CSA295165

Organizacion y
Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

09-22290

21. **EXPEDIENTE No.** _____

54. **TÍTULO** DERIVADO HETEROCICLICO FUSIONADO Y SU USO

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** TAKEDA PHARMACEUTICAL COMPANY LIMITED

DOMICILIO OSAKA, JAPON

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,** _____

991

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-022290- -00000-0000
Fecha: 2009-03-04 16:34:23 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1273

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 5410045,
Japón

Domicilio: Osaka 5410045,
Japón

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

3 REPRESENTANTE O APODERADO

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

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

4 INVENTOR (ES) (72)

1. Nozomu SAKAI
17-85, Jusohonmachi 2-chome,
Yodogawa-ku,
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2. Shinichi, IMAMURA
535 Pierre St. Apt. 1308,
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California 94706,
Estados Unidos de América

(Ver folio 1278)

3. Naoki MIYAMOTO
10 Wadai,
Tsukuba-shi,
Ibaraki 3004293,
Japón

4. Takaharu HIRAYAMA
10 Wadai,
Tsukuba-shi,
Ibaraki 3004293,
Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2007/065681 Fecha: 3 de agosto de 2007
Publicación Internacional No. WO 2008/016192 A3 Fecha: 7 de febrero de 2008

6 Título (54)

DERIVADO HETEROCÍCLICO FUSIONADO Y SU USO (Ver folio 1271)

7 Clasificación Internacional (51) C07D 487/004

8 Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	4 de agosto de 2006	2006-213981
JP	7 de diciembre de 2006	2006-331230
JP	30 de mayo de 2007	2007-144072

9

Comprobante de pago No.: 09-16,799 **Fecha:** 2 de marzo de 2009
Comprobante de pago No.: 08-46,005 **Fecha:** 9 de junio de 2008
Comprobante de pago No.: 09-16,851 **Fecha:** 2 de marzo de 2009
Comprobante de pago No.: 09-16,705 **Fecha:** 2 de marzo de 2009
Comprobante de pago No.: 09-12,691 **Fecha:** 16 de febrero de 2009

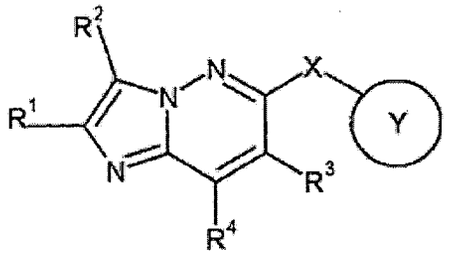
10

Anexos:

- [x] Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- [x] Comprobante de pago por 10 reivindicaciones adicionales después de la decimoquinta reivindicación por $250.000.oo.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

SCT

C66

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/016192 A3

   Descripción:

   Páginas 528 en el idioma original

   Páginas 676 en español

   Reivindicaciones: Número (s) 25

   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 N° 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 of the consumer, oppositions or observations, administrative or judicial cancellation, nullity, infringement, granting of licenses, the action for writ of mandamus, the protection of trade secrets, and in general the civil, criminal and administrative suits relating to those rights, as well as suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA(S) FIRMA(S) QUE APARECE(N) EN EL PRESENTE DOCUMENTO CORRESPONDE(N) A LA(S) PERSONA(S) QUE LO HA(N) SUSCRITO
BOGOTA D.C. 14 JUN 2010
MARIA FERNANDA CAMACHO DE LA CALLE
NOTARIA ENCARGADA

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COJO 14656-841-043-6

6

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 (E) 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
14 ENE 2009
MARÍA FERNANDA CASAS CRUZ
NOTARIA ENCARGADA

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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 attache
to The Osaka L
Affairs Bureau

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA. BOGOTA D.C. REPUBLICA DE COLOMBIA
14 ENE 2005
MARIA FERNANDA CASAS SOTO
NOTARIA ENCARGADA

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: **JAPAN**

   This public document

2. has been signed by — Kiyoomi FUJITA

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

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

Certified

5. at **Osaka**

6. DEC. 17. 2004

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

8. No. 04149

9. Seal/stamp:

10. Signature:

COMO NOTARIA SEXTA (E) 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
14 ENE 2019
MARIA FERNANDA GAVIRIA COLL
NOTARIA ENCARGADA

Tsutomu HIGUCHI

For the Minister for Foreign Affairs

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 (E) DEL CIRCULO DE BOGOTA, D.C., HAGO CONSTAR QUE LA PRESENTE FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
14 ENE 2009
MARIA FERNANDA GASCA COLL
NOTARIA ENCARGADA

(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 (E) 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
14 ENE 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

A [illegible]149

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 FEB -4 A 2:33

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

EMBAJADA DE COLOMBIA - SECCION CONSULAR

Tokio, Japón, DICIEMBRE 20, 2004
No. 299

El encargado de las funciones consulares de Colombia
CERTIFICA:

