 H), 6.71 (dd, J = 3.4, 0.8 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.17 - 7.22 (m,1 H), 7.68 (d, J = 1.7 Hz, 1 H).

Ejemplo 74

{[(4-metoxibencil)amino]sulfonil}carbamato de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenida en el Ejemplo de referencia 66, isocianato de clorosulfonilo y 4-metoxibencilamine.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.50 - 1.62 (m, 2 H), 2.16 - 2.37 (m, 5 H), 3.47 (s, 3 H), 3.76 (s, 3 H), 3.82 - 3.95 (m, 2 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.30 (br s, 1 H), 6.69 (dd, J = 3.2, 0.8 Hz, 1 H), 6.79 - 6.85 (m, 2 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.14 - 7.22 (m, 3 H), 7.68 (d, J = 1.9 Hz, 1 H).

Ejemplo 75

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acetamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acético obtenido en el Ejemplo de referencia 67 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.93 (m, 3 H), 1.19 - 1.38 (m, 4 H), 1.52 - 1.70 (m, 2 H), 2.29 (s, 3 H), 3.09 - 3.32 (m, 4 H), 3.52 (s, 3 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Ejemplo 76

3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)propanamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 68 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 - 0.93 (m, 3 H), 1.21 - 1.43 (m, 4 H), 1.64 - 1.77 (m, 2 H), 2.10 - 2.19 (m, 2 H), 2.29 (s, 3 H), 2.53 - 2.66 (m, 2 H), 3.24 - 3.32 (m, 2 H), 3.44 (s, 3 H), 6.69 (dd, J = 3.3, 0.8 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 77

(2E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)but-2-enamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-4-[5-

(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]but-2-enoico obtenida en el Ejemplo de referencia 70 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.94 (m, 3 H), 1.22 - 1.45 (m, 4 H), 1.67 - 1.81 (m, 2 H), 2.39 (s, 3 H), 3.02 (dd, J = 7.3, 1.1 Hz, 2 H), 3.28 - 3.37 (m, 2 H), 3.51 (s, 3 H), 5.15 - 5.27 (m, 1 H), 6.09 (d, J = 16.2 Hz, 1 H), 6.72 - 6.76 (m, 1 H), 6.90 - 6.99 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.22 (dd, J = 8.7, 2.1 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Ejemplo 78

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acetamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido [5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acético obtenido en el Ejemplo de referencia 67 y N-pentilsulfamida obtenida en el Ejemplo de referencia 287.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.9 Hz, 3 H), 1.16 - 1.33 (m, 4 H), 1.37 - 1.49 (m, 2 H), 2.28 (s, 3 H), 2.71 (d, J = 6.2 Hz, 2 H), 3.14 - 3.31 (m, 2 H), 3.51 (s, 3 H), 5.08 (br s, 1 H), 6.67 - 6.71 (m, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Ejemplo 79

4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]butanamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido 4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]butanoico obtenido en el Ejemplo de referencia 71 y N-pentilsulfamida obtenida en el Ejemplo de referencia 287.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.6 Hz, 3 H), 1.24 - 1.32 (m, 4 H), 1.43 - 1.67 (m, 4 H), 2.00 - 2.09 (m, 2 H), 2.16 - 2.36 (m, 5 H), 2.81 - 2.91 (m, 2 H), 3.48 (s, 3 H), 5.05 (br s, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Ejemplo 80

N-[({[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}amino)carbonil]pentan-1-sulfonamida

A una solución de 1-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanamina obtenida en el Ejemplo de referencia 75 (508 mg) en N,N-dimetilformamida (18 ml) se añadió N,N'-carbonildiimidazol (449 mg), y la mezcla se agitó a 50°C durante 2 h. Pentan-1-sulfonamida (419 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (478 mg) y 4-dimetilaminopiridina (384 mg) se añadieron a esta mezcla de reacción, y la mezcla se agitó a 50°C durante 4 h. Después de

dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (612 mg, rendimiento del 73%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.93 (m, 3 H), 1.23 - 1.38 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.33 (s, 3 H), 2.92 - 3.00 (m, 2 H), 3.47 (s, 3 H), 3.99 - 4.12 (m, 2 H), 6.33 - 6.42 (m, 1 H), 6.69 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo 81

N-[({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}amino)carbonil]pentan-1-sulfonamida

Por medio de un método similar al del Ejemplo 80, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etanamina obtenida en el Ejemplo de referencia 76 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.0 Hz, 3 H), 1.24 - 1.45 (m, 4 H), 1.70 - 1.83 (m, 2 H), 2.30 (s, 3 H), 2.34 - 2.57 (m, 2 H), 3.06 - 3.18 (m, 4 H), 3.46 (s, 3 H),

6.31 (br s, 1 H), 6.68 (d, J = 3.2 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.15 - 7.22 (m, 2 H), 7.65 (d, J = 1.9 Hz, 1 H)

Ejemplo 82

N-[({3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propil}amino)carbonil]pentan-1-sulfonamida

Por medio de un método similar al del Ejemplo 80, se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-amina obtenida en el Ejemplo de referencia 77 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 - 0.93 (m, 3 H), 1.29 - 1.40 (m, 4 H), 1.42 - 1.54 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.14 - 2.34 (m, 5 H), 3.02 - 3.12 (m, 4 H), 3.45 (s, 3 H), 6.24 (t, J = 5.3 Hz, 1 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Ejemplo 83

N-[({[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}amino)carbonil]-4-metilbencensulfonamida

Por medio de un método similar al del Ejemplo 80, se obtuvo el compuesto del título a partir de 1-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metanamina obtenida en el Ejemplo de referencia 75 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.23 (s, 3 H), 2.42 (s, 3

H), 3.48 (s, 3 H), 3.98 (d, J = 4.9 Hz, 2 H), 6.56 (br s, 1 H), 6.68 (d, J = 3.0 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.11 - 7.30 (m, 4 H), 7.53 - 7.70 (m, 3 H).

Ejemplo 84

(5Z)-5-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilen}-1,3-tiazolidin-2,4-diona

A una solución de 5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-carbaldehído obtenida en el Ejemplo de referencia 37 (560 mg) en etanol (6.8 ml) se añadieron 1,3-tiazolidin-2,4-diona (719 mg) y piperidina (382 mg), y la mezcla se calentó a reflujo durante 20 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 70:30, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (213 mg, rendimiento del 28%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 3.45 (s, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.0 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (s, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.07 (br s, 1 H).

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Ejemplo 85

(5Z)-5-{3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propiliden}-1,3-tiazolidin-2,4-diona

Por medio de un método similar al del Ejemplo 84, se obtuvo el compuesto del título a partir de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propanal obtenido en el Ejemplo de referencia 78 y 1,3-tiazolidin-2,4-diona.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.14 (q, J = 7.3 Hz, 2 H), 2.30 (s, 3 H), 2.37 - 2.57 (m, 2 H), 3.48 (s, 3 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.76 (t, J = 7.6 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H), 8.20 (br s, 1 H).

Ejemplo 86

5-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}-1,3-tiazolidin-2,4-diona

(5Z)-5-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metilen}-1,3-tiazolidin-2,4-diona obtenido en el Ejemplo 84 (86 mg) se disolvió en un solvente mixto de tetrahidrofurano (2 ml) y etanol (2 ml), se añadió paladio sobre carbón al 10% (30 mg), y la mezcla se agitó bajo 1 átomo de atmósfera de hidrógeno a temperatura ambiente durante 6 días. El catalizador se eliminó por filtración, y el filtrado se concentró. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v), y se cristalizó en hexano-etanol para dar

el compuesto del título (33 mg, rendimiento del 37%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.50 (br s, 3 H), 2.67 (br s, 1 H), 3.13 (br s, 1 H), 3.38 (s, 3 H), 4.29 (br s, 1 H), 6.77 (br s, 1 H), 6.96 - 7.10 (m, 1 H), 7.20 (d, J = 7.2 Hz, 1 H), 7.59 (br s, 1 H), 7.75 (br s, 1 H), 11.94 (d, J = 1.5 Hz, 1 H).

Ejemplo 87

5-{3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propil}-1,3-tiazolidin-2,4-diona

Por medio de un método similar al del Ejemplo 86, se obtuvo el compuesto del título a partir de (5Z)-5-{3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propilidene}-1,3-tiazolidin-2,4-diona obtenida en el Ejemplo 85.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.39 (d, J = 0.9 Hz, 2 H), 1.64 - 1.78 (m, 1 H), 1.93 (br s, 1 H), 2.20 - 2.36 (m, 5 H), 3.47 (d, J = 2.4 Hz, 3 H), 4.02 - 4.10 (m, 1 H), 6.68 (d, J = 3.2 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.08 (dd, J = 3.2, 1.3 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.67 (s, 1 H), 8.02 (br s, 1 H).

Ejemplo 88

(2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se

obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 81 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.91 (m, 3 H), 1.23 - 1.46 (m, 4 H), 1.68 - 1.80 (m, 2 H), 2.46 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.53 (s, 3 H), 5.45 (d, J = 15.6 Hz, 1 H), 6.93 (d, J = 3.2 Hz, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.51 (dd, J = 8.5, 1.3 Hz, 1 H), 8.10 (d, J = 0.9 Hz, 1 H).

Ejemplo 89

(2E)-3-[5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 83 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.90 (m, 3 H), 1.19 - 1.44 (m, 4 H), 1.66 - 1.79 (m, 2 H), 2.44 (s, 3 H), 3.29 - 3.38 (m, 2 H), 3.53 (s, 3 H), 5.40 (d, J = 15.8 Hz, 1 H), 6.67 (dd, J = 9.1, 2.4 Hz, 1 H), 6.80 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 7.08 (m, 2 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.65 (dd, J = 8.8, 5.2 Hz, 1 H).

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Ejemplo 90

{(2E)-3-[5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 89.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.76 - 0.85 (m, 3 H), 1.15 - 1.26 (m, 4 H), 1.37 - 1.49 (m, 2 H), 2.34 (s, 3 H), 2.81 - 2.91 (m, 2 H), 3.43 (s, 3 H), 5.55 (d, J = 15.9 Hz, 1 H), 6.71 - 6.85 (m, 3 H), 6.99 - 7.09 (m, 1 H), 7.52 (d, J = 3.0 Hz, 1 H), 7.71 (dd, J = 8.7, 5.3 Hz, 1 H).

Ejemplo 91

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-3-(metoximetil)-1-metil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 88 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.91 (m, 3 H), 1.25 - 1.41 (m, 4 H), 1.68 - 1.81 (m, 2 H), 3.30 - 3.39 (m, 2 H), 3.46 (s, 3 H), 3.57 (s, 3 H), 4.54 - 4.65 (m, 2 H), 5.76 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.13 (d, J = 3.4 Hz, 1 H),

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7.34 - 7.47 (m, 2 H).

Ejemplo 92

3-{(E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]vinil}-1,2,4-oxadiazol-5(4H)-ona

A una solución de (1Z,2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N'-hidroxiprop-2-enimidamida obtenida en el Ejemplo de referencia 90 (152 mg) en tetrahidrofurano (4.6 ml) se añadieron N,N'-carbonildiimidazol (112 mg) y 1,8-diazabiciclo[5.4.0]undec-7-eno (281 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. ácido clorhídrico 1 N se añadió a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (109 mg, rendimiento del 67%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.47 (s, 3 H), 3.54 (s, 3 H), 5.75 (d, J = 17.0 Hz, 1 H), 6.73 (d, J = 17.0 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.6, 2.0 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

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Ejemplo 93

2-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metoxi}-N-(pentilsulfonil)acetamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido {[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metoxi}acético obtenido en el Ejemplo de referencia 93 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.94 (m, 3 H), 1.27 - 1.45 (m, 4 H), 1.73 - 1.86 (m, 2 H), 2.35 (s, 3 H), 3.31 - 3.40 (m, 2 H), 3.53 (s, 3 H), 3.82 (s, 2 H), 4.14 - 4.32 (m, 2 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.0 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H).

Ejemplo 94

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(1-propilbutil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(1-propilbutil)sulfamida obtenida en el Ejemplo de referencia 112.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.82 (t, J = 7.0 Hz, 6 H), 1.18 - 1.46 (m, 8 H), 2.43 (s, 3 H), 3.20 - 3.31 (m, 1 H),

3.53 (s, 3 H), 4.86 (d, J = 8.0 Hz, 1 H), 5.27 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.83 (br s, 1 H).

Ejemplo 95

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(ciclohexilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-ciclohexilsulfamida obtenida en el Ejemplo de referencia 114.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10 - 1.30 (m, 6 H), 1.62 - 1.72 (m, 2 H), 1.77 - 1.88 (m, 2 H), 2.44 (s, 3 H), 3.08 - 3.22 (m, 1 H), 3.53 (s, 3 H), 4.94 (d, J = 7.2 Hz, 1 H), 5.23 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.88 - 6.93 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.9 Hz, 1 H), 7.72 (d, J = 1.9 Hz, 1 H).

Ejemplo 96

(3E)-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-oxo-N-(pentilsulfonil)but-3-enamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (3E)-4-[5-

(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-2-oxobut-3-enoico obtenido en el Ejemplo de referencia 94 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.1 Hz, 3 H), 1.27 - 1.45 (m, 4 H), 1.75 - 1.88 (m, 2 H), 2.53 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.55 (s, 3 H), 6.76 - 6.83 (m, 2 H), 6.88 - 6.94 (m, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.64 (d, J = 16.2 Hz, 1 H), 7.72 (d, J = 1.9 Hz, 1 H), 9.11 (br s, 1 H).

Ejemplo 97

5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-1,3-tiazolidin-2,4-diona

A una solución de 2-cloro-4-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]butanoato de etilo obtenida en el Ejemplo de referencia 97 (99 mg) en etanol (2.5 ml) se añadieron tiourea (76 mg) y acetato de sodio (82 mg), y la mezcla se calentó a reflujo durante 36 h. Se agregó ácido clorhídrico 6 N (10 ml) a esta mezcla de reacción, y la mezcla se calentó a reflujo durante 8 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 70:30, v/v) para dar el

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compuesto del título (59 mg, rendimiento del 61%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.75 - 1.92 (m, 1 H), 2.06 - 2.21 (m, 1 H), 2.25 - 2.54 (m, 5 H), 3.48 (s, 3 H), 3.95 - 4.06 (m, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 1 H), 7.08 - 7.12 (m, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.16 (br s, 1 H).

Ejemplo 98

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(morfolin-4-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y morfolin-4-sulfonamida obtenida en el Ejemplo de referencia 109.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 3.25 - 3.32 (m, 4 H), 3.52 (s, 3 H), 3.65 - 3.73 (m, 4 H), 5.35 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 7.67 - 7.75 (m, 2 H).

Ejemplo 99

(2E)-N-[(butilamino)sulfonil]-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62,

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se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3 H), 1.23 - 1.39 (m, 2 H), 1.40 - 1.54 (m, 2 H), 2.44 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.53 (s, 3 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 2.6 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.75 (br s, 1 H).

Ejemplo 100

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3 H), 1.24 - 1.40 (m, 2 H), 1.41 - 1.55 (m, 2 H), 2.38 (s, 3 H), 2.97 (q, J = 6.8 Hz, 2 H), 3.59 (s, 3 H), 5.12 (t, J = 6.2 Hz, 1 H), 5.45 (d, J = 15.6 Hz, 1 H), 6.80 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 8.06 (dd, J = 7.9, 1.5 Hz, 1 H), 8.16 (br s, 1

H), 8.35 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo 101

N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido 3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propanoico obtenido en el Ejemplo de referencia 45 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.2 Hz, 3 H), 1.31 - 1.44 (m, 2 H), 1.45 - 1.55 (m, 2 H), 2.01 - 2.16 (m, 1 H), 2.26 (s, 3 H), 2.29 - 2.40 (m, 1 H), 2.53 - 2.68 (m, 2 H), 2.72 - 3.00 (m, 2 H), 3.30 (s, 3 H), 4.96 (s, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 7.29 (dd, J = 7.9, 4.8 Hz, 1 H), 8.11 (dd, J = 7.9, 1.5 Hz, 1 H), 8.42 (dd, J = 4.8, 1.5 Hz, 1 H), 11.87 (s, 1 H).

Ejemplo 102

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.17 (m, 2 H), 0.46 - 0.54 (m, 2 H), 0.84 - 1.00 (m, 1 H), 2.43 (s, 3 H), 2.78 - 2.83 (m, 2 H), 3.53 (s, 3 H), 5.17 - 5.22 (m, 2 H), 6.78 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.9, 2.0 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.70 (s, 1 H), 7.71 (d, J = 2.0 Hz, 1 H).

Ejemplo 103

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(1-etilpropil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(1-etilpropil)sulfamida obtenida en el Ejemplo de referencia 113.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.81 - 0.86 (m, 6 H), 1.30 - 1.55 (m, 4 H), 2.43 (s, 3 H), 3.08 - 3.20 (m, 1 H), 3.53 (s, 3 H), 4.86 (d, J = 7.6 Hz, 1 H), 5.25 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 2.3 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.42 (d, J = 15.9 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.77 (s, 1 H).

Ejemplo 104

N-[({(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}amino)sulfonil]glicinato de etilo

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(aminosulfonil)glicinato de etilo obtenido en el Ejemplo de referencia 117.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.42 (s, 3 H), 3.52 (s, 3 H), 3.87 (s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 15.6 Hz, 1 H), 5.59 (s, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.88 - 6.95 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.43 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 2.0 Hz, 1 H), 7.80 (br s, 1 H).

Ejemplo 105

(2E)-N-[(butilamino)sulfonil]-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 2 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.2 Hz, 3

H), 1.07 - 1.30 (m, 2 H), 1.30 - 1.41 (m, 2 H), 2.40 (s, 3 H), 2.71 - 2.85 (m, 2 H), 3.47 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 6.85 (d, J = 3.0 Hz, 1 H), 6.92 - 7.06 (m, 2 H), 7.11 - 7.25 (m, 2 H), 7.52 (t, J = 5.7 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.68 - 7.81 (m, 1 H), 11.31 (s, 1 H).

Ejemplo 106

(2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 2 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, J = 7.4 Hz, 3 H), 1.25 - 1.52 (m, 2 H), 2.40 (s, 3 H), 2.63 - 2.86 (m, 2 H), 3.47 (s, 3 H), 6.12 (d, J = 16.3 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.92 - 7.07 (m, 2 H), 7.13 - 7.25 (m, 2 H), 7.52 (br s, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.65 - 7.78 (m, 1 H), 11.31 (s, 1 H).

Ejemplo 107

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

obtenido en el Ejemplo de referencia 2 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.05 - 0.15 (m, 2 H), 0.24 - 0.39 (m, 2 H), 0.72 - 0.94 (m, 1 H), 2.40 (s, 3 H), 2.71 (t, J = 6.4 Hz, 2 H), 3.47 (s, 3 H), 6.11 (d, J = 16.0 Hz, 1 H), 6.85 (dd, J = 3.3, 0.8 Hz, 1 H), 6.99 (d, J = 16.0 Hz, 1 H), 6.98 - 7.04 (m, 1 H), 7.15 - 7.25 (m, 2 H), 7.52 - 7.64 (m, 2 H), 7.67 - 7.82 (m, 1 H), 11.32 (s, 1 H).

Ejemplo 108

(2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 130 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, J = 7.1 Hz, 3 H), 1.10 - 1.42 (m, 4 H), 1.46 - 1.65 (m, 2 H), 2.40 (s, 3 H), 3.24 - 3.32 (m, 2 H), 3.50 (s, 3 H), 6.07 (d, J = 16.0 Hz, 1 H), 6.91 - 7.13 (m, 2 H), 7.20 - 7.41 (m, 2 H), 7.60 - 7.73 (m, 1 H), 7.92 (s, 1 H), 11.62 (s, 1 H).

Ejemplo 109

(2E)-N-[(butilamino)sulfonil]-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 130 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.3 Hz, 3 H), 1.12 - 1.28 (m, 2 H), 1.28 - 1.42 (m, 2 H), 2.40 (s, 3 H), 2.67 - 2.87 (m, 2 H), 3.49 (s, 3 H), 6.08 (d, J = 16.2 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.04 - 7.12 (m, 1 H), 7.19 - 7.41 (m, 2 H), 7.54 (t, J = 5.6 Hz, 1 H), 7.57 - 7.71 (m, 1 H), 7.92 (s, 1 H), 11.32 (s, 1 H).

Ejemplo 110

(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 60 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.36 (s, 3 H), 2.37 (s, 3 H), 3.46 (s, 3 H), 3.66 (s, 3 H), 6.05 (d, J = 16.0 Hz, 1 H), 6.44 (d, J = 1.9 Hz, 1 H), 6.73 (d, J = 2.8 Hz, 1 H), 6.83

(dd, J = 8.5, 2.3 Hz, 1 H), 6.95 (d, J = 16.0 Hz, 1 H), 7.25 - 7.39 (m, 3 H), 7.58 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 12.02 (s, 1 H).

Ejemplo 111

{(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}[(4-metilfenil)sulfonil]azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida obtenida en el Ejemplo 110.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.27 (s, 3 H), 2.32 (s, 3 H), 3.41 (s, 3 H), 3.67 (s, 3 H), 5.56 (d, J = 16.0 Hz, 1 H), 6.41 (d, J = 2.3 Hz, 1 H), 6.66 - 6.76 (m, 2 H), 6.81 (dd, J = 8.5, 2.3 Hz, 1 H), 7.09 (d, J = 7.9 Hz, 2 H), 7.29 (d, J = 3.2 Hz, 1 H), 7.48 - 7.60 (m, 3 H).

Ejemplo 112

(2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 136 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, J = 7.1 Hz, 3

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H), 0.97 - 1.41 (m, 4 H), 1.49 - 1.68 (m, 2 H), 2.36 (d, J = 1.1 Hz, 3 H), 2.38 (s, 3 H), 3.27 - 3.35 (m, 2 H), 3.48 (s, 3 H), 6.12 (d, J = 15.9 Hz, 1 H), 7.03 (d, J = 15.9 Hz, 1 H), 7.27 (dd, J = 7.8, 4.7 Hz, 1 H), 7.47 (d, J = 0.8 Hz, 1 H), 8.13 (dd, J = 8.0, 1.5 Hz, 1 H), 8.25 (dd, J = 4.5, 1.5 Hz, 1 H), 11.59 (s, 1 H).

Ejemplo 113

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 136 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.3 Hz, 3 H), 1.13 - 1.28 (m, 2 H), 1.29 - 1.43 (m, 2 H), 2.36 (d, J = 0.9 Hz, 3 H), 2.38 (s, 3 H), 2.79 (q, J = 6.8 Hz, 2 H), 3.48 (s, 3 H), 6.13 (d, J = 16.0 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.26 (dd, J = 7.9, 4.7 Hz, 1 H), 7.47 (d, J = 1.1 Hz, 1 H), 7.48 - 7.51 (m, 1 H), 8.13 (dd, J = 7.8, 1.6 Hz, 1 H), 8.25 (dd, J = 4.7, 1.3 Hz, 1 H), 11.29 (s, 1 H).

Ejemplo 114

(2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 136 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.34 (d, J = 1.1 Hz, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 3.46 (s, 3 H), 6.07 (d, J = 16.0 Hz, 1 H), 6.92 (d, J = 16.0 Hz, 1 H), 7.25 (dd, J = 7.9, 4.7 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 2 H), 7.43 (d, J = 1.1 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 2 H), 8.12 (dd, J = 7.8, 1.6 Hz, 1 H), 8.23 (dd, J = 4.7, 1.5 Hz, 1 H), 12.00 (s, 1 H).

Ejemplo 115

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 136 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.04 - 0.16 (m, 2 H), 0.26 - 0.46 (m, 2 H), 0.70 - 0.97 (m, 1 H), 2.36 (d, J = 1.1 Hz, 3 H), 2.37 (s, 3 H), 2.72 (t, J = 6.4 Hz, 2 H), 3.48 (s, 3 H), 6.12 (d, J = 16.0 Hz, 1 H), 6.99 (d, J = 16.0 Hz, 1 H), 7.26 (dd, J = 7.8, 4.8 Hz, 1 H), 7.47 (d, J = 1.1 Hz, 1 H), 7.62 (t, J = 6.1 Hz, 1 H), 8.13 (dd, J = 7.9, 1.5 Hz, 1 H), 8.25 (dd, J = 4.7, 1.5 Hz, 1 H), 11.30 (s, 1 H).

Ejemplo 116

(2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 140 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.82 (t, J = 7.0 Hz, 3 H), 1.17 - 1.40 (m, 4 H), 1.53 - 1.66 (m, 2 H), 2.38 (s, 3 H), 3.26 - 3.40 (m, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 6.29 (d, J = 16.0 Hz, 1 H), 7.08 - 7.17 (m, 1 H), 7.25 - 7.31 (m, 2 H), 7.35 (d, J = 16.0 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 7.68 (s, 1 H), 11.49 (s, 1 H).

Ejemplo 117

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62,

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se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1-metil-1H-indol-3-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 140 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, J = 7.3 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.31 - 1.44 (m, 2 H), 2.37 (s, 3 H), 2.75 - 2.85 (m, 2 H), 3.65 (s, 3 H), 3.92 (s, 3 H), 6.27 (d, J = 15.8 Hz, 1 H), 7.02 - 7.17 (m, 1 H), 7.23 - 7.36 (m, 3 H), 7.39 - 7.52 (m, 1 H), 7.59 (d, J = 8.9 Hz, 1 H), 7.67 (s, 1 H), 11.20 (s, 1 H).

Ejemplo 118

(2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 143 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.87 (t, J = 7.0 Hz, 3 H), 1.29 - 1.40 (m, 4 H), 1.56 - 1.78 (m, 2 H), 2.45 (s, 3 H), 2.63 (s, 3 H), 3.24 - 3.38 (m, 2 H), 3.56 (s, 3 H), 5.45 - 5.62 (m, 1 H), 7.08 (d, J = 8.5 Hz, 1 H), 7.28 - 7.36 (m, 1 H), 7.40 - 7.53 (m, 2 H), 7.78 (d, J = 8.1 Hz, 1 H), 7.86 (br s, 1 H).

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Ejemplo 119

{(2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 118.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.80 (t, J = 6.6 Hz, 3 H), 1.14 - 1.24 (m, 4 H), 1.32 - 1.50 (m, 2 H), 2.35 (s, 3 H), 2.62 (s, 3 H), 2.85 (t, J = 7.8 Hz, 2 H), 3.44 (s, 3 H), 5.64 (d, J = 16.2 Hz, 1 H), 6.75 (d, J = 16.2 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 1 H), 7.20 - 7.35 (m, 1 H), 7.42 - 7.52 (m, 1 H), 7.89 (d, J = 8.1 Hz, 1 H).

Ejemplo 120

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 143 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.79 (t, J = 7.3 Hz, 3 H), 1.11 - 1.27 (m, 2 H), 1.27 - 1.43 (m, 2 H), 2.40 (s, 3 H), 2.63 (s, 3 H), 2.68 - 2.88 (m, 2 H), 3.52 (s, 3 H), 6.09 (d,

J = 16.4 Hz, 1 H), 7.04 (d, J = 16.0 Hz, 1 H), 7.20 (d, J = 8.3 Hz, 1 H), 7.25 - 7.37 (m, 1 H), 7.42 - 7.59 (m, 2 H), 7.92 (d, J = 7.9 Hz, 1 H), 11.28 (s, 1 H).

Ejemplo 121

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-indazol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 143 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.04 - 0.16 (m, 2 H), 0.25 - 0.44 (m, 2 H), 0.71 - 0.93 (m, 1 H), 2.39 (s, 3 H), 2.62 (s, 3 H), 2.67 - 2.74 (m, 2 H), 3.52 (s, 3 H), 6.06 (d, J = 16.6 Hz, 1 H), 7.02 (d, J = 16.2 Hz, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 7.32 (t, J = 7.1 Hz, 1 H), 7.44 - 7.52 (m, 1 H), 7.53 - 7.68 (m, 1 H), 7.92 (d, J = 7.7 Hz, 1 H), 11.30 (s, 1 H).

Ejemplo 122

(2E)-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-

(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 145 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.8 Hz, 3 H), 1.21 - 1.47 (m, 4 H), 1.69 - 1.86 (m, 2 H), 2.45 (s, 3 H), 3.28 - 3.48 (m, 2 H), 3.66 (s, 3 H), 3.83 (s, 3 H), 5.51 (d, J = 15.8 Hz, 1 H), 6.65 - 6.75 (m, 2 H), 6.95 (d, J = 3.2 Hz, 1 H), 7.50 (d, J = 15.8 Hz, 1 H), 7.89 (d, J = 8.7 Hz, 1 H).

Ejemplo 123

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-metoxi-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 145 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.80 (t, J = 7.3 Hz, 3 H), 1.14 - 1.30 (m, 2 H), 1.31 - 1.47 (m, 2 H), 2.38 (s, 3 H), 2.75 - 2.85 (m, 2 H), 3.57 (s, 3 H), 3.73 (s, 3 H), 6.16 (d, J = 16.0 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.11 (d, J = 16.0 Hz, 1 H), 7.44 (d, J = 3.6 Hz, 1 H), 7.50 (t, J = 5.5 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 11.34 (br s, 1 H).

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Ejemplo 124

(2E)-N-[(butilamino)sulfonil]-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 155 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.3 Hz, 3 H), 0.92 - 1.08 (m, 4 H), 1.25 - 1.38 (m, 2 H), 1.41 - 1.53 (m, 2 H), 1.91 - 2.02 (m, 1 H), 2.92 (q, J = 6.6 Hz, 2 H), 3.50 (s, 3 H), 5.02 - 5.11 (m, 1 H), 5.40 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.87 - 6.94 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.38 (dd, J = 9.0, 2.4 Hz, 1 H), 7.55 (d, J = 15.8 Hz, 1 H).

Ejemplo 125

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 218 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.16 - 0.21 (m, 2 H), 0.48 - 0.54 (m, 3 H), 0.77 - 0.81 (m, 2 H), 0.90 - 1.02 (m, 2 H), 1.63 - 1.72 (m, 1 H), 2.87 - 2.93 (m, 2 H), 3.54 (s, 3 H), 5.27 (t, J = 6.0 Hz, 1 H), 5.75 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.18 - 7.24 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.03 - 8.07 (m, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H).

Ejemplo 126

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 230 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.07 - 0.09 (m, 2 H), 0.27 - 0.33 (m, 2 H), 0.75 - 0.87 (m, 1 H), 2.70 (t, J = 6.6 Hz, 2 H), 3.63 (s, 3 H), 5.88 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.9 Hz, 1 H), 7.15 (d, J = 15.9 Hz, 1 H), 7.30 (dd, J = 7.8, 4.5 Hz, 1 H), 7.69 - 7.71 (m, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.19 (dd, J = 7.8, 1.5 Hz, 1 H), 8.28 (dd, J = 4.8, 1.5 Hz, 1 H).

Ejemplo 127

(2E)-N-[(butilamino)sulfonil]-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 230 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 (t, J = 7.2 Hz, 3 H), 1.14 - 1.38 (m, 4 H), 2.74 - 2.80 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 16.2 Hz, 1 H), 6.93 (d, J = 3.3 Hz, 1 H), 7.16 (d, J = 15.3 Hz, 1 H), 7.31 (dd, J = 8.1, 4.8 Hz, 1 H), 7.58 - 7.60 (m, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.19 (dd, J = 7.8, 1.5 Hz, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H).

Ejemplo 128

(2E)-N-{[(3-metilbutil)amino]sulfonil}-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 230 y N-(3-metilbutil)sulfamida

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obtenida en el Ejemplo de referencia 125.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.76 (d, J = 6.6 Hz, 6 H), 1.20 - 1.28 (m, 2 H), 1.46 - 1.58 (m, 1 H), 2.76 - 2.82 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 15.9 Hz, 1 H), 7.31 (dd, J = 7.8, 4.8 Hz, 1 H), 7.60 (br s, 1 H), 7.78 (d, J = 3.9 Hz, 1 H), 8.19 (dd, J = 7.8, 1.8 Hz, 1 H), 8.29 (dd, J = 4.8, 1.8 Hz, 1 H).

Ejemplo 129

(2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 230 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 (t, J = 7.2 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 2.70 - 2.77 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 15.9 Hz, 1 H), 6.93 (d, J = 3.9 Hz, 1H), 7.16 (d, J = 15.9 Hz, 1 H), 7.31 (dd, J = 8.1, 5.1 Hz, 1 H), 7.63 (t, J = 5.7 Hz, 1 H), 7.78 (d, J = 3.9 Hz, 1 H), 8.19 (dd, J = 8.1, 1.8 Hz, 1 H), 8.29 (dd, J = 5.1, 1.8 Hz, 1 H).

Ejemplo 130

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.2 Hz, 3 H), 1.46 - 1.58 (m, 2 H), 2.43 (s, 3 H), 2.85 - 2.92 (m, 2 H), 3.52 (s, 3 H), 5.10 (t, J = 6.3 Hz, 1 H), 5.25 (d, J = 15.9 Hz, 1 H), 6.77 (d, J = 3.3 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.09 (d, J = 3.3 Hz, 1 H), 7.20 (dd, J = 8.7, 1.8 Hz, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 7.70 (d, J = 1.8 Hz, 1 H), 7.81 (br s, 1 H).

Ejemplo 131

(2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 218 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.60 - 0.67 (m, 1 H), 0.81 - 0.95 (m, 6 H), 1.49 - 1.62 (m, 2 H), 1.68 - 1.78 (m, 1 H), 2.93 - 3.02 (m, 2 H), 3.55 (s, 3 H), 5.16 (t, J = 6.0 Hz, 1 H), 5.75 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.9 Hz, 1 H), 6.99 - 7.23 (m, 2 H), 7.38 (d, J = 15.6 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.31 (d, J = 4.8 Hz, 1 H), 9.14 (br s, 1 H).

Ejemplo 132

(2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-{[(3-metilbutil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 218 y N-(3-metilbutil)sulfamida obtenida en el Ejemplo de referencia 125.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.50 - 0.57 (m, 1 H), 0.78 - 0.94 (m, 9 H), 1.40 (q, J = 7.2 Hz, 2 H), 1.60 - 1.69 (m, 2 H), 3.02 - 3.05 (m, 2 H), 3.55 (s, 3 H), 5.14 (t, J = 6.0 Hz, 1 H), 5.79 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.6 Hz, 1 H), 7.18 - 7.23 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.06 (d, J = 7.8 Hz, 1 H), 8.29 (d, J = 4.8 Hz, 1 H), 9.56 (br s, 1 H).

Ejemplo 133

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-(difluorometil)-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 265 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.06 - 0.10 (m, 2 H), 0.28 - 0.35 (m, 2 H), 0.78 - 0.85 (m, 1 H), 2.70 (t, J = 6.3 Hz, 2 H), 3.59 (s, 3 H), 5.96 (d, J = 15.9 Hz, 1 H), 6.91 (d, J = 3.6 Hz, 1 H), 7.01 - 7.36 (m, 3 H), 7.67 (t, J = 6.3 Hz, 1 H), 7.77 (d, J = 3.6 Hz, 1 H), 8.17 - 8.20 (m, 1 H), 8.27 (dd, J = 4.8, 1.5 Hz, 1 H).

Ejemplo 134

(2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 218 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.44 - 0.50 (m, 1 H),

0.73 - 0.76 (m, 2 H), 0.87 - 0.94 (m, 4 H), 1.28 - 1.42 (m, 4 H), 1.58 - 1.65 (m, 1 H), 1.76 - 1.86 (m, 2 H), 3.43 (q, J = 7.8 Hz, 2 H), 3.52 (s, 3 H), 5.83 (d, J = 15.6 Hz, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.34 (d, J = 15.6 Hz, 1 H), 8.04 (dd, J = 7.8, 1.5 Hz, 1 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H), 9.87 (br s, 1 H).

Ejemplo 135

(2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 230 y N-pentilsulfamida obtenida en el Ejemplo de referencia 287.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.70 - 0.85 (m, 3 H), 1.05 - 1.24 (m, 4 H), 1.25 - 1.44 (m, 2 H), 2.68 - 2.83 (m, 2 H), 3.63 (s, 3 H), 5.90 (d, J = 16.0 Hz, 1 H), 6.94 (d, J = 3.8 Hz, 1 H), 7.17 (d, J = 16.0 Hz, 1 H), 7.31 (dd, J = 7.8, 4.8 Hz, 1 H), 7.60 (br s, 1 H), 7.78 (d, J = 3.6 Hz, 1 H), 8.20 (dd, J = 7.8, 1.6 Hz, 1 H), 8.30 (dd, J = 4.7, 1.5 Hz, 1 H), 11.53 (s, 1 H).

Ejemplo 136

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-pentilsulfamida obtenida en el Ejemplo de referencia 287.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.70 - 0.83 (m, 3 H), 1.09 - 1.26 (m, 4 H), 1.28 - 1.44 (m, 2 H), 2.39 (s, 3 H), 2.79 (q, J = 6.8 Hz, 2 H), 3.49 (s, 3 H), 6.11 (d, J = 16.2 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.27 (dd, J = 7.9, 4.7 Hz, 1 H), 7.51 (br s, 1 H), 7.71 (d, J = 3.8 Hz, 1 H), 8.16 (dd, J = 7.8, 1.6 Hz, 1 H), 8.27 (dd, J = 4.7, 1.5 Hz, 1 H), 11.29 (s, 1 H).

Ejemplo 137

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(etilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-etilsulfamida obtenida en el Ejemplo de referencia 152.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.13 (t, J = 7.3 Hz, 3 H), 2.42 (s, 3 H), 2.92 - 3.04 (m, 2 H), 3.52 (s, 3 H), 5.13 (br

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s, 1 H), 5.29 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.7 Hz, 1 H), 8.04 (br s, 1 H).

Ejemplo 138

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(1,4-dioxa-8-azaespiro[4.5]dec-8-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y 1,4-dioxa-8-azaespiro[4.5]decan-8-sulfonamida obtenida en el Ejemplo de referencia 120.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.66 - 1.80 (m, 4 H), 2.42 (s, 3 H), 3.33 - 3.55 (m, 7 H), 3.93 (s, 4 H), 5.43 (d, J = 15.9 Hz, 1 H), 6.73 - 6.78 (m, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 1 H), 7.40 (d, J = 15.5 Hz, 1 H), 7.68 (s, 1 H), 8.14 (br s, 1 H).

Ejemplo 139

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(3-metilbutil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-

il]acrílico obtenido en el Ejemplo de referencia 38 y N-(3-metilbutil)sulfamida obtenida en el Ejemplo de referencia 125.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 (d, J = 6.6 Hz, 6 H), 1.37 (q, J = 7.0 Hz, 2 H), 1.52 - 1.68 (m, 1 H), 2.42 (s, 3 H), 2.92 (q, J = 7.1 Hz, 2 H), 3.52 (s, 3 H), 5.15 (t, J = 6.1 Hz, 1 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.69 (d, J = 1.7 Hz, 1 H), 8.19 (br s, 1 H).

Ejemplo 140

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclohexilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(ciclohexilmetil)sulfamida obtenida en el Ejemplo de referencia 123.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.80 - 0.94 (m, 2 H), 1.09 - 1.19 (m, 2 H), 1.37 - 1.49 (m, 1 H), 1.61 - 1.74 (m, 6 H), 2.42 (s, 3 H), 2.74 (t, J = 6.6 Hz, 2 H), 3.51 (s, 3 H), 5.21 (t, J = 6.3 Hz, 1 H), 5.32 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.69 (d, J = 1.7 Hz, 1 H), 8.13 (br s, 1 H).

Ejemplo 141

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(3-isopropoxipropil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(3-isopropoxipropil)sulfamida obtenida en el Ejemplo de referencia 121.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.12 (d, J = 6.0 Hz, 6 H), 1.70 - 1.80 (m, 2 H), 2.45 (s, 3 H), 3.02 - 3.12 (m, 2 H), 3.42 - 3.60 (m, 6 H), 5.31 (d, J = 15.8 Hz, 1 H), 5.72 (br s, 1 H), 6.79 (d, J = 2.8 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.71 (d, J = 1.7 Hz, 1 H), 7.90 (br s, 1 H).

Ejemplo 142

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-oxopiperidin-1-il)sulfonil]acrilamida

A una solución de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(1,4-dioxa-8-azaespiro[4.5]dec-8-ilsulfonil)acrilamida obtenida en el Ejemplo 138 (2.53 g) en tetrahidrofurano (10 ml) se añadió ácido clorhídrico 1 N (10 ml), y la mezcla se agitó con

calentamiento a 70°C durante 3 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 35:65, v/v) para dar el compuesto del título (2.23 g, rendimiento del 96%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3 H), 2.52 (t, J = 6.2 Hz, 4 H), 3.52 (s, 3 H), 3.66 (t, J = 6.1 Hz, 4 H), 5.28 (d, J = 15.6 Hz, 1 H), 6.78 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.7, 1.9 Hz, 1 H), 7.43 (d, J = 15.6 Hz, 1 H), 7.71 (d, J = 1.9 Hz, 1 H), 7.81 (br s, 1 H).

Ejemplo 143

N-[({(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}amino)sulfonil]-β-alaninato de etilo

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-(aminosulfonil)-β-alaninato de etilo obtenida en el Ejemplo de referencia 260.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 - 1.25 (m, 3 H), 2.40 (s, 3 H), 2.53 (t, J = 6.4 Hz, 2 H), 3.23 (q, J = 5.7 Hz, 2 H), 3.50 (s, 3 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.81 (br s, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.18 (dd, J = 8.7, 2.3 Hz, 1 H), 7.36 - 7.43 (m, 1 H), 7.67 (d, J = 1.9 Hz, 1 H), 8.60 (br s, 1 H).

Ejemplo 144

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-{[(1-propilbutil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-(1-propilbutil)sulfamida obtenida en el Ejemplo de referencia 112.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.82 (t, J = 6.8 Hz, 6 H), 1.19 - 1.47 (m, 8 H), 2.37 (s, 3 H), 3.24 - 3.37 (m, 1 H), 3.59 (s, 3 H), 4.95 (d, J = 7.6 Hz, 1 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 7.8, 4.7 Hz, 1 H), 7.36 (d, J = 15.9 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.33 (dd, J = 4.9, 1.5 Hz, 1 H).

Ejemplo 145

(2E)-N-[(ciclohexilamino)sulfonil]-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-ciclohexilsulfamida obtenida en el Ejemplo de referencia 114.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.17 - 1.32 (m, 5 H), 1.49 - 1.57 (m, 1 H), 1.63 - 1.73 (m, 2 H), 1.79 - 1.91 (m, 2 H), 2.37 (s, 3 H), 3.15 - 3.26 (m, 1 H), 3.59 (s, 3 H), 5.05 (d, J = 6.8 Hz, 1 H), 5.47 (d, J = 15.9 Hz, 1 H), 6.80 (d, J = 3.8 Hz, 1 H), 7.19 (d, J = 3.8 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.37 (d, J = 15.5 Hz, 1 H), 8.06 (dd, J = 7.6, 1.5 Hz, 1 H), 8.32 - 8.36 (m, 1 H).

Ejemplo 146

(2E)-N-{[(ciclohexilmetil)amino]sulfonil}-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-(ciclohexilmetil)sulfamida obtenida en el Ejemplo de referencia 123.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.82 - 0.96 (m, 2 H), 1.08 - 1.29 (m, 4 H), 1.65 - 1.77 (m, 5 H), 2.31 (s, 3 H), 2.83 (t, J = 6.4 Hz, 2 H), 3.56 (s, 3 H), 5.26 (t, J = 6.2 Hz, 1 H), 5.49 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.23 (dd, J = 8.0, 4.5 Hz, 1 H), 7.33 (d, J = 15.9 Hz, 1 H), 8.03 - 8.07 (m, 1 H), 8.30 - 8.34 (m, 1 H), 8.82 (br s, 1 H).

Ejemplo 147

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.47 - 1.58 (m, 2 H), 2.31 (s, 3 H), 2.97 (q, J = 6.3 Hz, 2 H), 3.56 (s, 3 H), 5.23 (br s, 1 H), 5.50 (d, J = 15.9 Hz, 1 H), 6.78 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.21 - 7.27 (m, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 8.05 (d, J = 7.6 Hz, 1 H), 8.32 (d, J = 4.2 Hz, 1 H), 8.86 (br s, 1 H).

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Ejemplo 148

(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.10 (d, J = 4.5 Hz, 2 H), 0.33 (d, J = 7.6 Hz, 2 H), 0.84 (t, J = 7.4 Hz, 1 H), 2.38 (s, 3 H), 2.72 (t, J = 6.1 Hz, 2 H), 3.50 (s, 3 H), 6.05 (d, J = 15.9 Hz, 1 H), 7.01 (d, J = 16.3 Hz, 1 H), 7.40 (dd, J = 7.8, 4.7 Hz, 1 H), 7.63 (br s, 1 H), 8.06 (s, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 11.31 (br s, 1 H).

Ejemplo 149

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-{[(3-metilbutil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 13 y N-(3-

metilbutil)sulfamida obtenida en el Ejemplo de referencia 125.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (d, J = 6.8 Hz, 6 H), 1.40 (q, J = 6.9 Hz, 2 H), 1.56 - 1.70 (m, 1 H), 2.27 (s, 3 H), 2.98 - 3.09 (m, 2 H), 3.55 (s, 3 H), 5.22 (t, J = 6.1 Hz, 1 H), 5.53 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.18 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.0, 4.5 Hz, 1 H), 7.30 (d, J = 15.9 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 8.30 (d, J = 3.4 Hz, 1 H), 9.27 (br s, 1 H).

Ejemplo 150

(2E)-N-[(butilamino)sulfonil]-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 81 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.4 Hz, 3 H), 1.27 - 1.38 (m, 2 H), 1.42 - 1.51 (m, 2 H), 2.46 (s, 3 H), 2.93 (q, J = 6.8 Hz, 2 H), 3.53 (s, 3 H), 5.06 (t, J = 6.1 Hz, 1 H), 5.33 (d, J = 15.5 Hz, 1 H), 6.93 (d, J = 3.4 Hz, 1 H), 7.07 (d, J = 8.7 Hz, 1 H), 7.23 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.5 Hz, 1 H), 7.51 (dd, J = 8.3, 1.5 Hz, 1 H), 8.10 (s, 1 H).