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

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

Firma del Encargado de Funciones Consulares)

Derechos: US$23.oo

RAFAEL RICARDO OROZCO
Segundo Secretario

DE RELACIONES
ERIORES

085749

COMO NOTARIA SEXTA (E) 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
14 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

11

総第 3603 号

証　　明

大阪法務局所属公証人　藤田清臣

平成 16 年 12 月 14 日付

平成16年 登簿 第 334 号

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

平成16年12月17日
平成　　年　　月　　日

大阪法務局長　梅津和宏

CERTIFICATE

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

Date 04.12.17

Director of the Osaka Legal Affairs Bureau

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO FE QUE LA FOTOCOPIA
COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA
14 ENE 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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

A continuación se traducen los sellos y legalizaciones de un documento por medio del cual **TAKEDA PHARMACEUTICAL COMPANY LIMIMTED** domiciliado en el 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japón, otorga derechos de Representación y Poder a los Doctores EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PÁEZ, tpa. 23555; y GERMÁN CAVELIER, tpa. 832, domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia.
Dado y firmado el 14 de diciembre de 2004 en Osaka, Japón.

Firma Ilegible

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

REGISTRO NÚMERO **334** / 2004

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

COMO NOTARIA SEXTA (E) 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
14 ENE 2005
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

Expedido hoy 14 de diciembre de 2004

10-8, Edobori 1-chome

Nishi-ku, Osaka, Japón

Firma ilegible

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

DOCUMENTO ANTERIOR EN JAPONÉS

(Anexo)

Texto en Japonés

CERTIFICADO

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

Fecha: 04.12.17

Director de la Oficina de Asuntos Legales de Tokio

APOSTILLA

(Convention de La Haye du 5 octubre 1961)

COMO NOTARIA SEXTA (E) 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
14 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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

14

La Cámara de Comercio e Industria de Osaka

Firma Ilegible

Yoshinobu Kobayashi

Signatario Autorizado

(Respaldo)

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

Firmado por RAFAEL RICARDO OROZCO, Segundo Secretario.

Pagados los derechos consulares.

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

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 NOTARIA SEXTA (E) 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
14 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S)
Diego Fernando
COINCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA, 08 FEB2005
CODEX JURISPRUDENCIUS

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

Diego Cuervo
COMPARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

COMO NOTARIA SEXTA (E) 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
14 ENE 2005
MARIA FERNANDA CADAVID COLL
NOTARIA ENCARGADA

15

Certificado

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

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

8. **No. 04149**

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
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MINISTERIO DE JUSTICIA

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

MINISTERIO DE RELACIONES EXTERIORES · JAPÓN ·

Firma Ilegible

Tsutomu HIGUCHI

Por el Ministro de Relaciones Exteriores

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

Noviembre 17 de 2004

A quién pueda interesar:

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 2001)

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

Número de Membresía: KT-01-00080

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, CERTIFICO: QUE LA FOTOCOPIA QUE ANTECEDE COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA
14 ENE 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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

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

CODEX JURIS CIVILIS

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JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
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SE APARECE EN EL
PRESENTO DESEMPEÑA
FUNCIONES INDICADAS

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA,
D.C. HAGO CONSTAR QUE LA FOTOCOPIA
CONCUERDA CON EL ORIGINAL QUE HE VENIDO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA

14 ENE 2009

MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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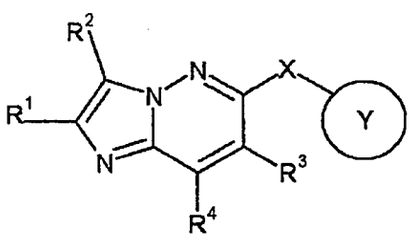
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(54) Title: FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF



(57) Abstract: The present invention provides a fused heterocyclic derivative having a potent kinase inhibitory activity and use thereof. A compound represented by the formula (I): wherein each symbol is as defined in the specification, except a particular compound, or a salt thereof, and a pharmaceutical agent containing the compound or a prodrug thereof, which is a kinase (VEGFR, VEGFR2, PDGFR, Raf) inhibitor, an angiogenesis inhibitor, an agent for the prophylaxis or treatment of cancer, a cancer growth inhibitor or a cancer metastasis suppressor.

WO 2008/016192 A3

DESCRIPTION

FUSED HETEROCYCLIC DERIVATIVE AND USE THEREOF

Technical Field

The present invention relates to fused heterocyclic derivatives and use thereof. More particularly, the present invention relates to imidazopyridazine derivatives having potent kinase inhibitory activity and useful for the prophylaxis or treatment of cancer and the like.