Ejemplo 151

(2E)-N-[(butilamino)sulfonil]-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.2 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.30 - 1.43 (m, 2 H), 2.38 (s, 3 H), 2.79 (q, J = 6.4 Hz, 2 H), 3.50 (s, 3 H), 6.07 (d, J = 15.9 Hz, 1 H), 7.02 (d, J = 15.9 Hz, 1 H), 7.40 (dd, J = 7.6, 4.5 Hz, 1 H), 7.48 - 7.56 (m, 1 H), 8.06 (s, 1 H), 8.16 (d, J = 8.0 Hz, 1 H), 8.38 (d, J = 4.2 Hz, 1 H), 11.30 (br s, 1 H).

Ejemplo 152

(2E)-N-[(butilamino)sulfonil]-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.90 (m, 3 H),

1.24 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.42 (s, 3 H), 2.91 (q, J = 6.7 Hz, 2 H), 3.53 (s, 3 H), 5.13 (t, J = 6.1 Hz, 1 H), 5.29 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.4 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.04 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.34 - 7.45 (m, 2 H), 7.97 (br s, 1 H).

Ejemplo 153

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.18 (m, 2 H), 0.44 - 0.53 (m, 2 H), 0.86 - 1.00 (m, 1 H), 2.43 (s, 3 H), 2.81 (t, J = 6.1 Hz, 2 H), 3.54 (s, 3 H), 5.18 - 5.26 (m, 2 H), 6.80 (d, J = 3.4 Hz, 1 H), 6.86 - 6.92 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.35 - 7.46 (m, 2 H).

Ejemplo 154

(2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-

[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 81 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.11 - 0.17 (m, 2 H), 0.50 (d, J = 7.9 Hz, 2 H), 0.86 - 0.99 (m, 1 H), 2.45 (s, 3 H), 2.81 (t, J = 6.1 Hz, 2 H), 3.53 (s, 3 H), 5.23 (br s, 1 H), 5.31 (d, J = 15.8 Hz, 1 H), 6.93 (d, J = 3.4 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 1 H), 7.22 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 7.50 (dd, J = 8.6, 1.4 Hz, 1 H), 8.10 (s, 1 H).

Ejemplo 155

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-hidroxipiperidin-1-il)sulfonil]acrilamida

A una solución de (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-oxopiperidin-1-il)sulfonil]acrilamida obtenida en el Ejemplo 142 (301 mg) en un solvente mixto de tetrahidrofurano (5 ml) y metanol (1 ml) se añadió borohidruro de sodio (26.3 mg), y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió agua a esta mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 20:80,

v/v) para dar el compuesto del título (176 mg, rendimiento del 58%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55 - 1.67 (m, 2 H), 1.83 - 1.94 (m, 2 H), 2.43 (s, 3 H), 3.09 - 3.19 (m, 2 H), 3.51 (s, 3 H), 3.53 - 3.62 (m, 2 H), 3.83 (br s, 1 H), 5.36 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.0 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 1 H), 7.76 (br s, 1 H).

Ejemplo 156

(2E)-N-[(butilamino)sulfonil]-3-[5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-indazol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 40 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3 H), 1.25 - 1.39 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.45 (s, 3 H), 2.93 (q, J = 6.4 Hz, 2 H), 3.60 (s, 3 H), 5.11 (t, J = 6.2 Hz, 1 H), 5.53 (d, J = 15.9 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 7.36 - 7.45 (m, 2 H), 7.54 (t, J = 7.4 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H).

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Ejemplo 157

(2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-5-(5-fluoro-1H-indol-1-il)-1-metil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 155 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.18 (m, 2 H), 0.43 - 0.54 (m, 2 H), 0.86 - 1.07 (m, 5 H), 1.90 - 2.02 (m, 1 H), 2.75 - 2.86 (m, 2 H), 3.50 (s, 3 H), 5.25 (br s, 1 H), 5.40 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 3.2 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.94 - 7.03 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.38 (dd, J = 9.0, 2.1 Hz, 1 H), 7.54 (d, J = 15.8 Hz, 1 H).

Ejemplo 158

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.3 Hz, 3 H), 1.45 - 1.56 (m, 2 H), 2.44 (s, 3 H), 2.85 - 2.92 (m, 2 H), 3.54 (s, 3 H), 5.08 (br s, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.80 (d, J = 3.2 Hz, 1 H), 6.87 - 6.94 (m, 1 H), 6.96 - 7.04 (m, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.34 - 7.48 (m, 2 H).

Ejemplo 159

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 60 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3 H), 1.24 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.44 (s, 3 H), 2.91 (q, J = 6.8 Hz, 2 H), 3.55 (s, 3 H), 3.77 (s, 3 H), 5.00 (br s, 1 H), 5.22 (d, J = 15.5 Hz, 1 H), 6.40 (d, J = 1.9 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.90 (dd, J = 8.5, 2.1 Hz, 1 H), 6.95 (d, J = 3.0 Hz, 1 H), 7.47 (d, J = 15.5 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 1 H).

Ejemplo 160

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-hidroxi-4-metilpiperidin-1-il)sulfonil]acrilamida

A una solución de (2E)-3-[5-(5-cloro-1H-indol-1-

il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-oxopiperidin-1-il)sulfonil]acrilamida obtenida en el Ejemplo 142 (308 mg) en tetrahidrofurano (6 ml) se añadió bromuro de metilmagnesio (solución 1 M de éter dietílico, 1.4 ml) con agitación, y la mezcla se agitó a temperatura ambiente durante 1 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 25:75, v/v) para dar el compuesto del título (155 mg, rendimiento del 49%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 3 H), 1.58 - 1.73 (m, 4 H), 2.44 (s, 3 H), 3.15 - 3.32 (m, 2 H), 3.43 - 3.58 (m, 5 H), 5.33 (d, J = 15.8 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.22 (dd, J = 8.8, 1.8 Hz, 1 H), 7.38 - 7.47 (m, 2 H), 7.71 (d, J = 1.9 Hz, 1 H).

Ejemplo 161

(2E)-N-[(butilamino)sulfonil]-3-[5-(3-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

A una solución de (2E)-N-[(butilamino)sulfonil]-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida obtenida en el Ejemplo 159 (248 mg) en

acetonitrilo (2.5 ml) se añadió N-clorosuccinimida (76 mg), y la mezcla se agitó a temperatura ambiente durante 24 h. Se añadió acetato de etilo a la mezcla de reacción, y la capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 95:5 - 60:40, v/v). El sólido obtenido se cristalizó en hexano-acetato de etilo, y luego agua-etanol. Los cristales obtenidos se purificaron por HPLC preparativa (la herramienta y las condiciones preparativas eras iguales a las del Ejemplo de referencia 97), y el eluato se concentró. El aceite obtenido se disolvió en acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título (43 mg, rendimiento del 16%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.2 Hz, 3 H), 1.16 - 1.28 (m, 2 H), 1.29 - 1.44 (m, 2 H), 2.39 (s, 3 H), 2.78 (q, J = 6.8 Hz, 2 H), 3.50 (s, 3 H), 3.70 (s, 3 H), 6.10 (d, J = 16.3 Hz, 1 H), 6.52 (d, J = 1.9 Hz, 1 H), 6.95 (dd, J = 8.7, 1.9 Hz, 1 H), 7.03 (d, J = 15.9 Hz, 1 H), 7.44 - 7.59 (m, 1 H), 7.54 (d, J = 8.7 Hz, 1 H), 7.72 (s, 1 H), 11.33 (s, 1 H)

Ejemplo 162

(2E)-N-[(butilamino)sulfonil]-3-{1,3-dimetil-5-[6-(2-oxopropoxi)-1H-indol-1-il]-1H-pirazol-4-il}acrilamida

A una solución de (2E)-3-{1,3-dimetil-5-[6-(2-oxopropoxi)-1H-indol-1-il]-1H-pirazol-4-il}acrilato de etilo obtenido en el Ejemplo de referencia 157 (2.25 g) en un solvente mixto de tetrahidrofurano (10 ml) y etanol (10 ml) se añadió una solución acuosa 1 N de hidróxido de sodio (12 ml), y la mezcla se agitó con calentamiento a 50°C durante 5 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente, y se concentró a presión reducida. El residuo se neutralizó con una solución acuosa (10 ml) de sulfato de potasio ácido (1.6 g), y los cristales precipitados se recogieron por filtración. Los cristales obtenidos se disolvieron en acetato de etilo y tetrahidrofurano, y la solución se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (metanol-acetato de etilo 5:95, v/v) para dar un sólido amorfo de color amarillo pálido.

El sólido amorfo obtenido se disolvió en acetonitrilo (40 ml), anhídrido 2-metil-6-nitrobenzoico (1.68 g), N-butilsulfamida obtenida en el Ejemplo de referencia 111 (651 mg), trietilamina (1.23 g) y 4-dimetilaminopiridina (497 mg) se añadieron, y la mezcla se agitó a temperatura ambiente

durante 48 h. Una solución acuosa saturada de cloruro de amonio (20 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 35:65, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (245 mg, rendimiento del 85%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3 H), 1.23 - 1.37 (m, 2 H), 1.40 - 1.51 (m, 2 H), 2.26 (s, 3 H), 2.45 (s, 3 H), 2.93 (d, J = 6.6 Hz, 2 H), 3.54 (s, 3 H), 4.53 (s, 2 H), 5.02 (br s, 1 H), 5.27 (d, J = 15.8 Hz, 1 H), 6.39 - 6.43 (m, 1 H), 6.76 (d, J = 3.0 Hz, 1 H), 6.91 (dd, J = 8.6, 2.2 Hz, 1 H), 6.98 (d, J = 3.2 Hz, 1 H), 7.44 (d, J = 15.8 Hz, 1 H), 7.62 (d, J = 8.7 Hz, 1 H).

Ejemplo 163

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(3-hidroxi-3-metilbutil)amino]sulfonil}acrilamida

A una solución de N-[({(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}amino)sulfonil]-β-alaninato de etilo obtenido en el Ejemplo 143 (380 mg) en tetrahidrofurano (8 ml) se añadió bromuro de metilmagnesio (solución 1 M de éter dietílico, 5

ml) con agitación, y la mezcla se agitó a temperatura ambiente durante 16 h. Una solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 35:65, v/v) para dar el compuesto del título (130 mg, rendimiento del 35%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.19 (d, J = 2.7 Hz, 6 H), 1.65 (t, J = 6.6 Hz, 2 H), 2.43 (s, 3 H), 3.09 - 3.18 (m, 2 H), 3.52 (s, 3 H), 5.28 - 5.35 (m, 1 H), 6.03 (br s, 1 H), 6.78 (d, J = 2.7 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.70 (d, J = 1.9 Hz, 1 H).

Ejemplo 164

(2E)-N-[(butilamino)sulfonil]-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 159 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

974

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.42 (s, 3 H), 2.91 (q, J = 6.7 Hz, 2 H), 3.42 (s, 3 H), 3.53 (s, 3 H), 3.68 - 3.78 (m, 2 H), 4.02 - 4.10 (m, 2 H), 5.05 (br s, 1 H), 5.26 (d, J = 15.8 Hz, 1 H), 6.46 (d, J = 1.3 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.88 - 6.98 (m, 2 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.91 (br s, 1 H).

Ejemplo 165

(2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{5-[6-(2-metoxietoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 159 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.3 Hz, 3 H), 1.46 - 1.54 (m, 2 H), 2.43 (s, 3 H), 2.89 (q, J = 6.8 Hz, 2 H), 3.43 (s, 3 H), 3.54 (s, 3 H), 3.70 - 3.75 (m, 2 H), 4.03 - 4.11 (m, 2 H), 5.03 (br s, 1 H), 5.20 (d, J = 15.8 Hz, 1 H), 6.46 (d, J = 1.7 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.91 - 6.97 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.70 (br s, 1 H).

975

Ejemplo 166

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

A una solución de (2E)-N-[(butilamino)sulfonil]-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida obtenida en el Ejemplo 159 (1.65 g) en diclorometano (30 ml) se añadió gota a gota tribromuro de boro (solución de diclorometano 1 M, 7.4 ml) con agitación a -78°C, y la mezcla se agitó a -78°C durante 1 h, y luego a temperatura ambiente durante 17 h. La mezcla de reacción se neutralizó con metanol (10 ml), y se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (1.44 g, rendimiento del 91%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.80 (t, J = 7.3 Hz, 3 H), 1.16 - 1.29 (m, 2 H), 1.31 - 1.42 (m, 2 H), 2.39 (s, 3 H), 2.80 (q, J = 6.8 Hz, 2 H), 3.46 (s, 3 H), 6.15 (d, J = 16.0 Hz, 1 H), 6.30 (d, J = 1.9 Hz, 1 H), 6.67 - 6.72 (m, 1 H), 7.02 (d, J = 16.0 Hz, 1 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.45 - 7.55 (m, 2 H), 9.22 (s, 1 H), 11.32 (s, 1 H).

Ejemplo 167

(2E)-N-[(butilamino)sulfonil]-3-{5-[6-(ciclopropilmetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{5-[6-(ciclopropilmetoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 161 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.33 (d, J = 4.7 Hz, 2 H), 0.63 (d, J = 7.3 Hz, 2 H), 0.87 (t, J = 7.2 Hz, 3 H), 1.20 - 1.37 (m, 3 H), 1.45 (d, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.85 - 2.97 (m, 2 H), 3.54 (s, 3 H), 3.74 (d, J = 6.8 Hz, 2 H), 5.02 (br s, 1 H), 5.23 (d, J = 15.8 Hz, 1 H), 6.40 (s, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.87 - 6.97 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.5 Hz, 1 H), 7.72 (br s, 1 H).

Ejemplo 168

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 163 y N-

(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.14 (d, J = 4.7 Hz, 2 H), 0.45 - 0.53 (m, 2 H), 0.86 - 0.98 (m, 1 H), 1.27 - 1.32 (m, 6 H), 2.43 (s, 3 H), 2.80 (t, J = 6.2 Hz, 2 H), 3.55 (s, 3 H), 4.43 - 4.54 (m, 1 H), 5.18 - 5.25 (m, 2 H), 6.42 (d, J = 1.9 Hz, 1 H), 6.72 - 6.75 (m, 1 H), 6.88 (dd, J = 8.7, 2.1 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 15.8 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H).

Ejemplo 169

1-[4-((1E)-3-{[(butilamino)sulfonil]amino}-3-oxoprop-1-en-1-il)-1,3-dimetil-1H-pirazol-5-il]-1H-indol-6-il metansulfonato de

A una solución de (2E)-N-[(butilamino)sulfonil]-3-[5-(6-hidroxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida obtenida en el Ejemplo 166 (335 mg) en tetrahidrofurano (2 ml) se añadieron trietilamina (118 mg) y cloruro de metansulfonilo (124 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en éter dietílico-etanol para dar el compuesto del

título (284 mg, rendimiento del 72%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.2 Hz, 3 H), 1.24 - 1.38 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.42 (s, 3 H), 2.94 (q, J = 6.4 Hz, 2 H), 3.15 (s, 3 H), 3.57 (s, 3 H), 5.15 (t, J = 6.1 Hz, 1 H), 5.48 (d, J = 15.9 Hz, 1 H), 6.85 (d, J = 2.7 Hz, 1 H), 7.01 (d, J = 1.5 Hz, 1 H), 7.12 - 7.18 (m, 2 H), 7.34 (d, J = 15.9 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 1 H), 8.24 (br s, 1 H).

Ejemplo 170

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-isopropoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 163 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.3 Hz, 3 H), 1.25 - 1.38 (m, 8 H), 1.42 - 1.53 (m, 2 H), 2.43 (s, 3 H), 2.91 (q, J = 6.8 Hz, 2 H), 3.55 (s, 3 H), 4.43 - 4.54 (m, 1 H), 5.00 - 5.08 (m, 1 H), 5.25 (d, J = 15.8 Hz, 1 H), 6.43 (d, J = 1.9 Hz, 1 H), 6.74 (d, J = 3.2 Hz, 1 H), 6.88 (dd, J = 8.6, 2.2 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.46 (d, J = 15.8 Hz, 1 H).

Ejemplo 171

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propoxiamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y N-propoxisulfamida obtenida en el Ejemplo de referencia 165.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.3 Hz, 3 H), 1.58 - 1.64 (m, 2 H), 2.44 (s, 3 H), 3.53 (s, 3 H), 3.88 (t, J = 6.8 Hz, 2 H), 5.28 (d, J = 15.8 Hz, 1 H), 6.79 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.20 - 7.25 (m, 1 H), 7.46 (d, J = 15.8 Hz, 1 H), 7.72 (d, J = 1.5 Hz, 1 H), 7.81 (br s, 1 H).

Ejemplo 172

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 167 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.11 - 0.17 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.86 - 0.98 (m, 1 H), 1.39 (t, J = 7.0

Hz, 3 H), 2.44 (s, 3 H), 2.80 (t, J = 6.4 Hz, 2 H), 3.55 (s, 3 H), 3.96 (q, J = 7.0 Hz, 2 H), 5.13 - 5.24 (m, 2 H), 6.40 (d, J = 1.7 Hz, 1 H), 6.74 (d, J = 3.4 Hz, 1 H), 6.86 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.59 (d, J = 8.7 Hz, 1 H), 7.68 (br s, 1 H).

Ejemplo 173

(2E)-N-[(butilamino)sulfonil]-3-{5-[6-(2-metoxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{5-[6-(2-metoxi-1-metiletoxi)-1H-indol-1-il]-1,3-dimetil-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 172 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 5 H), 1.41 - 1.53 (m, 2 H), 2.42 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.37 (d, J = 0.9 Hz, 3 H), 3.42 - 3.60 (m, 5 H), 4.43 - 4.54 (m, 1 H), 5.04 (br s, 1 H), 5.25 (dd, J = 15.8, 2.8 Hz, 1 H), 6.50 (d, J = 1.7 Hz, 1 H), 6.73 (d, J = 3.0 Hz, 1 H), 6.89 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.88 (br s, 1 H).

Ejemplo 174

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 175 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.11 - 0.17 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.86 - 0.96 (m, 1 H), 2.43 (s, 3 H), 2.48 (s, 3 H), 2.80 (t, J = 6.5 Hz, 2 H), 3.54 (s, 3 H), 5.10 - 5.21 (m, 2 H), 6.73 - 6.76 (m, 1 H), 6.87 (d, J = 8.5 Hz, 1 H), 7.02 (d, J = 3.4 Hz, 1 H), 7.08 (d, J = 8.7 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.52 (s, 1 H).

Ejemplo 175

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-indol-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 175 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3 H), 1.25 - 1.37 (m, 2 H), 1.45 (d, J = 7.2 Hz, 2 H), 2.42 (s, 3

H), 2.48 (s, 3 H), 2.90 (q, J = 6.3 Hz, 2 H), 3.53 (s, 3 H), 5.04 (br s, 1 H), 5.22 (d, J = 15.8 Hz, 1 H), 6.74 (d, J = 2.8 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 7.02 (d, J = 3.0 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 1 H), 7.45 (d, J = 15.8 Hz, 1 H), 7.51 (s, 1 H), 7.75 (br s, 1 H).

Ejemplo 176

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-etoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 167 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.3 Hz, 3 H), 1.24 - 1.52 (m, 7 H), 2.43 (s, 3 H), 2.91 (q, J = 6.6 Hz, 2 H), 3.54 (s, 3 H), 3.96 (q, J = 7.0 Hz, 2 H), 5.00 - 5.10 (m, 1 H), 5.25 (d, J = 15.6 Hz, 1 H), 6.40 (s, 1 H), 6.74 (d, J = 3.0 Hz, 1 H), 6.85 - 6.96 (m, 2 H), 7.46 (d, J = 15.6 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.84 (br s, 1 H).

Ejemplo 177

(2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-

4-il}acrílico obtenido en el Ejemplo de referencia 42 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.44 - 1.55 (m, 2 H), 2.47 (s, 3 H), 2.87 (q, J = 6.8 Hz, 2 H), 3.54 (s, 3 H), 5.09 - 5.17 (m, 1 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.22 - 7.27 (m, 2 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.48 - 7.53 (m, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Ejemplo 178

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(ciclohexilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y N-ciclohexilsulfamida obtenida en el Ejemplo de referencia 114.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.01 - 1.20 (m, 5 H), 1.42 - 1.52 (m, 1 H), 1.57 - 1.74 (m, 4 H), 2.38 (s, 3 H), 3.01 (br s, 1 H), 3.48 (s, 3 H), 6.01 (d, J = 16.0 Hz, 1 H), 6.88 (d, J = 3.6 Hz, 1 H), 7.00 (d, J = 16.0 Hz, 1 H), 7.56 (br s, 1 H), 7.83 (d, J = 3.6 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H), 8.32 (d, J = 2.1 Hz, 1 H), 11.27 (s, 1 H).

Ejemplo 179

(2E)-N-[(butilamino)sulfonil]-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 42 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.3 Hz, 3 H), 1.23 - 1.37 (m, 2 H), 1.40 - 1.52 (m, 2 H), 2.46 (s, 3 H), 2.90 (q, J = 6.7 Hz, 2 H), 3.54 (s, 3 H), 5.04 - 5.13 (m, 1 H), 5.30 (d, J = 15.8 Hz, 1 H), 6.91 (d, J = 3.2 Hz, 1 H), 7.22 - 7.28 (m, 2 H), 7.40 (d, J = 15.8 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Ejemplo 180

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 42 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.16 (m, 2 H),

0.42 - 0.52 (m, 2 H), 0.83 - 0.98 (m, 1 H), 2.47 (s, 3 H), 2.75 - 2.86 (m, 2 H), 3.54 (s, 3 H), 5.18 - 5.29 (m, 2 H), 6.91 (d, J = 3.4 Hz, 1 H), 7.22 - 7.27 (m, 2 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.85 (d, J = 8.3 Hz, 1 H).

Ejemplo 181

(2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 25 y N-propilsulfamida obtenida en el Ejemplo de referencia 127.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.93 (m, 3 H), 1.45 - 1.56 (m, 2 H), 2.45 (s, 3 H), 2.85 - 2.94 (m, 2 H), 3.54 (s, 3 H), 5.09 (br s, 1 H), 5.24 (d, J = 15.8 Hz, 1 H), 6.82 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.5, 1.9 Hz, 1 H), 7.42 (d, J = 15.6 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H).

Ejemplo 182

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(piperidin-1-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico

obtenido en el Ejemplo de referencia 21 y piperidin-1-sulfonamida obtenida en el Ejemplo de referencia 177.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.50 (br s, 2 H), 1.56 - 1.63 (m, 4 H), 2.43 (s, 3 H), 3.22 - 3.30 (m, 4 H), 3.52 (s, 3 H), 5.37 (d, J = 15.6 Hz, 1 H), 6.79 (d, J = 2.6 Hz, 1 H), 6.86 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.35 - 7.46 (m, 2 H), 7.68 (br s, 1 H).

Ejemplo 183

(2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 25 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.12 - 0.18 (m, 2 H), 0.45 - 0.52 (m, 2 H), 0.84 - 0.98 (m, 1 H), 2.44 (s, 3 H), 2.78 - 2.86 (m, 2 H), 3.54 (s, 3 H), 5.18 - 5.27 (m, 2 H), 6.81 (d, J = 3.4 Hz, 1 H), 6.97 (s, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.23 (dd, J = 8.5, 1.7 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H).

Ejemplo 184

(2E)-N-[(butilamino)sulfonil]-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 25 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.91 (m, 3 H), 1.24 - 1.38 (m, 2 H), 1.41 - 1.53 (m, 2 H), 2.44 (s, 3 H), 2.92 (q, J = 6.8 Hz, 2 H), 3.54 (s, 3 H), 5.10 (br s, 1 H), 5.27 (d, J = 15.8 Hz, 1 H), 6.81 (dd, J = 3.3, 0.8 Hz, 1 H), 6.96 - 6.99 (m, 1 H), 7.07 (d, J = 3.2 Hz, 1 H), 7.23 (dd, J = 8.4, 1.8 Hz, 1 H), 7.42 (d, J = 15.8 Hz, 1 H), 7.65 (d, J = 8.5 Hz, 1 H).

Ejemplo 185

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(piperidin-1-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 y piperidin-1-sulfonamida obtenida en el Ejemplo de referencia 177.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.48 - 1.55 (m, 2 H), 1.56 - 1.65 (m, 4 H), 2.43 (s, 3 H), 3.25 (t, J = 5.2 Hz, 4

H), 3.51 (s, 3 H), 5.38 (d, J = 15.8 Hz, 1 H), 6.77 (d, J = 2.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.41 (d, J = 15.8 Hz, 1 H), 7.66 - 7.73 (m, 2 H).

Ejemplo 186

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

A una solución de butanol (88.2 mg) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (209 mg), y la mezcla se agitó a 60°C durante 1 h. Se añadieron 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179 (350 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (226 mg) y 4-dimetilaminopiridina (181 mg) a la mezcla de reacción, y la mezcla se agitó a 60(C durante 20 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 50:50, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (299 mg, rendimiento del 67%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.4 Hz, 3 H),

1.22 - 1.41 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.46 (s, 3 H), 4.05 (t, J = 6.8 Hz, 2 H), 6.70 (d, J = 3.4 Hz, 1 H), 6.89 - 6.94 (m, 2 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 187

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de 3,3,3-trifluoropropilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 3,3,3-trifluoropropan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, DMSO-d_6): 2.20 (s, 3 H), 2.38 - 2.47 (m, 1 H), 2.54 - 2.72 (m, 3 H), 3.21 - 3.29 (m, 2 H), 3.38 (s, 3 H), 4.19 (t, J = 5.9 Hz, 2 H), 6.77 (d, J = 3.2 Hz, 1 H), 7.04 (d, J = 8.9 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.59 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 11.69 (br s, 1 H).

Ejemplo 188

({2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-

1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 181, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.93 (t, J = 7.3 Hz, 3 H), 1.25 - 1.41 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.90 (m, 2 H), 3.32 (t, J = 7.9 Hz, 2 H), 3.47 (s, 3 H), 4.07 (t, J = 6.7 Hz, 2 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.5, 1.9 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Ejemplo 189

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo

A una solución de ciclopropilmetanol (78.4 mg) en N,N-dimetilformamida (9 ml) se añadió N,N'-carbonildiimidazol (191 mg), y la mezcla se agitó a 60°C durante 1 h. 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179 (320 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (207 mg) y 4-dimetilaminopiridina (166 mg) se añadieron a esta mezcla de reacción, y la mezcla se agitó a 60°C durante 20 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a

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cromatografía en columna de gel de sílice (hexano-acetato de etilo 45:55, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (182 mg, rendimiento del 45%) en forma de cristales incoloros. Punto de fusión 169.8-170.4°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.24 - 0.30 (m, 2 H), 0.54 - 0.62 (m, 2 H), 0.98 - 1.11 (m, 1 H), 2.32 (s, 3 H), 2.66 - 2.87 (m, 2 H), 3.32 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 3.87 (d, J = 7.3 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.18 - 7.23 (m, 1 H), 7.25 - 7.27 (m, 1 H), 7.66 (d, J = 2.1 Hz, 1 H).

Ejemplo 190

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.3 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.53 - 1.64 (m, 2 H), 2.31 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.11 - 3.20 (m, 1 H), 3.36 (s, 3 H), 3.90 - 4.04 (m, 2 H), 4.06 - 4.18 (m, 1 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.1 Hz, 1

H), 8.28 (d, J = 2.1 Hz, 1 H), 10.57 (br s, 1 H).

Ejemplo 191

({(E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]vinil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 178, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.50 - 1.62 (m, 2 H), 2.45 (s, 3 H), 3.54 (s, 3 H), 4.00 - 4.15 (m, 2 H), 5.86 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Ejemplo 192

({2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 186, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.96 (m, 3 H), 1.25 - 1.40 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.31 (s, 3 H),

2.66 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 4.06 (t, J = 6.6 Hz, 2 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.95 - 7.03 (m, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.34 (dd, J = 9.1, 2.3 Hz, 1 H).

Ejemplo 193

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de propilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, propanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.53 - 1.67 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.46 (s, 3 H), 4.01 (t, J = 6.7 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 194

({2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 188,

butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.4 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.53 - 1.64 (m, 2 H), 2.32 (s, 3 H), 2.79 - 2.87 (m, 2 H), 3.08 - 3.18 (m, 1 H), 3.34 (s, 3 H), 3.87 - 3.98 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.74 (d, J = 3.8 Hz, 1 H), 7.11 (d, J = 3.8 Hz, 1 H), 7.22 - 7.28 (m, 1 H), 8.07 (dd, J = 8.0, 1.5 Hz, 1 H), 8.31 (dd, J = 4.9, 1.5 Hz, 1 H), 11.71 (br s, 1 H).

Ejemplo 195

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de isobutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 2-metilpropan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (d, J = 6.8 Hz, 6 H), 1.79 - 1.92 (m, 1 H), 2.31 (s, 3 H), 2.65 - 2.88 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.83 (d, J = 6.8 Hz, 2 H), 6.70 (dd, J = 3.4, 0.8 Hz, 1 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 196

({2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 190, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.41 (m, 2 H), 1.50 - 1.62 (m, 2 H), 2.32 (s, 3 H), 2.67 - 2.89 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.48 (s, 3 H), 3.78 (s, 3 H), 4.05 (t, J = 6.7 Hz, 2 H), 6.43 (d, J = 2.3 Hz, 1 H), 6.64 - 6.68 (m, 1 H), 6.86 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 1 H).

Ejemplo 197

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

A una solución de butanol (109 mg) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (254 mg), y la mezcla se agitó a 60°C durante 1 h. 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 193 (400 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (209 mg) y 4-

dimetilaminopiridina (168 mg) se añadieron a esta mezcla de reacción, y la mezcla se agitó a 60°C durante 22 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (150 mg, rendimiento del 30%) en forma de cristales incoloros. Punto de fusión 136.1-137.3°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.2 Hz, 3 H), 1.30 - 1.44 (m, 2 H), 1.54 - 1.66 (m, 2 H), 2.87 - 3.08 (m, 2 H), 3.21 - 3.31 (m, 1 H), 3.54 (s, 3 H), 3.83 - 3.96 (m, 1 H), 4.08 (t, J = 6.6 Hz, 2 H), 6.76 (d, J = 3.4 Hz, 1 H), 7.21 (d, J = 3.8 Hz, 1 H), 8.06 (d, J = 2.3 Hz, 1 H), 8.30 (d, J = 2.3 Hz, 1 H), 9.32 (br s, 1 H).

Ejemplo 198

[(2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 195,

butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.51 - 1.62 (m, 2 H), 2.34 (s, 3 H), 2.64 - 2.76 (m, 1 H), 2.79 - 2.91 (m, 1 H), 3.33 (t, J = 7.9 Hz, 2 H), 3.47 (s, 3 H), 4.06 (t, J = 6.7 Hz, 2 H), 6.83 (dd, J = 3.3, 0.8 Hz, 1 H), 7.24 - 7.28 (m, 2 H), 7.47 (dd, J = 8.3, 0.9 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H).

Ejemplo 199

N-({(E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]vinil}sulfonil)hexanamida

Una mezcla de (E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 178 (213 mg), ácido hexanoico (74.1 mg), anhídrido 2-metil-6-nitrobenzoico (251 mg), trietilamina (184 mg), 4-dimetilaminopiridina (74.3 mg) y acetonitrilo (6 ml) se agitó a temperatura ambiente durante 24 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (198 mg, rendimiento del 73%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.9 Hz, 3 H),

1.20 - 1.35 (m, 4 H), 1.49 - 1.62 (m, 2 H), 2.14 (t, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 3.55 (s, 3 H), 5.79 (d, J = 15.6 Hz, 1 H), 6.77 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.35 (d, J = 15.6 Hz, 1 H), 7.61 (br s, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Ejemplo 200

N-({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)hexanamida

Por medio de un método similar al del Ejemplo 199, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179 y ácido hexanoico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.9 Hz, 3 H), 1.17 - 1.34 (m, 4 H), 1.42 - 1.55 (m, 2 H), 1.98 - 2.06 (m, 2 H), 2.30 (s, 3 H), 2.58 - 2.70 (m, 1 H), 2.71 - 2.84 (m, 1 H), 3.33 (t, J = 7.7 Hz, 2 H), 3.46 (s, 3 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo 201

N-({2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etil}sulfonil)hexanamida

Por medio de un método similar al del Ejemplo 199, se obtuvo el compuesto del título a partir de 2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-

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il]etansulfonamida obtenida en el Ejemplo de referencia 188 y ácido hexanoico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.93 (m, 3 H), 1.23 - 1.39 (m, 4 H), 1.53 - 1.66 (m, 2 H), 1.81 - 1.92 (m, 1 H), 2.03 - 2.16 (m, 1 H), 2.29 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.07 - 3.16 (m, 1 H), 3.36 (s, 3 H), 3.98 - 4.14 (m, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.13 (d, J = 3.6 Hz, 1 H), 7.25 - 7.30 (m, 1 H), 8.10 (dd, J = 7.9, 1.5 Hz, 1 H), 8.29 (dd, J = 4.9, 1.5 Hz, 1 H), 11.49 (br s, 1 H).

Ejemplo 202

N-({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)hexanamida

Por medio de un método similar al del Ejemplo 199, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184 y ácido hexanoico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 6.8 Hz, 3 H), 1.23 - 1.39 (m, 4 H), 1.52 - 1.65 (m, 2 H), 1.80 - 1.92 (m, 1 H), 2.00 - 2.13 (m, 1 H), 2.28 (s, 3 H), 2.80 - 2.87 (m, 2 H), 3.09 - 3.19 (m, 1 H), 3.38 (s, 3 H), 3.95 - 4.12 (m, 1 H), 6.72 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 8.07 (d, J = 2.1 Hz, 1 H), 8.26 (d, J = 2.3 Hz, 1 H), 10.61 (br s, 1 H).

Ejemplo 203

{(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}sulfamato de butilo

Una mezcla de ácido (2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 38 (342 mg), anhídrido 2-metil-6-nitrobenzoico (448 mg), sulfamato de butilo obtenido en el Ejemplo de referencia 196 (174 mg), trietilamina (329 mg), 4-dimetilaminopiridina (132 mg) y acetonitrilo (10 ml) se agitó a temperatura ambiente durante 16 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 40:60, v/v) para dar el compuesto del título (187 mg, rendimiento del 38%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.4 Hz, 3 H), 1.28 - 1.43 (m, 2 H), 1.59 - 1.70 (m, 2 H), 2.44 (s, 3 H), 3.52 (s, 3 H), 4.26 (t, J = 6.6 Hz, 2 H), 5.56 (d, J = 15.5 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 1.9 Hz, 1 H), 7.47 (d, J = 15.9 Hz, 1 H), 7.70 (d, J = 1.5 Hz, 1 H).

Ejemplo 204

{(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}sulfamato de metilo

Por medio de un método similar al del Ejemplo 203, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y sulfamato de butilo obtenida en el Ejemplo de referencia 196.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.82 (t, J = 7.2 Hz, 3 H), 1.20 - 1.33 (m, 2 H), 1.50 - 1.63 (m, 2 H), 2.39 (s, 3 H), 3.51 (s, 3 H), 4.16 (t, J = 5.9 Hz, 2 H), 6.06 (d, J = 16.3 Hz, 1 H), 7.08 (d, J = 15.9 Hz, 1 H), 7.37 - 7.45 (m, 1 H), 8.07 (s, 1 H), 8.18 (d, J = 7.2 Hz, 1 H), 8.38 (d, J = 3.0 Hz, 1 H), 12.07 (br s, 1 H).

Ejemplo 205

{(2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}sulfamato de butilo

Por medio de un método similar al del Ejemplo 203, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-ciano-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 81 y sulfamato de butilo obtenida en el Ejemplo de referencia 196.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.3 Hz, 3 H), 1.31 - 1.43 (m, 2 H), 1.59 - 1.71 (m, 2 H), 2.46 (s, 3 H),

3.52 (s, 3 H), 4.28 (t, J = 6.6 Hz, 2 H), 5.68 (d, J = 15.8 Hz, 1 H), 6.90 - 6.94 (m, 1 H), 7.07 (d, J = 8.5 Hz, 1 H), 7.24 (d, J = 3.4 Hz, 1 H), 7.42 (d, J = 15.6 Hz, 1 H), 7.47 - 7.52 (m, 1 H), 8.07 (d, J = 0.8 Hz, 1 H), 8.26 (br s, 1 H).

Ejemplo 206

{(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}sulfamato de butilo

Por medio de un método similar al del Ejemplo 203, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y sulfamato de butilo obtenida en el Ejemplo de referencia 196.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.3 Hz, 3 H), 1.29 - 1.43 (m, 2 H), 1.59 - 1.71 (m, 2 H), 2.44 (s, 3 H), 3.52 (s, 3 H), 4.27 (t, J = 6.5 Hz, 2 H), 5.56 (d, J = 15.8 Hz, 1 H), 6.77 - 6.80 (m, 1 H), 6.87 - 6.93 (m, 1 H), 6.95 - 7.04 (m, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.37 (dd, J = 9.0, 2.4 Hz, 1 H), 7.47 (d, J = 15.8 Hz, 1 H), 7.93 (br s, 1 H).

Ejemplo 207

N-[({[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}amino)sulfonil]hexanamida

Una mezcla de N-{[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]metil}sulfamida obtenida en el Ejemplo de referencia 197 (63.3 mg), anhídrido 2-metil-6-nitrobenzoico (70.4 mg), ácido hexanoico (19.7 mg),

trietilamina (51.7 mg), 4-dimetilaminopiridina (20.8 mg) y acetonitrilo (2 ml) se agitó a temperatura ambiente durante 48 h. Una solución acuosa saturada de cloruro de amonio (5 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 50:50, v/v) para dar el compuesto del título (53.3 mg, rendimiento del 66%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.8 Hz, 3 H), 1.15 - 1.33 (m, 4 H), 1.39 - 1.51 (m, 2 H), 1.96 - 2.07 (m, 2 H), 2.35 (s, 3 H), 3.47 (s, 3 H), 3.63 - 3.94 (m, 2 H), 5.15 (br s, 1 H), 6.69 (d, J = 2.7 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.15 - 7.24 (m, 2 H), 7.62 - 7.78 (m, 2 H).

Ejemplo 208

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(2,2,2-trifluoroetil)amino]carbonil}etansulfonamida

A una solución de 2,2,2-trifluoroetanamina (134 mg) en N,N-dimetilformamida (11 ml) se añadió N,N'-carbonildiimidazol (238 mg), y la mezcla se agitó a 60°C durante 1 h. 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179 (400 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno

(241 mg) y 4-dimetilaminopiridina (193 mg) se añadieron a la mezcla de reacción, y la mezcla se agitó a 60°C durante 16 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 30:70, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (207 mg, rendimiento del 38%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.18 (s, 3 H), 2.37 - 2.47 (m, 1 H), 2.54 - 2.65 (m, 1 H), 3.23 - 3.30 (m, 2 H), 3.37 (s, 3 H), 3.73 - 3.88 (m, 2 H), 6.77 (d, J = 2.6 Hz, 1 H), 6.98 - 7.07 (m, 2 H), 7.20 (dd, J = 8.8, 2.0 Hz, 1 H), 7.58 (d, J = 3.4 Hz, 1 H), 7.75 (d, J = 1.9 Hz, 1 H), 10.48 (br s, 1 H).

Ejemplo 209

N-[(butilamino)carbonil]-2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 181, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.95 (m, 3 H), 1.23 - 1.34 (m, 2 H), 1.35 - 1.49 (m, 2 H), 2.31 (s, 3 H), 2.68 - 2.90 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.17 (br s, 1 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 (d, J = 0.8 Hz, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.5, 1.7 Hz, 1 H), 7.59 - 7.63 (m, 1 H).

Ejemplo 210

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.2 Hz, 3 H), 1.22 - 1.35 (m, 2 H), 1.36 - 1.48 (m, 2 H), 2.30 (s, 3 H), 2.69 - 2.89 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.47 (s, 3 H), 6.13 (br s, 1 H), 6.71 (d, J = 3.2 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (1 H, d, J = 3.4 Hz), 7.20 (dd, J = 8.8, 1.8 Hz, 1 H), 7.67 (d, J = 1.5 Hz, 1 H).

Ejemplo 211

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208,

se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, ciclopropilmetilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.12 - 0.19 (m, 2 H), 0.44 - 0.52 (m, 2 H), 0.79 - 0.91 (m, 1 H), 2.30 (s, 3 H), 2.73 - 2.89 (m, 2 H), 2.93 - 3.10 (m, 4 H), 3.47 (s, 3 H), 6.21 (br s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 2.1 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo 212

(E)-N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de (E)-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilensulfonamida obtenida en el Ejemplo de referencia 178, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.2 Hz, 3 H), 1.22 - 1.31 (m, 2 H), 1.33 - 1.43 (m, 2 H), 2.43 (s, 3 H), 3.03 - 3.21 (m, 2 H), 3.54 (s, 3 H), 5.85 (d, J = 15.6 Hz, 1 H), 6.18 (br s, 1 H), 6.78 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.16 (d, J = 15.4 Hz, 1 H), 7.23 (dd, J = 8.9, 1.9 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H).

Ejemplo 213

N-[(butilamino)carbonil]-2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 188, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.2 Hz, 3 H), 1.25 - 1.37 (m, 2 H), 1.39 - 1.51 (m, 2 H), 2.33 (s, 3 H), 2.79 - 2.89 (m, 2 H), 2.95 - 3.07 (m, 1 H), 3.11 - 3.25 (m, 2 H), 3.38 (s, 3 H), 3.92 (br s, 1 H), 5.39 - 5.49 (m, 1 H), 6.76 (d, J = 3.6 Hz, 1 H), 7.15 (d, J = 3.6 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 8.10 (dd, J = 7.8, 1.4 Hz, 1 H), 8.29 - 8.33 (m, 1 H).

Ejemplo 214

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.96 (m, 3 H),

1.25 - 1.37 (m, 2 H), 1.40 - 1.52 (m, 2 H), 2.31 (s, 3 H), 2.77 - 2.88 (m, 2 H), 3.04 - 3.25 (m, 3 H), 3.42 (s, 3 H), 3.75 (br s, 1 H), 5.54 (br s, 1 H), 6.71 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 8.05 (d, J = 2.1 Hz, 1 H), 8.27 (d, J = 2.1 Hz, 1 H).

Ejemplo 215

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 193, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.2 Hz, 3 H), 1.24 - 1.39 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.84 - 3.05 (m, 2 H), 3.10 - 3.21 (m, 2 H), 3.30 (br s, 1 H), 3.49 - 3.63 (m, 4 H), 6.05 (br s, 1 H), 6.76 (d, J = 3.8 Hz, 1 H), 7.23 (d, J = 3.8 Hz, 1 H), 8.05 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H).

Ejemplo 216

N-[(butilamino)carbonil]-2-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(6-metoxi-

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1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 190, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 - 0.94 (m, 3 H), 1.24 - 1.34 (m, 2 H), 1.35 - 1.48 (m, 2 H), 2.31 (s, 3 H), 2.74 - 2.89 (m, 2 H), 3.00 - 3.16 (m, 4 H), 3.50 (s, 3 H), 3.78 (s, 3 H), 6.07 (br s, 1 H), 6.43 (d, J = 2.1 Hz, 1 H), 6.67 (dd, J = 3.2, 0.8 Hz, 1 H), 6.87 (dd, J = 8.7, 2.3 Hz, 1 H), 6.96 (d, J = 3.2 Hz, 1 H), 7.56 (d, J = 8.5 Hz, 1 H).

Ejemplo 217

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)carbonil]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, propilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.4 Hz, 3 H), 1.38 - 1.51 (m, 2 H), 2.30 (s, 3 H), 2.68 - 2.88 (m, 2 H), 2.99 - 3.12 (m, 4 H), 3.48 (s, 3 H), 6.15 (br s, 1 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 218

N-[(butilamino)carbonil]-2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 186, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.95 (m, 3 H), 1.23 - 1.48 (m, 4 H), 2.30 (s, 3 H), 2.68 - 2.89 (m, 2 H), 2.99 - 3.16 (m, 4 H), 3.48 (s, 3 H), 6.13 (br s, 1 H), 6.72 (d, J = 2.7 Hz, 1 H), 6.87 - 6.93 (m, 1 H), 6.94 - 7.03 (m, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.34 (dd, J = 9.1, 2.3 Hz, 1 H).

Ejemplo 219

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(isobutilamino)carbonil]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, isobutilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (d, J = 6.6 Hz, 6 H), 1.67 (dd, J = 13.6, 6.6 Hz, 1 H), 2.30 (s, 3 H), 2.69 - 2.89 (m, 2 H), 2.95 (t, J = 6.4 Hz, 2 H), 2.99 - 3.11 (m, 2 H),

3.47 (s, 3 H), 6.22 (br s, 1 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.11 (d, J = 3.0 Hz, 1 H), 7.20 (dd, J = 8.7, 1.3 Hz, 1 H), 7.67 (d, J = 1.3 Hz, 1 H).

Ejemplo 220

N-[(butilamino)carbonil]-2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[6-(trifluorometil)-1H-indol-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 195, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.94 (m, 3 H), 1.22 - 1.34 (m, 2 H), 1.36 - 1.47 (m, 2 H), 2.33 (s, 3 H), 2.66 - 2.78 (m, 1 H), 2.79 - 2.91 (m, 1 H), 2.98 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.16 (br s, 1 H), 6.83 (dd, J = 3.4, 0.8 Hz, 1 H), 7.23 - 7.28 (m, 2 H), 7.47 (dd, J = 8.3, 1.1 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H).

Ejemplo 221

({2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de propilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 181, propanol y N,N'-

carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.54 - 1.67 (m, 2 H), 2.31 (s, 3 H), 2.65 - 2.90 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.02 (t, J = 6.8 Hz, 2 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 - 6.99 (m, 1 H), 7.09 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.4, 1.8 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Ejemplo 222

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(3-metilbutil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 3-metilbutan-1-amina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, J = 6.6 Hz, 6 H), 1.33 (q, J = 7.0 Hz, 2 H), 1.50 - 1.63 (m, 1 H), 2.30 (s, 3 H), 2.70 - 2.89 (m, 2 H), 2.94 - 3.08 (m, 2 H), 3.09 - 3.20 (m, 2 H), 3.45 - 3.50 (m, 3 H), 6.09 (br s, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.8, 1.8 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 223

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de bencilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, alcohol bencílico y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.26 (s, 3 H), 2.62 - 2.86 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.45 (s, 3 H), 5.07 (s, 2 H), 6.66 (dd, J = 3.3, 0.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.28 - 7.33 (m, 2 H), 7.36 - 7.40 (m, 3 H), 7.64 (d, J = 1.7 Hz, 1 H).

Ejemplo 224

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de 2,2,2-trifluoroetilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 2,2,2-trifluoroetanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.29 (s, 3 H), 2.67 - 2.84 (m, 2 H), 3.26 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.32 - 4.43 (m, 2 H), 6.70 (dd, J = 3.3, 0.8 Hz, 1 H), 6.89 - 6.93

(m, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (t, J = 1.7 Hz, 1 H).

Ejemplo 225 N-[(butilamino)carbonil]-2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 200, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.87 - 0.95 (m, 3 H), 1.22 - 1.48 (m, 4 H), 2.32 (s, 3 H), 2.68 - 2.93 (m, 2 H), 3.02 - 3.16 (m, 4 H), 3.49 (s, 3 H), 3.83 (s, 3 H), 6.10 (br s, 1 H), 6.46 (s, 1 H), 6.63 (d, J = 3.2 Hz, 1 H), 6.99 (d, J = 3.4 Hz, 1 H), 7.67 (s, 1 H).

Ejemplo 226

({2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 200, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.96 (m, 3 H), 1.27 - 1.40 (m, 2 H), 1.50 - 1.61 (m, 2 H), 2.33 (s, 3 H),

2.69 - 2.89 (m, 2 H), 3.32 (t, J = 7.8 Hz, 2 H), 3.48 (s, 3 H), 3.85 (s, 3 H), 4.04 (t, J = 6.6 Hz, 2 H), 6.47 (s, 1 H), 6.63 (dd, J = 3.4, 0.8 Hz, 1 H), 6.99 (d, J = 3.2 Hz, 1 H), 7.67 (s, 1 H).

Ejemplo 227

(2E)-N-(butilsulfonil)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 203 y butan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.3 Hz, 3 H), 1.35 - 1.49 (m, 2 H), 1.67 - 1.79 (m, 2 H), 2.43 (s, 3 H), 3.34 - 3.42 (m, 2 H), 3.57 (s, 3 H), 5.64 (d, J = 15.8 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.38 (d, J = 15.8 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Ejemplo 228

2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(propilamino)carbonil]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

obtenida en el Ejemplo de referencia 181, propilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.38 - 1.52 (m, 2 H), 2.31 (s, 3 H), 2.68 - 2.91 (m, 2 H), 2.96 - 3.17 (m, 4 H), 3.48 (s, 3 H), 6.20 (br s, 1 H), 6.73 (dd, J = 3.4, 0.8 Hz, 1 H), 6.97 (d, J = 0.9 Hz, 1 H), 7.08 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.4, 1.8 Hz, 1 H), 7.58 - 7.63 (m, 1 H).

Ejemplo 229

({2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 181, ciclopropilmetanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.23 - 0.30 (m, 2 H), 0.53 - 0.61 (m, 2 H), 0.99 - 1.12 (m, 1 H), 2.32 (s, 3 H), 2.65 - 2.91 (m, 2 H), 3.34 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.89 (d, J = 7.3 Hz, 2 H), 6.73 (d, J = 3.4 Hz, 1 H), 6.98 (s, 1 H), 7.09 (d, J = 3.2 Hz, 1 H), 7.18 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 1 H).

Ejemplo 230

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(2.2-dimetilpropil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 2.2-dimetilpropan-1-amina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 (s, 9 H), 2.30 (s, 3 H), 2.69 - 2.86 (m, 2 H), 2.91 - 2.95 (m, 2 H), 2.98 - 3.12 (m, 2 H), 3.47 (s, 3 H), 6.29 (br s, 1 H), 6.70 (dd, J = 3.3, 0.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.19 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 231

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(piperidin-1-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y piperidin-1-sulfonamida obtenida en el Ejemplo de referencia 177.

P018

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.21 - 1.27 (m, 1 H), 1.47 - 1.54 (m, 2 H), 1.57 - 1.65 (m, 3 H), 2.43 (s, 3 H), 3.23 - 3.30 (m, 4 H), 3.58 (s, 3 H), 5.60 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.22 (d, J = 3.6 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.1 Hz, 1 H).

Ejemplo 232

(2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Una mezcla de ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 206 (346 mg), anhídrido 2-metil-6-nitrobenzoico (483 mg), pentan-1-sulfonamida (185 mg), trietilamina (354 mg), 4-dimetilaminopiridina (142 mg) y acetonitrilo (12 ml) se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y se cristalizó en éter diisopropílico-etanol para dar el compuesto del título (448 mg, rendimiento del 89%) en forma de cristales incoloros. Punto de fusión 211.1-212.9°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H),

1.25 - 1.44 (m, 4 H), 1.73 - 1.87 (m, 2 H), 2.30 (s, 3 H), 2.48 (s, 3 H), 3.38 - 3.47 (m, 2 H), 3.52 (s, 3 H), 5.53 (d, J = 15.6 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.11 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 15.8 Hz, 1 H), 7.81 (s, 1 H), 8.13 (d, J = 1.5 Hz, 1 H).

Ejemplo 233

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de 3-metilbutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 3-metilbutan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.6 Hz, 6 H), 1.43 - 1.51 (m, 2 H), 1.58 - 1.70 (m, 1 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 7.9 Hz, 2 H), 3.46 (s, 3 H), 4.08 (t, J = 6.9 Hz, 2 H), 6.70 (d, J = 3.2 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.2 Hz, 1 H), 7.20 (dd, J = 8.9, 1.9 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 234

2-[5-(6-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(6-cloro-

1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 181, ciclopropilmetilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.12 - 0.18 (m, 2 H), 0.42 - 0.51 (m, 2 H), 0.79 - 0.91 (m, 1 H), 2.30 (s, 3 H), 2.67 - 2.90 (m, 2 H), 2.98 (dd, J = 7.1, 5.6 Hz, 2 H), 3.03 - 3.19 (m, 2 H), 3.47 (s, 3 H), 6.27 (br s, 1 H), 6.73 (dd, J = 3.3, 0.8 Hz, 1 H), 6.97 (d, J = 0.9 Hz, 1 H), 7.08 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.5, 1.7 Hz, 1 H), 7.60 (d, J = 8.5 Hz, 1 H).

Ejemplo 235

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, ciclopropilmetanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.30 (t, J = 5.6 Hz, 2 H), 0.53 - 0.61 (m, 2 H), 1.02 - 1.15 (m, 1 H), 2.30 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.13 (br s, 1 H), 3.36 (s, 3 H), 3.71 - 3.82 (m, 1 H), 3.90 - 4.05 (m, 2 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.31 (d, J = 2.3 Hz, 1 H), 10.60 (br s, 1 H).

Ejemplo 236

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de 4,4,4-trifluorobutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 4,4,4-trifluorobutan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.79 - 1.92 (m, 2 H), 2.04 - 2.20 (m, 2 H), 2.31 (s, 3 H), 2.66 - 2.88 (m, 2 H), 3.28 (t, J = 7.8 Hz, 2 H), 3.47 (s, 3 H), 4.08 (t, J = 6.4 Hz, 2 H), 6.70 (dd, J = 3.2, 0.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.21 (dd, J = 8.7, 2.1 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

Ejemplo 237

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de isobutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, isobutanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (d, J = 6.8 Hz, 6 H), 1.82 - 1.97 (m, 1 H), 2.31 (s, 3 H), 2.79 - 2.88 (m, 2 H), 3.10 - 3.22 (m, 1 H), 3.34 (s, 3 H), 3.66 - 3.77 (m, 1 H),

3.85 - 4.10 (m, 2 H), 6.70 (d, J = 3.8 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 10.52 (br s, 1 H).

Ejemplo 238

N-({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)piperidin-1-carboxamida

A una solución de ({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo obtenido en el Ejemplo 186 (347 mg) en tolueno (8 ml) se añadió piperidina (196 mg), y la mezcla se agitó a 90(C durante 4 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 30:70, v/v) para dar el compuesto del título (118 mg, rendimiento del 33%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 - 1.65 (m, 6 H), 2.31 (s, 3 H), 2.61 - 2.86 (m, 2 H), 3.19 - 3.26 (m, 4 H), 3.41 - 3.53 (m, 5 H), 6.68 (dd, J = 3.3, 0.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.15 - 7.21 (m, 2 H), 7.65 (d, J = 1.7 Hz, 1 H).

Ejemplo 239

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de propilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, propanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.4 Hz, 3 H), 1.59 - 1.70 (m, 2 H), 2.31 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.10 - 3.21 (m, 1 H), 3.35 (s, 3 H), 3.86 - 4.11 (m, 3 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.28 (d, J = 2.3 Hz, 1 H), 10.60 (br s, 1 H).

Ejemplo 240

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de 4,4,4-trifluorobutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 184, 4,4,4-trifluorobutan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.84 - 1.96 (m, 2 H), 2.08 - 2.24 (m, 2 H), 2.30 (s, 3 H), 2.79 - 2.88 (m, 2 H),

3.18 (br s, 1 H), 3.34 (s, 3 H), 3.95 - 4.21 (m, 3 H), 6.71 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.05 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.1 Hz, 1 H), 10.88 (br s, 1 H).

Ejemplo 241

2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(4,4,4-trifluorobutil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179, 4,4,4-trifluorobutan-1-amina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.66 - 1.79 (m, 2 H), 2.00 - 2.17 (m, 2 H), 2.30 (s, 3 H), 2.69 - 2.88 (m, 2 H), 2.94 - 3.09 (m, 2 H), 3.17 (q, J = 6.8 Hz, 2 H), 3.48 (s, 3 H), 6.21 (br s, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 6.89 - 6.94 (m, 1 H), 7.11 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 242

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-

pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 206 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.3 Hz, 3 H), 1.27 - 1.41 (m, 2 H), 1.45 - 1.56 (m, 2 H), 2.30 (s, 3 H), 2.48 (s, 3 H), 3.03 (q, J = 6.7 Hz, 2 H), 3.51 (s, 3 H), 5.22 - 5.29 (m, 1 H), 5.45 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.8 Hz, 1 H), 7.33 (d, J = 15.8 Hz, 1 H), 7.81 (d, J = 1.1 Hz, 1 H), 8.12 (d, J = 1.3 Hz, 1 H).

Ejemplo 243

(2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 215 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (t, J = 7.2 Hz, 3 H), 1.30 - 1.48 (m, 4 H), 1.78 - 1.92 (m, 2 H), 2.13 (s, 3 H), 3.16 - 3.26 (m, 2 H), 3.45 - 3.54 (m, 2 H), 3.63 (s, 3 H), 3.76 - 3.94 (m, 2 H), 5.84 (d, J = 15.9 Hz, 1 H), 6.71 (dd, J = 7.2, 4.8 Hz, 1 H), 7.35 - 7.42 (m, 2 H), 7.88 (d, J = 4.8 Hz, 1 H), 10.63 (s, 1 H).

Ejemplo 244

(2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 215 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.24 (s, 3 H), 2.37 (s, 3 H), 3.20 - 3.31 (m, 2 H), 3.52 (s, 3 H), 3.78 - 3.86 (m, 2 H), 6.17 (d, J = 15.8 Hz, 1 H), 6.67 (dd, J = 7.1, 5.2 Hz, 1 H), 7.18 (d, J = 15.8 Hz, 1 H), 7.40 (d, J = 8.1 Hz, 2 H), 7.50 (dd, J = 7.1, 1.2 Hz, 1 H), 7.71 - 7.75 (m, 1 H), 7.79 (d, J = 8.1 Hz, 2 H), 12.01 (s, 1 H).

Ejemplo 245

(2E)-N-[(butilamino)sulfonil]-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 215 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.81 (t, J = 7.3 Hz, 3 H), 1.17 - 1.45 (m, 4 H), 2.28 (s, 3 H), 2.78 - 2.87 (m, 2 H), 3.22 - 3.38 (m, 2 H), 3.54 (s, 3 H), 3.81 - 3.89 (m, 2 H), 6.21 (d, J = 16.0 Hz, 1 H), 6.68 (dd, J = 7.2, 5.3 Hz, 1 H), 7.26 (d, J = 16.0 Hz, 1 H), 7.47 - 7.58 (m, 2 H), 7.74 - 7.78 (m, 1 H), 11.31 (s, 1 H).

Ejemplo 246

(2E)-N-[(butilamino)sulfonil]-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 218 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.57 - 0.70 (m, 1 H), 0.75 - 0.98 (m, 6 H), 1.26 - 1.40 (m, 2 H), 1.42 - 1.56 (m, 2 H), 1.65 - 1.80 (m, 1 H), 2.96 - 3.03 (m, 2 H), 3.55 (s, 3 H), 5.11 - 5.18 (m, 1 H), 5.75 (d, J = 15.7 Hz, 1 H), 6.78 (d, J = 3.4 Hz, 1 H), 7.19 (d, J = 3.4 Hz, 1 H), 7.21 - 7.26 (m, 1 H), 7.38 (d, J = 15.7 Hz, 1 H), 8.06 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 - 8.35 (m, 1 H), 9.20 (br s, 1 H).

Ejemplo 247

(2E)-N-[(butilamino)sulfonil]-3-[3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-ciclopropil-5-(2,3-dihidro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 221 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.45 - 0.58 (m, 1 H), 0.60 - 0.80 (m, 1 H), 0.82 - 0.88 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H), 1.32 - 1.46 (m, 2 H), 1.50 - 1.69 (m, 3 H), 3.08 - 3.18 (m, 2 H), 3.20 - 3.30 (m, 2 H), 3.64 (s, 3 H), 3.82 - 3.95 (m, 2 H), 5.25 - 5.32 (m, 1 H), 6.04 (d, J = 15.7 Hz, 1 H), 6.67 (dd, J = 7.3, 5.0 Hz, 1 H), 7.39 (d, J = 7.3 Hz, 1 H), 7.44 (d, J = 15.7 Hz, 1 H), 7.83 (d, J = 5.0 Hz, 1 H), 10.61 (br s, 1 H).

Ejemplo 248

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-

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il]acrílico obtenido en el Ejemplo de referencia 13 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.14 - 0.20 (m, 2 H), 0.49 - 0.55 (m, 2 H), 0.88 - 1.02 (m, 1 H), 2.30 (s, 3 H), 2.86 - 2.91 (m, 2 H), 3.56 (s, 3 H), 5.32 (t, J = 5.9 Hz, 1 H), 5.47 (d, J = 15.5 Hz, 1 H), 6.79 (d, J = 3.6 Hz, 1 H), 7.18 (d, J = 3.6 Hz, 1 H), 7.23 (dd, J = 8.0, 4.9 Hz, 1 H), 7.33 (d, J = 15.5 Hz, 1 H), 8.05 (dd, J = 8.0, 1.5 Hz, 1 H), 8.27 - 8.34 (m, 1 H), 8.77 (s, 1 H).

Ejemplo 249

(2E)-N-{[(ciclopropilmetil)amino]sulfonil}-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 60 y N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10 - 0.17 (m, 2 H), 0.44 - 0.53 (m, 2 H), 0.83 - 0.92 (m, 1 H), 2.44 (s, 3 H), 2.80 (d, J = 6.5 Hz, 2 H), 3.55 (s, 3 H), 3.76 (s, 3 H), 5.14 - 5.20 (m, 2 H), 6.40 (d, J = 2.2 Hz, 1 H), 6.75 (dd, J = 3.4, 0.8 Hz, 1 H), 6.90 (dd, J = 8.7, 2.2 Hz, 1 H), 6.94 (d, J = 3.4 Hz, 1 H), 7.47 (d, J = 15.8 Hz, 1 H), 7.58 - 7.63 (m, 2

H).

Ejemplo 250

(2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-3-(trifluorometil)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo 230 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H), 1.25 - 1.42 (m, 4 H), 1.71 - 1.84 (m, 2 H), 3.34 - 3.40 (m, 2 H), 3.70 (s, 3 H), 5.61 (d, J = 15.9 Hz, 1 H), 6.84 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.26 - 7.31 (m, 1 H), 7.41 (d, J = 15.9 Hz, 1 H), 8.06 - 8.10 (m, 1 H), 8.33 - 8.35 (m, 1 H), 8.40 (s, 1 H).

Ejemplo 251

(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 2.40 (s, 3 H), 3.55 (s, 3 H), 5.67 (d, J = 15.8 Hz, 1 H), 7.15 (s, 1 H), 7.23 - 7.34 (m, 4 H), 7.85 (d, J = 8.5 Hz, 2 H), 8.06 (dd, J = 7.9, 1.5 Hz, 1 H), 8.20 (br s, 1 H), 8.38 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo 252

(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.1 Hz, 3 H), 1.25 - 1.46 (m, 4 H), 1.72 - 1.86 (m, 2 H), 2.36 (s, 3 H), 3.35 - 3.46 (m, 2 H), 3.54 (s, 3 H), 5.66 (d, J = 15.8 Hz, 1 H), 7.19 (s, 1 H), 7.29 - 7.40 (m, 2 H), 8.08 (dd, J = 7.9, 1.5 Hz, 1 H), 8.39 (dd, J = 4.8, 1.5 Hz, 1 H), 8.49 (s, 1 H).

Ejemplo 253

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[3,2-c]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 224 y

pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 (t, J = 7.2 Hz, 3 H), 1.24 - 1.35 (m, 4 H), 1.65 - 1.75 (m, 2 H), 2.46 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.44 (s, 3 H), 5.54 (d, J = 16.1 Hz, 1 H), 6.85 (d, J = 3.4 Hz, 1 H), 6.95 (d, J = 6.1 Hz, 1 H), 7.16 (d, J = 3.4 Hz, 1 H), 7.68 (d, J = 16.1 Hz, 1 H), 8.06 (d, J = 6.1 Hz, 1 H), 8.24 (s, 1 H).

Ejemplo 254

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 227 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 3 H), 1.26 - 1.42 (m, 4 H), 1.66 - 1.78 (m, 2 H), 2.43 (s, 3 H), 3.32 - 3.40 (m, 2 H), 3.45 (s, 3 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.87 (d, J = 3.2 Hz, 1 H), 7.25 (d, J = 3.2 Hz, 1 H), 7.49 (d, J = 15.9 Hz, 1 H), 7.55 (d, J = 4.9 Hz, 1 H), 8.11 (d, J = 4.9 Hz, 1 H), 8.21 (s, 1 H).

Ejemplo 255

{(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 254.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 - 0.83 (m, 3 H), 1.18 - 1.23 (m, 4 H), 1.37 - 1.46 (m, 2 H), 2.35 (s, 3 H), 2.81 - 2.88 (m, 2 H), 3.46 (s, 3 H), 5.52 (d, J = 16.2 Hz, 1 H), 6.76 (d, J = 16.2 Hz, 1 H), 6.91 (d, J = 2.9 Hz, 1 H), 7.71 (dd, J = 5.4, 0.9 Hz, 1 H), 7.80 (d, J = 2.9 Hz, 1 H), 8.28 (d, J = 5.4 Hz, 1 H), 8.37 (s, 1 H).

Ejemplo 256

(2E)-N-[(butilamino)sulfonil]-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-c]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 227 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.4 Hz, 3 H), 1.15 - 1.40 (m, 4 H), 2.40 (s, 3 H), 2.74 - 2.81 (m, 2 H), 3.51 (s, 3 H), 6.05 (d, J = 16.1 Hz, 1 H), 6.94 (d, J = 3.2

Hz, 1 H), 7.00 (d, J = 16.1 Hz, 1 H), 7.53 (t, J = 5.7 Hz, 1 H), 7.74 (d, J = 5.5 Hz, 1 H), 7.85 (d, J = 3.2 Hz, 1 H), 8.31 (d, J = 5.5 Hz, 1 H), 8.41 (s, 1 H), 11.31 (s, 1 H).

Ejemplo 257

{(2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de sodio

Por medio de un método similar al del Ejemplo 28, se obtuvo el compuesto del título a partir de (2E)-3-[5-(6-metoxi-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 38.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 - 0.84 (m, 3 H), 1.18 - 1.24 (m, 4 H), 1.42 - 1.48 (m, 2 H), 2.34 (s, 3 H), 2.82 - 2.88 (m, 2 H), 3.42 (s, 3 H), 3.68 (s, 3 H), 5.61 (d, J = 15.9 Hz, 1 H), 6.43 (d, J = 1.9 Hz, 1 H), 6.71 (d, J = 3.4 Hz, 1 H), 6.75 - 6.84 (m, 2 H), 7.33 (d, J = 3.4 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H).

Ejemplo 258

(2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(1-metil-1H-imidazol-4-il)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(3-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 133 y 1-metil-1H-imidazol-4-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3 H), 3.48 (s, 3 H), 3.67 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.93 (d, J = 16.0 Hz, 1 H), 7.40 (dd, J = 7.9, 4.7 Hz, 1 H), 7.73 (d, J = 1.1 Hz, 1 H), 7.87 (d, J = 1.1 Hz, 1 H), 8.04 (s, 1 H), 8.16 (dd, J = 7.9, 1.5 Hz, 1 H), 8.36 (dd, J = 4.7, 1.5 Hz, 1 H), 11.87 (s, 1 H).

Ejemplo 259

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-metoxi-4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 21 y 2-metoxi-4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3 H), 2.39 (s, 3 H), 3.48 (s, 3 H), 3.77 (s, 3 H), 5.59 (d, J = 15.8 Hz, 1 H), 6.70 (d, J = 3.4 Hz, 1 H), 6.74 (s, 1 H), 6.79 - 6.87 (m, 2 H), 6.90 - 7.00 (m, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.22 - 7.37 (m, 2 H), 7.76 (d, J = 8.1 Hz, 1 H), 8.26 (s, 1 H).

Ejemplo 260

(2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-hidroxi-4-metilfenil)sulfonil]acrilamida

A una solución de (2E)-3-[5-(5-fluoro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-metoxi-4-metilfenil)sulfonil]acrilamida obtenida en el Ejemplo 259

(312 mg) en diclorometano (30 ml) se añadió gota a gota tribromuro de boro (solución de diclorometano 1 M, 1.3 ml) con agitación a -78°C, y la mezcla se agitó a -78°C durante 1 h. La mezcla se dejó calentar hasta temperatura ambiente, y se agitó durante 30 h, y luego se calentó a reflujo durante 2 h. La mezcla de reacción se concentró a presión reducida, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 35:65, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (220 mg, rendimiento del 72%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.32 (s, 3 H), 2.39 (s, 3 H), 3.50 (s, 3 H), 5.19 (d, J = 15.8 Hz, 1 H), 6.73 - 6.88 (m, 4 H), 6.94 - 7.02 (m, 1 H), 7.07 (d, J = 3.4 Hz, 1 H), 7.36 (dd, J = 9.0, 2.4 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.89 (s, 1 H), 8.71 (s, 1 H).

Ejemplo 261

(2E)-3-[3-(1-naftil)-2-tienil]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-(1-naftil)-2-tienil]acrílico obtenido en el Ejemplo de referencia 233 y pentan-1-sulfonamida.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.90 (m, 3 H), 1.25 - 1.41 (m, 4 H), 1.72 - 1.82 (m, 2 H), 3.35 - 3.42 (m, 2 H), 6.18 (d, J = 15.1 Hz, 1 H), 7.18 (d, J = 4.9 Hz, 1 H), 7.33 (d, J = 5.7 Hz, 1 H), 7.40 - 7.65 (m, 6 H), 7.73 (s, 1 H), 7.88 - 7.98 (m, 2 H).

Ejemplo 262

(2E)-N-[(butilamino)sulfonil]-3-[3-(1-naftil)-2-tienil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[3-(1-naftil)-2-tienil]acrílico obtenido en el Ejemplo de referencia 233 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.3 Hz, 3 H), 1.23 - 1.38 (m, 2 H), 1.41 - 1.54 (m, 2 H), 2.91 - 3.00 (m, 2 H), 5.11 (t, J = 6.0 Hz, 1 H), 6.13 (d, J = 15.3 Hz, 1 H), 7.18 (d, J = 5.1 Hz, 1 H), 7.33 (dd, J = 7.0, 1.1 Hz, 1 H), 7.40 - 7.67 (m, 6 H), 7.84 (s, 1 H), 7.89 - 7.94 (m, 2 H).

Ejemplo 263

(2E)-N-[(butilamino)sulfonil]-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-

pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.3 Hz, 3 H), 1.27 - 1.40 (m, 2 H), 1.44 - 1.52 (m, 2 H), 2.39 (s, 3 H), 2.96 - 3.03 (m, 2 H), 3.53 (s, 3 H), 5.20 (t, J = 6.1 Hz, 1 H), 5.44 (d, J = 15.6 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 15.6 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.23 (d, J = 2.3 Hz, 1 H), 8.42 (s, 1 H).

Ejemplo 264

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida

Una mezcla de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 (380 mg), anhídrido 2-metil-6-nitrobenzoico (494 mg), N-(ciclopropilmetil)sulfamida obtenida en el Ejemplo de referencia 115 (186 mg), trietilamina (372 mg), 4-dimetilaminopiridina (151 mg) y acetonitrilo (8 ml) se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con

salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 35:65, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (290 mg, rendimiento del 53%) en forma de cristales incoloros. Punto de fusión 209.3-210.0°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.13 - 0.19 (m, 2 H), 0.48 - 0.56 (m, 2 H), 0.89 - 1.03 (m, 1 H), 2.40 (s, 3 H), 2.86 (dd, J = 7.2, 6.0 Hz, 2 H), 3.55 (s, 3 H), 5.28 (t, J = 6.0 Hz, 1 H), 5.42 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.20 (d, J = 3.6 Hz, 1 H), 7.36 (d, J = 15.8 Hz, 1 H), 8.03 (d, J = 2.3 Hz, 1 H), 8.12 (s, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Ejemplo 265

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.1 Hz, 3 H), 1.25 - 1.45 (m, 4 H), 1.70 - 1.82 (m, 2 H), 2.40 (s, 3 H), 3.36 - 3.43 (m, 2 H), 3.54 (s, 3 H), 5.53 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.20 (d, J = 3.8 Hz, 1 H),

7.38 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.19 (s, 1 H), 8.25 (d, J = 2.3 Hz, 1 H).

Ejemplo 266

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y 4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 2.41 (s, 3 H), 3.54 (s, 3 H), 5.55 (d, J = 15.8 Hz, 1 H), 6.71 (d, J = 3.8 Hz, 1 H), 7.17 (d, J = 3.8 Hz, 1 H), 7.26 - 7.37 (m, 3 H), 7.79 - 7.86 (m, 2 H), 7.94 (d, J = 2.2 Hz, 1 H), 8.17 (s, 1 H), 8.24 (d, J = 2.2 Hz, 1 H).

Ejemplo 267

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-metoxi-4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y 2-metoxi-4-metilbencensulfonamida.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3 H), 2.39 (s, 3 H), 3.53 (s, 3 H), 3.83 (s, 3 H), 5.83 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 6.76 (s, 1 H), 6.85 (d, J = 8.1 Hz, 1 H), 7.17 (d, J = 3.6 Hz, 1 H), 7.30 (d, J = 15.8 Hz, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.92 (d, J = 2.3 Hz, 1 H), 8.24 (d, J = 2.3 Hz, 1 H).

Ejemplo 268

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-hidroxi-4-metilfenil)sulfonil]acrilamida

A una solución de (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(2-metoxi-4-metilfenil)sulfonil]acrilamida obtenida en el Ejemplo 267 (396 mg) en diclorometano (15 ml) se añadió gota a gota tribromuro de boro (solución de diclorometano 1 M, 2.4 ml) con agitación a 0°C, y la mezcla se agitó a 0°C durante 4 h. La mezcla de reacción se neutralizó con metanol, y se concentró a presión reducida. Se agregó agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-etanol para dar el compuesto del título (190 mg, rendimiento del 49%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.24 (s, 3 H), 2.35 (s, 3 H), 3.46 (s, 3 H), 6.11 (d, J = 16.1 Hz, 1 H), 6.69 - 6.74

(m, 2 H), 6.84 (d, J = 3.8 Hz, 1 H), 6.89 (d, J = 16.1 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.77 (d, J = 3.8 Hz, 1 H), 8.25 - 8.30 (m, 2 H), 10.64 (s, 1 H), 11.80 (s, 1 H).

Ejemplo 269

(2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(butilamino)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 238 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.3 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.44 - 1.55 (m, 2 H), 2.41 (s, 3 H), 2.95 - 3.03 (m, 2 H), 3.54 (s, 3 H), 5.14 (t, J = 6.2 Hz, 1 H), 5.43 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.10 (s, 1 H), 8.18 (d, J = 2.2 Hz, 1 H), 8.34 (d, J = 2.2 Hz, 1 H).

Ejemplo 270

(2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(2-metoxi-4-metilfenil)sulfonil]acrilamida

Por medio de un método similar al del Ejemplo 1, se

obtuvo el compuesto del título a partir de ácido (2E)-3-[1,3-dimetil-5-(3-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 136 y 2-metoxi-4-metilbencensulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 3 H), 2.36 (s, 3 H), 2.37 (s, 3 H), 3.54 (s, 3 H), 3.82 (s, 3 H), 5.89 (d, J = 15.9 Hz, 1 H), 6.73 (s, 1 H) 6.78 (d, J = 8.3 Hz, 1 H), 6.90 (s, 1 H), 7.16 - 7.19 (m, 1 H), 7.31 (d, J = 15.9 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.93 - 7.96 (m, 1 H), 8.26 - 8.32 (m, 1 H), 8.40 (s, 1 H).

Ejemplo 271

3-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}imidazolidin-2,4-diona

A una solución de imidazolidin-2,4-diona (116 mg) en N,N-dimetilformamida (4 ml), que se enfrió a 0°C en un baño helado, se añadió hidruro de sodio al 60% (en aceite, 49 mg) con agitación, y la mezcla se agitó a 0°C durante 20 min. Se añadió metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo obtenido en el Ejemplo de referencia 239 (329 mg) a esta mezcla de reacción a 0°C, y la mezcla de reacción se agitó a 80°C durante 18 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El

filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo), y se cristalizó en hexano-etanol para dar el compuesto del título (195 mg, rendimiento del 58%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.18 (s, 3 H), 2.29 - 2.46 (m, 2 H), 3.26 (t, J = 7.0 Hz, 2 H), 3.33 (s, 3 H), 3.64 - 3.79 (m, 2 H), 6.75 (d, J = 3.0 Hz, 1 H), 7.06 (d, J = 8.7 Hz, 1 H), 7.19 (dd, J = 8.7, 2.0 Hz, 1 H), 7.53 (d, J = 3.0 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H), 7.92 (s, 1 H).

Ejemplo 272

3-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-5-propilimidazolidin-2,4-diona

Por medio de un método similar al del Ejemplo 271, se obtuvo el compuesto del título a partir de metansulfonato de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etilo obtenido en el Ejemplo de referencia 239 y 5-propilimidazolidin-2,4-diona.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.4 Hz, 3 H), 1.24 - 1.43 (m, 2 H), 1.46 - 1.58 (m, 1 H), 1.68 - 1.84 (m, 1 H), 2.27 (s, 3 H), 2.38 - 2.51 (m, 1 H), 2.61 - 2.74 (m, 1 H), 3.35 - 3.47 (m, 5 H), 3.70 - 3.89 (m, 1 H), 5.27 - 5.29 (m, 1 H), 6.69 (d, J = 3.4 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 1.9 Hz, 1 H), 7.29 (dd, J = 5.7, 3.4 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H).

Ejemplo 273

clorhidrato de 1-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}piperazin-2-ona

A una solución de 4-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-3-oxopiperazin-1-carboxilato de ter-butilo obtenida en el Ejemplo de referencia 240 (223 mg) en acetato de etilo (4 ml) se añadió una solución de cloruro de hidrógeno 4 M-acetato de etilo (2 ml), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, y el residuo se purificó por HPLC preparativa (la herramienta y las condiciones preparativas eras iguales a las del Ejemplo de referencia 97). El sólido amorfo obtenido se neutralizó con solución acuosa de carbonato de sodio ácido, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. Una solución de cloruro de hidrógeno 4 M-acetato de etilo (1 ml) se añadió al residuo obtenido, y la mezcla se concentró a presión reducida, y se secó para dar el compuesto del título (132 mg, rendimiento del 68%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.24 (s, 3 H), 2.25 - 2.46 (m, 2 H), 3.15 - 3.34 (m, 6 H), 3.38 (s, 3 H), 3.52 - 3.60 (m, 2 H), 6.77 (d, J = 3.3 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 1 H), 7.20 (dd, J = 8.7, 1.7 Hz, 1 H), 7.64 (d, J = 3.3 Hz, 1

H), 7.75 (d, J = 1.7 Hz, 1 H), 9.54 (s, 2 H).

Ejemplo 274

{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etoxi}carbamato de butilo

A una solución de 1-{4-[2-(aminooxi)etil]-1,3-dimetil-1H-pirazol-5-il}-5-cloro-1H-indol obtenida en el Ejemplo de referencia 242 (308 mg) en tetrahidrofurano (8 ml) se añadió trietilamina (330 mg), y luego una solución de cloroformiato de butilo (172 mg) en tetrahidrofurano (6 ml), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se concentró a presión reducida, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 25:75, v/v) para dar el compuesto del título (146 mg, rendimiento del 35%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3 H), 1.25 - 1.40 (m, 2 H), 1.49 - 1.62 (m, 2 H), 2.29 (s, 3 H), 2.45 - 2.68 (m, 2 H), 3.45 (s, 3 H), 3.71 (t, J = 6.6 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 2 H), 6.68 (d, J = 3.4 Hz, 1 H), 6.79 (s, 1 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.13 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.7, 1.7 Hz, 1 H), 7.66 (d, J = 1.7 Hz, 1 H).

Ejemplo 275

N-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etoxi}-N'-pentilurea

A una solución de 1-{4-[2-(aminooxi)etil]-1,3-dimetil-1H-pirazol-5-il}-5-cloro-1H-indol obtenida en el Ejemplo de referencia 242 (300 mg) en tetrahidrofurano (8 ml) se añadió isocianato de pentilo (175 mg), y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 25:75, v/v), y luego se purificó por HPLC preparativa (la herramienta y las condiciones preparativas son iguales a las del Ejemplo de referencia 97) para dar el compuesto del título (171 mg, rendimiento del 41%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.0 Hz, 3 H), 1.18 - 1.47 (m, 6 H), 2.30 (s, 3 H), 2.45 - 2.66 (m, 2 H), 3.10 - 3.20 (m, 2 H), 3.46 (s, 3 H), 3.66 (t, J = 6.7 Hz, 2 H), 5.29 - 5.38 (m, 1 H), 6.66 - 6.71 (m, 2 H), 6.92 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.2 Hz, 1 H), 7.19 (dd, J = 8.9, 1.7 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H).

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Ejemplo 276

1,1-dióxido de (4R)-5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-4-isopropil-1,2,5-tiadiazolidin-3-ona

Se disolvió (4R)-5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-4-isopropil-1,1-dióxido-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona obtenida en el Ejemplo de referencia 243 (205 mg) en ácido trifluoroacético (4 ml), y la solución se agitó con calentamiento a 65°C durante 7 h. La mezcla de reacción se concentró a presión reducida, se añadió agua al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El residuo se sometió a cromatografía en columna de gel de sílice (acetato de etilo-metanol 95:5, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (41 mg, rendimiento del 25%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.67 (dd, J = 14.0, 7.0 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 1.64 - 1.80 (m, 1 H), 2.32 (s, 3 H), 2.58 - 2.85 (m, 4 H), 3.06 - 3.30 (m, 1 H), 3.48 - 3.53 (m, 4 H), 6.70 (d, J = 2.9 Hz, 1 H), 6.93 (dd, J = 8.6, 4.8 Hz, 1 H), 7.11 (d, J = 2.9 Hz, 1 H), 7.20 - 7.24 (m, 1 H), 7.66 (s, 1 H).

Ejemplo 277

N-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etoxi}-4-metilbenzamida

Por medio de un método similar al del Ejemplo 274, se obtuvo el compuesto del título a partir de 1-{4-[2-(aminooxi)etil]-1,3-dimetil-1H-pirazol-5-il}-5-cloro-1H-indol obtenido en el Ejemplo de referencia 242 y cloruro de 4-metilbenzoílo.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3 H), 2.39 (s, 3 H), 2.64 (t, J = 6.2 Hz, 2 H), 3.48 (s, 3 H), 3.78 - 3.95 (m, 2 H), 6.66 (d, J = 3.4 Hz, 1 H), 7.02 (d, J = 8.7 Hz, 1 H), 7.14 - 7.27 (m, 6 H), 7.64 - 7.66 (m, 2 H).

Ejemplo 278

{(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 9.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.77 - 0.84 (m, 3 H), 1.16 - 1.25 (m, 4 H), 1.40 - 1.48 (m, 2 H), 2.33 (s, 3 H), 2.82 - 2.90 (m, 2 H), 3.43 (s, 3 H), 5.59 (d, J = 16.1 Hz, 1 H), 6.76 (d, J = 16.1 Hz, 1 H), 6.84 (d, J = 3.6 Hz, 1 H), 7.25 (dd, J = 8.0, 4.7 Hz, 1 H), 7.64 (d, J = 3.6 Hz, 1 H),

8.14 (dd, J = 8.0, 1.5 Hz, 1 H), 8.24 - 8.28 (m, 1 H).

Ejemplo 279

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida

A una solución de butilamina (110 mg) en N,N-dimetilformamida (8 ml) se añadió N,N'-carbonildiimidazol (265 mg), y la mezcla se agitó a 60°C durante 1 h. 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 246 (350 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (259 mg) y 4-dimetilaminopiridina (209 mg) se añadieron a la mezcla de reacción, y la mezcla se agitó a 60°C durante 16 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 60:40, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (200 mg, rendimiento del 45%) en forma de cristales incoloros. Punto de fusión 166.8-167.6°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 - 0.96 (m, 7 H), 1.23 - 1.52 (m, 4 H), 1.76 - 1.84 (m, 1 H), 2.75 - 3.02 (m, 2 H), 3.08 - 3.20 (m, 2 H), 3.21 - 3.34 (m, 1 H), 3.39 (s, 3 H),

3.75 - 3.90 (m, 1 H), 5.77 (s, 1 H), 6.70 (d, J = 3.6 Hz, 1 H), 7.19 (d, J = 3.6 Hz, 1 H), 8.04 (d, J = 2.3 Hz, 1 H), 8.26 (d, J = 2.3 Hz, 1 H), 8.68 (s, 1 H).

Ejemplo 280

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 246, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.78 - 1.00 (m, 7 H), 1.30 - 1.41 (m, 2 H), 1.53 - 1.65 (m, 2 H), 1.76 - 1.86 (m, 1 H), 2.80 - 3.03 (m, 2 H), 3.18 - 3.30 (m, 1 H), 3.33 (s, 3 H), 3.94 - 4.18 (m, 3 H), 6.69 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 8.03 (d, J = 2.3 Hz, 1 H), 8.27 (d, J = 2.3 Hz, 1 H), 10.37 (s, 1 H).

Ejemplo 281

1,1-dióxido de 5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-1,2,5-tiadiazolidin-3-ona

Por medio de un método similar al del Ejemplo 276, se obtuvo el compuesto del título a partir de 5-{2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}-1,1-dióxido-2-(4-metoxibencil)-1,2,5-tiadiazolidin-3-ona obtenida

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en el Ejemplo de referencia 247.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.22 (s, 3 H), 2.30 - 2.47 (m, 2 H), 2.90 (t, J = 7.1 Hz, 2 H), 3.37 (s, 3 H), 3.43 - 3.70 (m, 2 H), 6.76 (d, J = 3.4 Hz, 1 H), 7.03 (d, J = 8.7 Hz, 1 H), 7.18 (dd, J = 8.7, 2.0 Hz, 1 H), 7.56 (d, J = 3.4 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H).

Ejemplo 282

(2E)-3-[1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-bencil-3-metil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 251 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.90 (m, 3 H), 1.23 - 1.40 (m, 4 H), 1.70 - 1.82 (m, 2 H), 2.39 (s, 3 H), 3.35 - 3.40 (m, 2 H), 4.91 (d, J = 15.6 Hz, 1 H), 5.16 (d, J = 15.6 Hz, 1 H), 5.51 (d, J = 15.9 Hz, 1 H), 6.65 (d, J = 3.8 Hz, 1 H), 6.81 - 6.91 (m, 3 H), 7.12 - 7.25 (m, 4 H), 7.38 (d, J = 15.9 Hz, 1 H), 8.02 (dd, J = 7.9, 1.5 Hz, 1 H), 8.06 - 8.17 (m, 1 H), 8.32 (dd, J = 4.7, 1.5 Hz, 1 H).

Ejemplo 283

(2E)-N-(butilsulfonil)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

Una mezcla de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 (414 mg), anhídrido 2-metil-6-nitrobenzoico (547 mg), butan-1-sulfonamida (188 mg), trietilamina (412 mg), 4-dimetilaminopiridina (165 mg) y acetonitrilo (12 ml) se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró a presión reducida, una solución acuosa saturada de cloruro de amonio (10 ml) se añadió al residuo, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en gel de sílice (hexano-acetato de etilo 30:70, v/v), y se cristalizó en hexano-etanol para dar el compuesto del título (505 mg, rendimiento del 88%) en forma de cristales incoloros. Punto de fusión 245.3-248.1°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.4 Hz, 3 H), 1.35 - 1.50 (m, 2 H), 1.70 - 1.81 (m, 2 H), 2.39 (s, 3 H), 3.37 - 3.43 (m, 2 H), 3.53 (s, 3 H), 5.53 (d, J = 15.7 Hz, 1 H), 6.75 (d, J = 3.4 Hz, 1 H), 7.20 (d, J = 3.4 Hz, 1 H), 7.38 (d, J = 15.7 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.24 (d, J = 2.3 Hz, 1 H), 8.35 (s, 1 H).

Ejemplo 284

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(propilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 235 y propan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, J = 7.4 Hz, 3 H), 1.75 - 1.90 (m, 2 H), 2.40 (s, 3 H), 3.35 - 3.41 (m, 2 H), 3.54 (s, 3 H), 5.53 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.21 (d, J = 3.6 Hz, 1 H), 7.39 (d, J = 15.8 Hz, 1 H), 8.02 (d, J = 2.3 Hz, 1 H), 8.14 (s, 1 H), 8.26 (d, J = 2.3 Hz, 1 H).

Ejemplo 285

{(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]prop-2-enoil}(pentilsulfonil)azanida de potasio

Por medio de un método similar al del Ejemplo 7, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 265.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.78 - 0.83 (m, 3 H), 1.17 - 1.24 (m, 4 H), 1.38 - 1.50 (m, 2 H), 2.32 (s, 3 H), 2.80 - 2.89 (m, 2 H), 3.43 (s, 3 H), 5.56 (d, J = 16.3 Hz, 1

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H), 6.75 (d, J = 16.3 Hz, 1 H), 6.84 (d, J = 3.8 Hz, 1 H), 7.77 (d, J = 3.8 Hz, 1 H), 8.26 - 8.29 (m, 2 H).

Ejemplo 286

(2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 238 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, J = 7.0 Hz, 3 H), 1.30 - 1.45 (m, 4 H), 1.72 - 1.85 (m, 2 H), 2.41 (s, 3 H), 3.34 - 3.45 (m, 2 H), 3.54 (s, 3 H), 5.52 (d, J = 15.6 Hz, 1 H), 6.75 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 7.39 (d, J = 15.6 Hz, 1 H), 8.15 (br s, 1 H), 8.18 (d, J = 2.1 Hz, 1 H), 8.34 (d, J = 2.1 Hz, 1 H).

Ejemplo 287

(2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(butilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 238 y butan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 3 H),

1.36 - 1.49 (m, 2 H), 1.70 - 1.82 (m, 2 H), 2.41 (s, 3 H), 3.35 - 3.43 (m, 2 H), 3.54 (s, 3 H), 5.52 (d, J = 15.8 Hz, 1 H), 6.75 (d, J = 3.8 Hz, 1 H), 7.18 (d, J = 3.8 Hz, 1 H), 7.39 (d, J = 15.8 Hz, 1 H), 8.03 (br s, 1 H), 8.18 (d, J = 2.1 Hz, 1 H), 8.34 (d, J = 2.1 Hz, 1 H).

Ejemplo 288

(2E)-N-[(butilamino)sulfonil]-3-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida

A una mezcla de ácido (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-[(butilamino)sulfonil]acrilamida obtenida en el Ejemplo 269 (395 mg), ciclopropilborónico (408 mg), una solución acuosa 2.0 M de carbonato de sodio (1.6 ml) y 1.2-dimetoxietano (10 ml) se añadió tetraquis(trifenilfosfina)paladio (0) (92 mg), y la mezcla de reacción se calentó a reflujo bajo una atmósfera de nitrógeno durante 40 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió agua, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 45:55, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (125 mg, rendimiento del 34%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.74 - 0.80 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H), 1.05 - 1.10 (m, 2 H), 1.24 - 1.41 (m, 2 H), 1.44 - 1.55 (m, 2 H), 1.99 - 2.10 (m, 1 H), 2.32 (s, 3 H), 2.98 - 3.05 (m, 2 H), 3.53 (s, 3 H), 5.09 - 5.25 (m, 1 H), 5.44 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.6 Hz, 1 H), 7.34 (d, J = 15.8 Hz, 1 H), 7.66 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 2.1 Hz, 1 H), 8.73 (br s, 1 H).

Ejemplo 289

(2E)-3-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 288, se obtuvo el compuesto del título a partir de (2E)-3-[5-(5-bromo-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 286 y ácido ciclopropilborónico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.74 - 0.80 (m, 2 H), 0.88 (t, J = 7.1 Hz, 3 H), 1.07 (dd, J = 8.3, 1.3 Hz, 2 H), 1.26 - 1.47 (m, 4 H), 1.72 - 1.86 (m, 2 H), 2.00 - 2.12 (m, 1 H), 2.30 (s, 3 H), 3.39 - 3.45 (m, 2 H), 3.52 (s, 3 H), 5.51 (d, J = 15.8 Hz, 1 H), 6.67 (d, J = 3.8 Hz, 1 H), 7.10 (d, J = 3.8 Hz, 1 H), 7.35 (d, J = 15.8 Hz, 1 H), 7.66 (d, J = 1.9 Hz, 1 H), 8.16 (d, J = 1.9 Hz, 1 H), 8.81 (s, 1 H).

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extrajo con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1 N y salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 90:10 - 80:20, v/v) para dar el compuesto del título (210 mg, rendimiento del 48%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.70 - 0.84 (m, 2 H), 0.86 - 0.95 (m, 3 H), 1.14 - 1.52 (m, 4 H), 1.60 - 1.84 (m, 3 H), 1.95 - 2.21 (m, 1 H), 2.31 (s, 1.5 H), 2.32 (s, 1.5 H), 2.86 - 3.01 (m, 0.5 H), 3.10 - 3.24 (m, 0.5 H), 3.26 - 3.37 (m, 1 H), 3.54 (s, 1.5 H), 3.58 (s, 1.5 H), 6.74 - 6.84 (m, 1 H), 6.86 - 7.05 (m, 1 H), 7.14 (t, J = 3.5 Hz, 1 H), 7.21 - 7.26 (m, 1 H), 7.75 (d, J = 1.9 Hz, 1 H).

Ejemplo 293

trans-N-[(butilamino)sulfonil]-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]ciclopropancarboxamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido trans-2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]ciclopropanecarboxílico obtenido en el Ejemplo de referencia 148 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.31 - 0.60 (m, 1 H),

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0.73 - 0.90 (m, 3 H), 0.83 - 1.00 (m, 1 H), 1.14 - 1.49 (m, 3 H), 1.60 - 1.75 (m, 1 H), 1.81 - 2.04 (m, 2 H), 2.19 - 2.25 (m, 3 H), 2.57 - 2.93 (m, 2 H), 3.34 - 3.43 (m, 3 H), 6.76 (d, J = 3.4 Hz, 1 H), 6.94 - 7.12 (m, 1 H), 7.13 - 7.27 (m, 1 H), 7.44 - 7.57 (m, 1 H), 7.58 (dd, J = 3.2, 1.7 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 11.24 - 11.66 (m, 1 H).

Ejemplo 294.

N-[(butilamino)carbonil]-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida

A una solución de butilamina (90.6 mg) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (218 mg), y la mezcla se agitó a 60°C durante 1 h. 2-{1,3-Dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208 (400 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (220 mg) y 4-dimetilaminopiridina (176 mg) se añadieron a la mezcla de reacción, y la mezcla se agitó a 60°C durante 18 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo

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para dar el compuesto del título (323 g, rendimiento del 64%) en forma de cristales incoloros. Punto de fusión 162.7-164.0°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.96 (m, 3 H), 1.26 - 1.40 (m, 2 H), 1.41 - 1.52 (m, 2 H), 2.32 (s, 3 H), 2.78 - 2.92 (m, 2 H), 3.07 - 3.24 (m, 3 H), 3.43 (s, 3 H), 3.64 - 3.80 (m, 1 H), 5.59 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.6 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.3 Hz, 1 H).

Ejemplo 295

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de butilo

A una solución de butanol (91.8 mg) en N,N-dimetilformamida (10 ml) se añadió N,N'-carbonildiimidazol (217 mg), y la mezcla se agitó a 60°C durante 1 h. 2-{1,3-Dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208 (400 mg), 1,8-diazabiciclo[5.4.0]undec-7-eno (220 mg) y 4-dimetilaminopiridina (176 mg) se añadieron a esta mezcla de reacción, y la mezcla se agitó a 60°C durante 18 h. Una solución acuosa saturada de cloruro de amonio (10 ml) se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se

filtró. El filtrado se concentró, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 40:60, v/v), y se cristalizó en hexano-acetato de etilo para dar el compuesto del título (214 mg, rendimiento del 43%) en forma de cristales incoloros. Punto de fusión 122.3-123.2°C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.3 Hz, 3 H), 1.30 - 1.44 (m, 2 H), 1.54 - 1.66 (m, 2 H), 2.32 (s, 3 H), 2.74 - 2.90 (m, 2 H), 3.11 - 3.23 (m, 1 H), 3.37 (s, 3 H), 3.91 - 4.18 (m, 3 H), 6.85 (d, J = 3.6 Hz, 1 H), 7.25 - 7.27 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.61 (d, J = 1.3 Hz, 1 H), 10.41 (br s, 1 H).

Ejemplo 296

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de etilo

A una solución de 2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 179 (520 mg) en piridina (20 ml) se añadió clorocarbonato de etilo (10 ml), y la mezcla se calentó a reflujo durante 2 h. Se añadió ácido clorhídrico 1 N (20 ml) a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró. El filtrado se concentró, y el residuo se cristalizó en hexano-acetato de etilo para dar el compuesto del título

L064

(426 mg, rendimiento del 68%) en forma de cristales incoloros.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.2 Hz, 3 H), 2.31 (s, 3 H), 2.65 - 2.87 (m, 2 H), 3.30 (t, J = 8.0 Hz, 2 H), 3.47 (s, 3 H), 4.11 (q, J = 7.2 Hz, 2 H), 6.70 (d, J = 3.0 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 3.4 Hz, 1 H), 7.20 (dd, J = 8.7, 1.9 Hz, 1 H), 7.67 (d, J = 1.9 Hz, 1 H).

Ejemplo 297

({2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 210, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 3 H), 1.25 - 1.42 (m, 2 H), 1.52 - 1.64 (m, 2 H), 2.31 (s, 3 H), 2.47 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.07 - 3.18 (m, 1 H), 3.31 (s, 3 H), 3.85 - 3.96 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.65 (d, J = 3.8 Hz, 1 H), 7.05 (d, J = 3.6 Hz, 1 H), 7.85 (d, J = 1.1 Hz, 1 H), 8.14 (d, J = 1.9 Hz, 1 H), 11.91 (br s, 1 H).

Ejemplo 298

N-[(butilamino)carbonil]-2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 210, butilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 - 0.96 (m, 3 H), 1.25 - 1.37 (m, 2 H), 1.38 - 1.51 (m, 2 H), 2.32 (s, 3 H), 2.48 (s, 3 H), 2.80 - 2.89 (m, 2 H), 3.00 (br s, 1 H), 3.10 - 3.26 (m, 2 H), 3.35 (s, 3 H), 3.95 (br s, 1 H), 6.67 (d, J = 3.6 Hz, 1 H), 7.10 (d, J = 3.6 Hz, 1 H), 7.89 (d, J = 1.1 Hz, 1 H), 8.13 (d, J = 1.9 Hz, 1 H).

Ejemplo 299

(2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}-N-(propilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 203 y propan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.02 (t, J = 7.6 Hz, 3 H),

1.72 - 1.86 (m, 2 H), 2.42 (s, 3 H), 3.33 - 3.39 (m, 2 H), 3.57 (s, 3 H), 5.65 (d, J = 15.5 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.9 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.9 Hz, 1 H).

Ejemplo 300

(2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 203 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.91 (m, 3 H), 1.24 - 1.43 (m, 4 H), 1.69 - 1.82 (m, 2 H), 2.42 (s, 3 H), 3.33 - 3.42 (m, 2 H), 3.57 (s, 3 H), 5.63 (d, J = 15.8 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.32 (d, J = 3.8 Hz, 1 H), 7.37 (d, J = 15.8 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Ejemplo 301

(2E)-N-[(butilamino)sulfonil]-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrilamida

Por medio de un método similar al del Ejemplo 62, se obtuvo el compuesto del título a partir de ácido (2E)-3-

{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 203 y N-butilsulfamida obtenida en el Ejemplo de referencia 111.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.83 - 0.90 (m, 3 H), 1.25 - 1.38 (m, 2 H), 1.42 - 1.54 (m, 2 H), 2.43 (s, 3 H), 2.95 (q, J = 6.8 Hz, 2 H), 3.58 (s, 3 H), 5.17 (t, J = 5.9 Hz, 1 H), 5.52 (d, J = 15.9 Hz, 1 H), 6.90 (d, J = 3.8 Hz, 1 H), 7.31 - 7.39 (m, 2 H), 8.32 (d, J = 1.9 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H).

Ejemplo 302

(2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}-N-(piperidin-1-ilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}acrílico obtenido en el Ejemplo de referencia 203 y piperidin-1-sulfonamida obtenida en el Ejemplo de referencia 177.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 - 1.65 (m, 6 H), 2.45 (s, 3 H), 3.22 - 3.29 (m, 4 H), 3.59 (s, 3 H), 5.65 (d, J = 15.9 Hz, 1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.31 - 7.40 (m, 2 H), 7.91 (br s, 1 H), 8.32 (d, J = 1.9 Hz, 1 H), 8.61 (d, J = 1.9 Hz, 1 H).

Ejemplo 303

[(butilamino)sulfonil]carbamato de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propan-1-ol obtenida en el Ejemplo de referencia 212, isocianato de clorosulfonilo y butilamina.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.3 Hz, 3 H), 1.33 - 1.47 (m, 2 H), 1.51 - 1.62 (m, 3 H), 1.78 - 1.91 (m, 1 H), 2.29 (s, 3 H), 2.35 - 2.57 (m, 2 H), 3.11 (q, J = 6.7 Hz, 2 H), 3.53 (s, 3 H), 3.67 - 3.78 (m, 1 H), 4.16 - 4.26 (m, 1 H), 5.13 (t, J = 6.0 Hz, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.35 (d, J = 3.6 Hz, 1 H), 8.33 (d, J = 1.5 Hz, 1 H), 8.64 (d, J = 1.3 Hz, 1 H), 9.27 (s, 1 H).

Ejemplo 304

(2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]acrílico obtenido en el Ejemplo de referencia 258 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.80 - 0.94 (m, 6 H),

1.23 - 1.30 (m, 4 H), 1.33 - 1.48 (m, 2 H), 1.55 - 1.65 (m, 2 H), 1.68 - 1.83 (m, 2 H), 2.73 - 2.80 (m, 2 H), 3.11 - 3.18 (m, 2 H), 5.33 (s, 2 H), 5.39 (d, J = 15.5 Hz, 1 H), 7.09 (d, J = 7.2 Hz, 2 H), 7.30 - 7.57 (m, 9 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.87 - 7.96 (m, 2 H).

Ejemplo 305

3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]-N-(pentilsulfonil)propanamida

Por medio de un método similar al del Ejemplo 2, se obtuvo el compuesto del título a partir de (2E)-3-[1-bencil-2-butil-4-(1-naftil)-1H-imidazol-5-il]-N-(pentilsulfonil)acrilamida obtenida en el Ejemplo 304.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.84 - 0.89 (m, 6 H), 1.24 - 1.42 (m, 6 H), 1.55 - 1.75 (m, 4 H), 1.95 (t, J = 7.6 Hz, 2 H), 2.63 - 2.76 (m, 4 H), 3.04 - 3.12 (m, 2 H), 5.18 (s, 2 H), 7.04 (d, J = 7.2 Hz, 2 H), 7.28 - 7.53 (m, 7 H), 7.82 - 7.89 (m, 3 H).

Ejemplo 306

etilcarbamato de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propilo

A una solución de 3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]propan-1-ol obtenida en el Ejemplo de referencia 66 (374 mg) en piridina (4 ml) se añadió isocianato de etilo (525 mg), y la mezcla se agitó a temperatura ambiente durante 14 h, y luego se agitó con

calentamiento a 50°C durante 5 h. La mezcla de reacción se concentró a presión reducida, y el residuo se sometió a cromatografía en columna de gel de sílice (hexano-acetato de etilo 30:70, v/v) para dar el compuesto del título (398 mg, rendimiento del 86%) en forma de un aceite incoloro.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, J = 7.0 Hz, 3 H), 1.53 - 1.63 (m, 2 H), 2.19 - 2.38 (m, 5 H), 2.90 - 3.20 (m, 2 H), 3.45 (s, 3 H), 3.70 - 3.92 (m, 2 H), 4.28 (s, 1 H), 6.67 (d, J = 3.4 Hz, 1 H), 6.94 (d, J = 8.9 Hz, 1 H), 7.10 (d, J = 3.4 Hz, 1 H), 7.18 (dd, J = 8.9, 2.0 Hz, 1 H), 7.65 (d, J = 2.0 Hz, 1 H).

Ejemplo 307

(2E)-3-(2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-il)-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-(2,5-dimetil-4-(1-naftil)-1-{[2-(trimetilsilil)etoxi]metil}-1H-pirrol-3-il)acrílico obtenido en el Ejemplo de referencia 277 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.00 (s, 9 H), 0.79 - 0.87 (m, 3 H), 0.90 - 0.97 (m, 2 H), 1.20 - 1.29 (m, 4 H), 1.54 - 1.65 (m, 2 H), 1.96 (s, 3 H), 2.45 - 2.48 (m, 3 H), 3.11 - 3.20 (m, 2 H), 3.53 - 3.60 (m, 2 H), 4.83 (d, J = 15.3 Hz, 1 H), 5.18 - 5.28 (m, 2 H), 7.29 - 7.38 (m, 2 H), 7.42 -

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7.57 (m, 3 H), 7.70 - 7.76 (m, 1 H), 7.84 - 7.90 (m, 2 H).

Ejemplo 308

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de ciclopropilmetilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, ciclopropilmetanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.31 (t, J = 5.8 Hz, 2 H), 0.55 - 0.61 (m, 2 H), 1.03 - 1.16 (m, 1 H), 2.31 (s, 3 H), 2.75 - 2.88 (m, 2 H), 3.12 - 3.21 (m, 1 H), 3.39 (s, 3 H), 3.74 - 3.82 (m, 1 H), 3.91 - 4.08 (m, 2 H), 6.85 (d, J = 3.6 Hz, 1 H), 7.25 - 7.27 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.64 (d, J = 1.5 Hz, 1 H), 10.46 (br s, 1 H).

Ejemplo 309

N-{[(ciclopropilmetil)amino]carbonil}-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, ciclopropilmetilamina y N,N'-

carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.16 - 0.23 (m, 2 H), 0.47 - 0.54 (m, 2 H), 0.86 - 1.00 (m, 1 H), 2.32 (s, 3 H), 2.76 - 2.89 (m, 2 H), 2.99 (br s, 2 H), 3.19 (br s, 1 H), 3.43 (s, 3 H), 3.68 - 3.87 (m, 1 H), 5.61 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.35 (d, J = 1.5 Hz, 1 H), 8.61 (d, J = 1.5 Hz, 1 H).

Ejemplo 310

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propan-1-ol obtenida en el Ejemplo de referencia 212, isocianato de clorosulfonilo y éter 2-aminoetilisopropílico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.15 (d, J = 6.0 Hz, 6 H), 1.56 (dd, J = 12.6, 6.4 Hz, 1 H), 1.74 - 1.88 (m, 1 H), 2.30 (s, 3 H), 2.35 - 2.55 (m, 2 H), 3.21 - 3.30 (m, 2 H), 3.50 - 3.64 (m, 6 H), 3.71 - 3.81 (m, 1 H), 4.13 - 4.25 (m, 1 H), 5.52 (t, J = 5.9 Hz, 1 H), 6.86 (d, J = 3.8 Hz, 1 H), 7.36 (d, J = 3.6 Hz, 1 H), 8.32 (d, J = 1.5 Hz, 1 H), 8.63 (d, J = 1.3 Hz, 1 H), 9.19 (s, 1 H).

Ejemplo 311

({2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 282, butanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.73 - 0.80 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H), 1.00 - 1.08 (m, 2 H), 1.28 - 1.42 (m, 2 H), 1.52 - 1.64 (m, 2 H), 1.99 - 2.09 (m, 1 H), 2.31 (s, 3 H), 2.81 - 2.87 (m, 2 H), 3.09 - 3.18 (m, 1 H), 3.31 (s, 3 H), 3.86 - 3.96 (m, 1 H), 4.00 - 4.17 (m, 2 H), 6.64 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 3.6 Hz, 1 H), 7.69 (d, J = 1.9 Hz, 1 H), 8.16 (d, J = 2.1 Hz, 1 H), 11.93 (br s, 1 H).

Ejemplo 312

N-[(butilamino)carbonil]-2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-[5-(5-ciclopropil-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]etansulfonamida obtenida en el Ejemplo de referencia 282, butilamina y N,N'-carbonildiimidazol.

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^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.73 - 0.81 (m, 2 H), 0.89 - 0.96 (m, 3 H), 1.02 - 1.09 (m, 2 H), 1.24 - 1.52 (m, 4 H), 1.99 - 2.11 (m, 1 H), 2.32 (s, 3 H), 2.80 - 2.88 (m, 2 H), 3.00 (br s, 1 H), 3.09 - 3.24 (m, 2 H), 3.35 (s, 3 H), 3.94 (br s, 1 H), 5.43 (br s, 1 H), 6.66 (d, J = 3.6 Hz, 1 H), 7.09 (d, J = 3.8 Hz, 1 H), 7.72 (d, J = 2.1 Hz, 1 H), 8.15 (d, J = 1.9 Hz, 1 H).

Ejemplo 313

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de 3-metilbutilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, 3-metilbutan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.4 Hz, 6 H), 1.46 - 1.55 (m, 2 H), 1.62 - 1.73 (m, 1 H), 2.32 (s, 3 H), 2.78 - 2.91 (m, 2 H), 3.11 - 3.21 (m, 1 H), 3.37 (s, 3 H), 3.93 - 4.08 (m, 2 H), 4.10 - 4.22 (m, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H), 10.46 (br s, 1 H).

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Ejemplo 314

2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}-N-{[(3-metilbutil)amino]carbonil}etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, 3-metilbutan-1-amina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.91 (d, J = 6.6 Hz, 6 H), 1.32 - 1.41 (m, 2 H), 1.51 - 1.66 (m, 1 H), 2.32 (s, 3 H), 2.75 - 2.88 (m, 2 H), 3.09 - 3.25 (m, 3 H), 3.44 (s, 3 H), 3.64 - 3.80 (m, 1 H), 5.58 (br s, 1 H), 6.87 (d, J = 3.6 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.59 (d, J = 1.3 Hz, 1 H).

Ejemplo 315

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de 2-ciclopropiletilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida

obtenida en el Ejemplo de referencia 208, 2-ciclopropiletanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.05 - 0.11 (m, 2 H), 0.43 - 0.50 (m, 2 H), 0.62 - 0.76 (m, 1 H), 1.46 - 1.55 (m, 2 H), 2.32 (s, 3 H), 2.77 - 2.90 (m, 2 H), 3.12 - 3.23 (m, 1 H), 3.37 (s, 3 H), 3.96 - 4.09 (m, 2 H), 4.14 - 4.26 (m, 1 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.25 - 7.28 (m, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.3 Hz, 1 H), 10.50 (br s, 1 H).

Ejemplo 316

(2E)-3-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida

Por medio de un método similar al del Ejemplo 1, se obtuvo el compuesto del título a partir de ácido (2E)-3-[5-(5-fluoro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrílico obtenido en el Ejemplo de referencia 285 y pentan-1-sulfonamida.

^{1}H-NMR (300 MHz, DMSO-d_6): 0.78 - 0.85 (m, 3 H), 1.22 - 1.36 (m, 4 H), 1.52 - 1.66 (m, 2 H), 2.39 (s, 3 H), 3.28 - 3.35 (m, 2 H), 3.50 (s, 3 H), 6.06 (d, J = 16.0 Hz, 1 H), 6.90 (d, J = 3.6 Hz, 1 H), 7.05 (d, J = 16.0 Hz, 1 H), 7.83 (d, J = 3.8 Hz, 1 H), 8.10 (dd, J = 9.2, 2.8 Hz, 1 H), 8.26 - 8.30 (m, 1 H), 11.65 (br s, 1 H).

Ejemplo 317

2,2-dióxido de 1-[(3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propoxi)carbonil]-3-(2-isopropoxietil)diazatian-1-ida de potasio

A una solución de {[(2-isopropoxietil)amino]sulfonil}carbamato de 3-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}propilo obtenido en el Ejemplo 310 (352 mg) en metanol (10 ml) se añadió una solución acuosa (2 ml) de hidrógeno-carbonato de potasio (64 mg), y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, y dio el compuesto del título (343 mg, rendimiento del 91%) en forma de un sólido amorfo incoloro.

^{1}H-NMR (300 MHz, DMSO-d_6): 1.03 (d, J = 6.0 Hz, 6 H), 1.33 - 1.45 (m, 2 H), 2.07 - 2.30 (m, 5 H), 2.71 - 2.79 (m, 2 H), 3.35 - 3.51 (m, 5 H), 3.53 - 3.60 (m, 2 H), 5.22 (t, J = 6.6 Hz, 1 H), 6.95 (d, J = 3.6 Hz, 1 H), 7.88 (d, J = 3.6 Hz, 1 H), 8.57 (d, J = 1.5 Hz, 1 H), 8.62 (s, 1 H).

Ejemplo 318

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de isobutilo

Por medio de un método similar al del Ejemplo 186,

se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, 2-metilpropan-1-ol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (d, J = 6.8 Hz, 6 H), 1.83 - 1.98 (m, 1 H), 2.32 (s, 3 H), 2.78 - 2.90 (m, 2 H), 3.11 - 3.22 (m, 1 H), 3.36 (s, 3 H), 3.69 - 3.79 (m, 1 H), 3.89 - 4.14 (m, 2 H), 6.86 (d, J = 3.8 Hz, 1 H), 7.27 (s, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.60 (d, J = 1.5 Hz, 1 H), 10.35 (s, 1 H).

Ejemplo 319

2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}-N-[(isobutilamino)carbonil]etansulfonamida

Por medio de un método similar al del Ejemplo 208, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, isobutilamina y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (d, J = 6.6 Hz, 6 H), 1.67 - 1.81 (m, 1 H), 2.32 (s, 3 H), 2.76 - 3.05 (m, 4 H), 3.20 (br s, 1 H), 3.43 (s, 3 H), 3.67 (br s, 1 H), 5.74 (br s, 1 H), 6.87 (d, J = 3.8 Hz, 1 H), 7.31 (d, J = 3.8 Hz, 1 H), 8.34 (d, J = 1.5 Hz, 1 H), 8.59 (d, J = 1.3 Hz, 1 H).

Ejemplo 320

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etil)sulfonil]carbamato de propilo

Por medio de un método similar al del Ejemplo 186, se obtuvo el compuesto del título a partir de 2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida obtenida en el Ejemplo de referencia 208, propanol y N,N'-carbonildiimidazol.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.94 (t, J = 7.4 Hz, 3 H), 1.60 - 1.71 (m, 2 H), 2.32 (s, 3 H), 2.77 - 2.89 (m, 2 H), 3.11 - 3.21 (m, 1 H), 3.37 (s, 3 H), 3.89 - 4.13 (m, 3 H), 6.86 (d, J = 3.6 Hz, 1 H), 7.24 - 7.27 (m, 1 H), 8.34 (d, J = 1.7 Hz, 1 H), 8.61 (d, J = 1.5 Hz, 1 H), 10.46 (s, 1 H).

Ejemplo 321

{[(2-isopropoxietil)amino]sulfonil}carbamato de 3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propilo

Por medio de un método similar al del Ejemplo 71, se obtuvo el compuesto del título a partir de 3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]propan-1-ol obtenida en el Ejemplo de referencia 289, isocianato de clorosulfonilo y éter 2-aminoetilisopropílico.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16 (d, J = 2.4 Hz, 3 H), 1.18 (d, J = 2.4 Hz, 3 H), 1.40 - 1.54 (m, 1 H), 1.83 - 1.96

(m, 1 H), 2.28 (s, 3 H), 2.41 - 2.64 (m, 5 H), 3.23 - 3.31 (m, 2 H), 3.51 (s, 3 H), 3.55 - 3.66 (m, 4 H), 4.25 - 4.35 (m, 1 H), 5.54 (t, J = 5.8 Hz, 1 H), 6.65 (d, J = 3.6 Hz, 1 H), 7.16 (d, J = 3.6 Hz, 1 H), 7.84 - 7.86 (m, 1 H), 8.22 (d, J = 1.9 Hz, 1 H), 10.85 (br s, 1 H).

Ejemplo experimental 1

(Actividad de ligando heterodimérico de PPARγ-RXRα)

Las células de PPARγ:RXRα:4ERPP/CHO-K1 descritas en el documento WO03/099793 se cultivaron en un medio Ham F12 [fabricado por Life Technologies, Inc., Estados Unidos] que contenía 10% de suero fetal de ternero [fabricado por Life Technologies, Inc., Estados Unidos], se sembraron en una placa blanca de 96 cavidades [fabricada por Corning Coster Corporation, Estados Unidos] a $1x10^4$ células/cavidad, y se incubaron durante la noche en una incubadora de gas dióxido de carbono a 37°C.

Luego se retiró el medio de la placa blanca de 96 cavidades, se añadieron 45 µl de medio Ham F12 que contenía 0.1% de albúmina de suero bovino libre de ácidos grasos (BSA) y un compuesto de ensayo (5 µl), y las células se incubaron durante un día en una incubadora de gas dióxido de carbono a 37°C. Se retiró el medio, se añadieron 20 µl de PicaGene 7.5 (fabricado por Wako Pure Chemical Industries, Ltd.) diluido 2 veces con HBSS (solución salina balanceada de HANKS) [fabricada por BIO WHITTAKER, Estados Unidos]. Después de

agitar, se determinó la actividad de la luciferasa usando el contador 1420 ARVO Multilabel Counter [fabricado por PerkinElmer, Estados Unidos].

La velocidad de inducción se calculó a partir de la actividad de la luciferasa de cada compuesto de ensayo en base a la actividad de la luciferasa del grupo de no administración del compuesto de ensayo como 1. La concentración del compuesto de ensayo y la velocidad de inducción se analizaron por medio de PRISM [fabricado por GraphPad Software, Inc., Estados Unidos] para calcular el valor de EC_{50} (concentración del compuesto que muestra un 50% del valor máximo de la velocidad de inducción) del compuesto de ensayo. Los resultados se muestran en la Tabla 1.

Tabla 1

Compuesto de ensayo (Ejemplo No.)	EC_{50} (nM)
6	19
7	39
9	64
24	54
27	6.1
31	5.5
33	88
40	12
55	44
62	37

1082

66 22

82 67

84 220

99 24

189 54

197 86

232 15

264 26

279 60

283 14

294 32

295 22

Como se indica con anterioridad, se mostró que el compuesto de la presente invención tiene una actividad de ligando heterodimérico de PPARγ-RXRα superior.

Ejemplo de formulación 1

(Producción de la cápsula)

1) compuesto del Ejemplo 1	30 mg
2) celulosa en polvo finamente dividida	10 mg
3) lactosa	19 mg
4) estearato de magnesio	1 mg
total	60 mg

1), 2), 3) y 4) se mezclan y llenan en una cápsula de gelatina.

Ejemplo de formulación 2

(Producción de comprimido)

1) compuesto del Ejemplo 1	30 g
2) lactosa	50 g
3) almidón de maíz	15 g
4) carboximetilcelulosa de calcio	44 g
5) estearato de magnesio	1 g
1000 comprimidos total	140 g

La cantidad total de 1), 2), 3) y 30 g de 4) se amasan con agua, se secan al vacío y se conforman. El polvo conformado se mezcla con 14 g de 4) y 1 g de 5) y la mezcla se saca con un sacabocado. De esta forma, se obtienen 1000 comprimidos que contienen 30 mg del compuesto de Ejemplo 1 por comprimido.

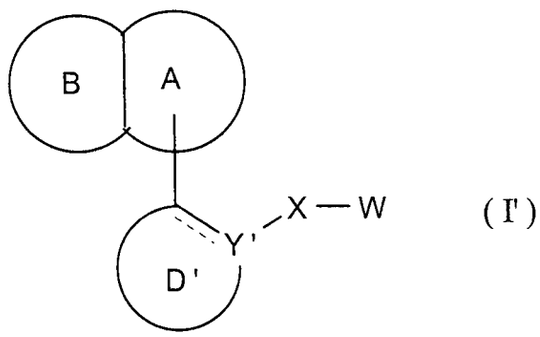
Aplicabilidad industrial

El compuesto de la presente invención es de utilidad para un agente para la prevención o el tratamiento de diabetes, que tiene una acción hipoglucémica superior, y está asociado con menores efectos secundarios tales como aumento de peso corporal, y similares.

Esta solicitud se base en la solicitud de patente No. 31221/2007 presentada en Japón, cuyo contenido se incorporan en la presente por referencia.

REIVINDICACIONES

1.- Un compuesto representado por la fórmula (I'):



(I')

caracterizado porque

el anillo A y el anillo B son iguales o diferentes y cada uno es un monociclo de 5 a 7 miembros opcionalmente sustituido;

el anillo D' es un heterociclo aromático monocíclico de 5 miembros opcionalmente sustituido, en donde Y' es N o C;

X es un espaciador que tiene 1 a 4 átomos en la cadena principal; y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

$-CONR^{1a}S(O)_mOR^2$,

$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-NR^{1b}S(O)_mNR^{1a}CO_nR^2$,

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$-S(O)_mNR^{1a}CO_nR^2$,

$-S(O)_mNR^{1a}CONR^{1c}R^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} y R^{1b} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-6};

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} o un grupo alcoxi de C_{1-6};

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; y

m y n son iguales o diferentes y cada uno es un número entero de 1 ó 2, o

un grupo heterocíclico de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido,

con la condición de que

1) cuando el anillo D' es un imidazol sustituido, entonces W no sea 2-amino-1H-imidazol-5-ilo, 1H-imidazol-2-ilo, 3.5-dimetil-1H-pirazol-4-ilo y piperazin-1-ilo;

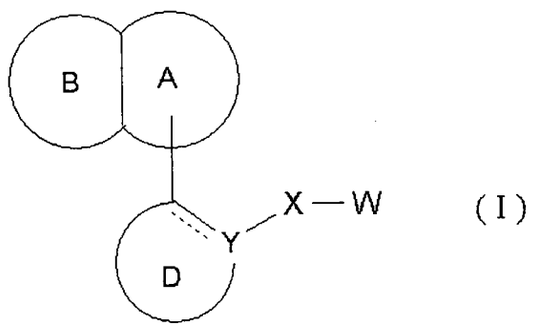
2) cuando el anillo D' es un pirazol sustituido, y X es -CH=, entonces W no sea 4-oxo-2-tioxo-1,3-tiazolidin-5-

ilideno, 5-oxo-2-tioxoimidazolidin-4-ilideno opcionalmente sustituido con grupo(s) fenilo, 3-metil-5-oxo-1.5-dihidro-4H-pirazol-4-ilideno, 2,4,6-trioxotetrahidropirimidin-5(2H)-ilideno y 4,6-dioxo-2-tioxotetrahidropirimidin-5(2H)-ilideno; y

3) se excluya 5-(6-metoxi-2-naftil)-1-(pirrolidin-2-ilmetil)-1H-1,2,3-triazol,

o una de sus sales.

2.- Un compuesto representado por la fórmula (I):



(I)

caracterizado porque

el anillo A y el anillo B son iguales o diferentes y cada uno es un monociclo de 5 a 7 miembros opcionalmente sustituido;

el anillo D es un monociclo de 5 miembros opcionalmente sustituido, en donde Y es N, C o CH;

X es un espaciador que tiene 1 a 4 átomos en la cadena principal; y

W es un grupo representado por

$-CONR^{1a}S(O)_mR^2$,

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$-CONR^{1a}CONR^{1c}R^2$,

$-CONR^{1a}S(O)_mNR^{1c}R^2$,

$-NR^{1b}CONR^{1a}S(O)_mR^2$,

$-S(O)_mNR^{1a}CO_nR^2$,

$-OCONR^{1a}S(O)_mR^2$,

$-OCONR^{1a}S(O)_mNR^{1c}R^2$,

$-ONR^{1a}CO_nR^2$,

$-OCONR^{1c}R^2$, o

$-ONR^{1a}CONR^{1c}R^2$

en donde

R^{1a} y R^{1b} son iguales o diferentes y cada uno es un átomo de hidrógeno o un grupo alquilo de C_{1-6};

R^{1c} es un átomo de hidrógeno, un grupo alquilo de C_{1-6} o un grupo alcoxi de C_{1-6};

R^2 es un átomo de hidrógeno, un grupo hidrocarburo opcionalmente sustituido o un grupo heterocíclico opcionalmente sustituido; y

m y n son iguales o diferentes y cada uno es un número entero de 1 ó 2, o

un grupo heterocíclico de 5 ó 6 miembros que contiene NH, que está opcionalmente sustituido,

con la condición de que

1) cuando el anillo D es un imidazol sustituido, entonces W no sea un aminoimidazol; y

2) cuando el anillo D es un pirazol sustituido, y X

es -CH=, entonces W no sea un oxotioxotiazolidinilo y un oxotioxoimidazolidinilo,

o una de sus sales.

3.- El compuesto de conformidad con la reivindicación 1, caracterizado porque el anillo D' es un pirazol opcionalmente sustituido.

4.- El compuesto de conformidad con la reivindicación 2, caracterizado porque el anillo D es un pirazol opcionalmente sustituido.

5.- El compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque X es un grupo alquileno de C_{1-4} o un grupo alquenileno de C_{2-4}.

6.- El compuesto de conformidad con la reivindicación 1 ó 2, caracterizado porque W es un grupo representado por $-CONR^{1a}S(O)_mR^2$, en donde cada símbolo es como se definió en la reivindicación 1.

7.- (2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 9),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 27),

(2E)-3-[1,3-dimetil-5-(1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-[(4-metilfenil)sulfonil]acrilamida (Ejemplo 33),

(2E)-3-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-

pirazol-4-il]-N-[(pentilamino)sulfonil]acrilamida (Ejemplo 62),

({2-[5-(5-cloro-1H-indol-1-il)-1,3-dimetil-1H-pirazol-4-il]etil}sulfonil)carbamato de ciclopropilmetilo (Ejemplo 189),

({2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1-metil-3-(trifluorometil)-1H-pirazol-4-il]etil}sulfonil)carbamato de butilo (Ejemplo 197),

(2E)-3-[1,3-dimetil-5-(5-metil-1H-pirrolo[2,3-b]piridin-1-il)-1H-pirazol-4-il]-N-(pentilsulfonil)acrilamida (Ejemplo 232),

(2E)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]-N-{[(ciclopropilmetil)amino]sulfonil}acrilamida (Ejemplo 264),

N-[(butilamino)carbonil]-2-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-3-ciclopropil-1-metil-1H-pirazol-4-il]etansulfonamida (Ejemplo 279),

(2E)-N-(butilsulfonil)-3-[5-(5-cloro-1H-pirrolo[2,3-b]piridin-1-il)-1,3-dimetil-1H-pirazol-4-il]acrilamida (Ejemplo 283),

N-[(butilamino)carbonil]-2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-il}etansulfonamida (Ejemplo 294), o

[(2-{1,3-dimetil-5-[5-(trifluorometil)-1H-pirrolo[2,3-b]piridin-1-il]-1H-pirazol-4-

il}etil)sulfonil]carbamato de butilo (Ejemplo 295),

o una de sus sales.

8.- Un profármaco caracterizado porque es un compuesto de conformidad con la reivindicación 1.

9.- Un agente farmacéutico caracterizado porque comprende un compuesto de conformidad con la reivindicación 1 o uno de sus profármacos.

10.- El agente farmacéutico de conformidad con la reivindicación 9, caracterizado porque es un sensibilizador de insulina.

11.- El agente farmacéutico de conformidad con la reivindicación 9, caracterizado porque es un agente para la prevención o el tratamiento de diabetes.

12.- Un método para mejorar la resistencia a la insulina en un mamífero, caracterizado porque comprende la administración de un compuesto de conformidad con la reivindicación 1 o uno de sus profármacos al mamífero.

13.- Un método para la prevención o el tratamiento de diabetes en un mamífero, caracterizado porque comprende la administración de un compuesto de conformidad con la reivindicación 1 o uno de sus profármacos al mamífero.

14.- Uso de un compuesto de conformidad con

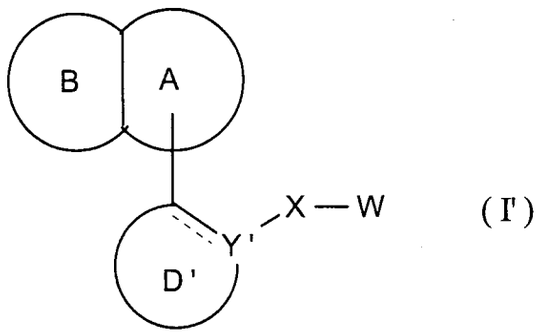
la reivindicación 1 o uno de sus profármacos para la producción de un sensibilizador de insulina.

15.- Uso de un compuesto de conformidad con la reivindicación 1 o uno de sus profármacos para la producción de un agente para la prevención o el tratamiento de diabetes.

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RESUMEN DE LA INVENCION

La presente invención provee un agente para la prevención o el tratamiento de diabetes, que tiene una acción hipoglucémica superior, y está asociado con menos efectos secundarios tales como aumento de peso corporal, y similares. La presente invención se refiere a un agente para la prevención o el tratamiento de diabetes, que comprende un compuesto representado por



(I')

en donde cada símbolo es como se definió en la descripción, o una de sus sales o uno de sus profármacos.

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PATENT COOPERATION TREATY

PCT



INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
091170		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP2008/052217	05/02/2008	09/02/2007
Applicant		
TAKEDA PHARMACEUTICAL COMPANY LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant

[X] the text has been established by this Authority to read as follows:

FUSED RING COMPOUNDS AS PARTIAL AGONISTS OF PPAR-GAMMA

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[ ] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

L094

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2008/052217

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/12 C07D401/14 C07D403/04 C07D405/14 C07D409/04
C07D409/14 C07D413/14 C07D417/14 C07D471/04 C07D491/113
A61K31/4155 A61P3/10

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, BEILSTEIN Data, WPI 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 1 142 879 A (FUJISAWA PHARMACEUTICAL CO [JP] ASTELLAS PHARMA INC [JP]) 10 October 2001 (2001-10-10) claims 1,8 page 42; examples 36,37	1,2,5,6, 8-15
X	WO 2006/075955 A (ASTRAZENECA AB [SE]; BAXTER ANDREW [GB]; FURBER MARK [GB]; KING SARAH) 20 July 2006 (2006-07-20) cited in the application claims page 4, line 4 - line 6 page 15, line 23	1-6,8-15
X	US 2006/148858 A1 (MAEKAWA TSUYOSHI [JP] ET AL) 6 July 2006 (2006-07-06) claims	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2008	04/07/2008

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2008/052217

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LU I-LIN ET AL: "Structure-based drug design of a novel family of PPARgamma partial agonists: virtual screening, X-ray crystallography, and in vitro/in vivo biological activities" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 49, no. 9, 4 May 2006 (2006-05-04), pages 2703-2712, XP002455932 ISSN: 0022-2623 the whole document	1-15

1096.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2008/052217

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

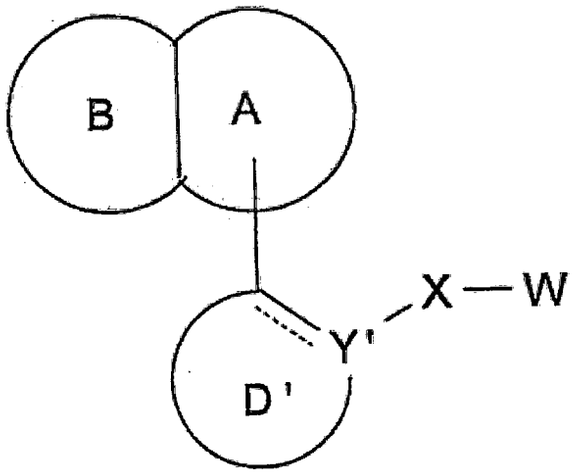
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

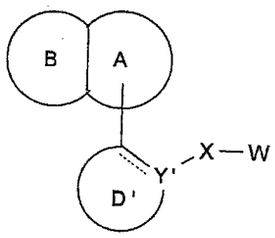
Information on patent family members

International application No
PCT/JP2008/052217

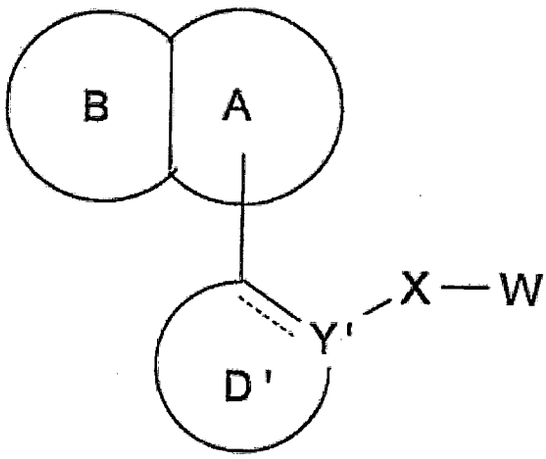
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1142879 A	10-10-2001	AT 375332 T	15-10-2007
		AU 758325 B2	20-03-2003
		AU 1690500 A	31-07-2000
		BR 9917112 A	29-01-2002
		CA 2356838 A1	06-07-2000
		CN 1335837 A	13-02-2002
		CZ 20012338 A3	12-12-2001
		DE 69937307 T2	07-02-2008
		ES 2292262 T3	01-03-2008
		HK 1043791 A1	03-06-2005
		HU 0104657 A2	29-05-2002
		WO 0039097 A1	06-07-2000
		RU 2238937 C2	27-10-2004
		TR 200101865 T2	21-12-2001
		TW 239330 B	11-09-2005
		US 7060721 B1	13-06-2006
WO 2006075955 A	20-07-2006	AR 052457 A1	21-03-2007
US 2006148858 A1	06-07-2006	AU 2003241173 A1	12-12-2003
		CA 2487315 A1	04-12-2003
		EP 1513817 A1	16-03-2005
		WO 03099793 A1	04-12-2003



(I')



(I')



(I')

1100

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-094451- -00000-0000
Fecha: 2009-09-04 15:36:33 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1100

RECIBO OFICIAL DE CAJA : 09 - 61,514
FECHA : AGOSTO 19 DE 2009

***** 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	17854620	19/08/2009	70,663,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

OOLO: 14656-841-052-7

1101

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [✓] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [✓]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- ◇ Descripción de la invención [✓]
- ◇ Dibujos de ser estos pertinentes [✓]
- ◇ Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Fechi
No. 09-094451- -00000-0000
Fecha: 2009-09-04 15:36:33 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1100

Carrera 13 No. 27-00 Piso 5,7y10
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 1101

2020
Bogotá D.C.,

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	9 94451
	Solicitud internacional	PCT/JP2008/052217
	Fecha inicio fase nacional	09/09/2009
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	8746
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 10 SET. 2009

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11

1102

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 09-094451

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **610** DE

FECHA **30** DE **NOVIEMBRE DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **25** DE **FEBRERO** DEL **2010**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI __ NO_ ___ **X** __ _

1103

/103

AVISO DE NOTIFICACION
CORREO CERTIFICADO

Industria y Comercio
SUPERINTENDENCIA

Radicación :	9-94451- -2-0 Fecha: 2010-06-28 08:10:37
Trámite :	11 PATENTEIYII
Evento :	378 FASENACIONALI
Actuación :	432 COMUNICACTOADM
Destinatario :	LUZ CLEMENCIA SUAREZ DE PAEZ Folios 1

Señor (a) (es)
LUZ CLEMENCIA SUAREZ DE PAEZ
CARRERA 4 NO. 72 - 35
BOGOTA D.C.

Referencia RESOLUCION :	32674
Fecha :	25/06/2010
Expediente :	9-94451
Trámite :	11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento :	378 FASE NACIONAL INCLUIDO CAPITULO I
Actuación :	432 COMUNICACION ACTO ADMINISTRATIVO

Comedidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Tercero (3), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:00 a.m. a 4:30 p.m. jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción servicios en línea bases de datos - otros servicios - consulta actos administrativos.

En caso de que se haya notificado, haga caso omiso de este aviso.

Secretaría General
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Al contestar favor indique el número de radicación consignado en el sticker

Sede Centro: Carrera 13 No. 27-00 pisos 3, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26- 55 int. 2 Tel 5880070
Call Center 6513240 . Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCIÓN No 3574
Por la cual se declara abandonada una solicitud

Rad. PCT/ 09-94451

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las conferidas en el numeral 38 del artículo 3° del Decreto 1687 de 2010, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el día 04 de septiembre del 2009 con el N° 09-094451-00000-0000, la doctora Luz Clemencia de Páez, en su calidad de apoderada de Takeda Pharmaceutical Company Limited, presentó la solicitud de patente de invención titulada "COMPUESTOS ANULARES FUSIONADOS COMO AGONISTAS PARCIALES DE PPAR-GAMMA", correspondiente a la solicitud internacional PCT/JP 2008/052217 de fecha 05 de febrero del 2008, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que el extracto de esta solicitud fue publicado en la Gaceta de la Propiedad Industrial Nº 610 del 30 de noviembre del 2009, sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, establece que: *"Dentro del plazo de seis meses contados desde la publicación de la solicitud, independientemente que se hubieren presentado oposiciones, el solicitante deberá pedir que se examine si la invención es patentable. Los Países Miembros podrán cobrar una tasa para la realización de este examen. Si transcurriera dicho plazo sin que el solicitante hubiera pedido que se realice el examen, la solicitud caerá en abandono."*

CUARTO: Que contados seis meses desde la publicación en la Gaceta de la Propiedad Industrial, no se presentó petición de parte del interesado para efectuar el examen de fondo, por lo que este Despacho considera abandonada la solicitud en los términos del mencionado artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina y, en consecuencia,

RESUELVE:

ARTICULO PRIMERO: Declarar abandonada la solicitud de patente de invención titulada "COMPUESTOS ANULARES FUSIONADOS COMO AGONISTAS PARCIALES DE PPAR-GAMMA", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 5870000
Fax: 5870284. Linea 0180000-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION No 2674
Por la cual se declara abandonada una solicitud

Rad. PCT/ 09-94451

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Luz Clemencia de Páez, en su calidad de apoderada de Takeda Pharmaceutical Company Limited, o a quien haga sus veces, entregándole copia de la misma y advirtiéndole que contra ella procede el recurso de reposición, ante el Superintendente de Industria y Comercio, el cual podrá ser interpuesto en el momento de la notificación o dentro de los cinco 5 dias hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 25 JUN. 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E)

GIANCARLO MARCENARO JIMENEZ

Doctora
LUZ CLEMENCIA DE PÁEZ
Carrera 4 N° 72 – 35.
Bogotá D.C.

202021

Sede Centro: Carrera 13 No 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 5870000
Fax: 5870284. Linea 0180000-910165
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Bogotá D.C. - Colombia