BACKGROUND OF THE INVENTION

For a solid tumor to grow to a certain size or above, angiogenesis is essential for ensuring sufficient supply of nutrition and oxygen to cancer cell (see, for example, New England Journal of Medicine, 1971, vol. 285, No. 21, pp. 1182-1186). One of the important factors causing angiogenesis toward tumor, a vascular endothelial growth factor (VEGF) is known. VEGF is bound to a vascular endothelial growth factor receptor (VEGFR) expressed on vascular endothelial cells and transmits signal for cell growth (see, for example, Endocrine Reviews, 1997, vol. 18, No. 1, pp. 4-25). Accordingly, inhibition of the VEGF-VEGFR signal transduction system is considered to enable suppression of angiogenesis and tumor growth (see, for example, Drug Discovery Today, 2001, vol. 6, No. 19, pp. 1005-1024). Moreover, since tumor blood vessels are involved in cancer hematogenous metastasis, inhibition of angiogenesis is considered to be effective for suppression of cancer metastasis.

As compounds inhibiting receptor-type tyrosine kinase including VEGFR, phthalazine derivatives (see, for example, WO 98/35958), pyrrole-substituted 2-indolinone derivatives (see, for example, WO 01/60814), quinazoline derivatives (see, for example, WO 01/32651), ω-carboxyaryl-substituted diphenylurea derivatives (see, for example, WO 00/42012), quinoline derivatives and quinazoline derivatives (see, for example, WO 00/43366), nitrogen-containing aromatic ring derivatives (see, for example, WO 02/32872) and the like are known.

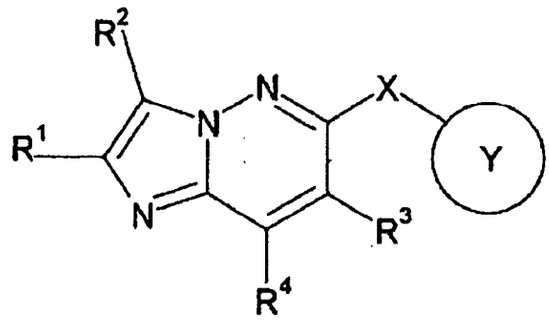
Disclosure of the Invention

A kinase inhibitor superior in the affinity for kinase, efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability is expected to show a therapeutically superior effect. At present, however, such inhibitor superior in the affinity for kinase, and sufficiently satisfactory in the efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability has not been found. Thus, there is a demand for the development of a compound having a superior kinase inhibitory activity, and sufficiently satisfactory as a pharmaceutical product. Accordingly, an object of the present invention is to provide a compound having a superior kinase inhibitory activity, low toxic and sufficiently satisfactory as a pharmaceutical product.

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

Accordingly, the present invention provides the following.

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



(I)

wherein

ring Y is an optionally substituted cyclic group;

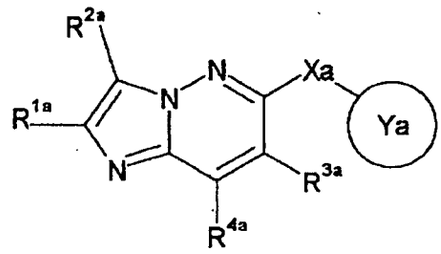
X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;
R^4 is a hydrogen atom or a substituent;
provided that
when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that
methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate,
methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate,
ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline,
and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof.

[2] The compound of the above-mentioned [1], wherein a compound represented by the formula (II):



(II)

wherein

ring Ya is an optionally substituted cyclic group;

Xa is -O-, -S-, -S(O)-, $-S(O)_2-$ or $-NR^a-$ (wherein R^a is a hydrogen atom or a substituent);

R^{1a} is an optionally substituted amino;

R^{2a} is a hydrogen atom or a substituent;

R^{3a} is a hydrogen atom or a substituent;

R^{4a} is a hydrogen atom or a substituent;

provided that

methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate and methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate are excluded,

or a salt thereof.

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

(1) amino,

(2) optionally substituted alkylcarbonylamino,

(3) optionally substituted alkenylcarbonylamino,

(4) optionally substituted alkynylcarbonylamino,

(5) optionally substituted cycloalkylcarbonylamino,

(6) optionally substituted cycloalkyl-alkylcarbonylamino,

(7) optionally substituted 6-membered heterocyclyl-carbonylamino,

(8) optionally substituted aminocarbonylamino,

(9) optionally substituted alkoxycarbonylamino,

(10) optionally substituted alkylsulfonylamino,

(11) optionally substituted cycloalkylsulfonylamino,

(12) optionally substituted arylamino, or

(13) optionally substituted heterocyclylamino.

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

(1) amino,

(2) C_{1-4} alkyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) hydroxy,

(c) C_{1-4} alkoxy,

(d) C_{1-4} alkyl-carbonyloxy,

(e) C_{1-4} alkylamino,

(f) di-C_{1-4} alkylamino,

(g) C_{1-4} alkylsulfonyl, and

(h) a 6-membered heterocyclic group optionally having 1 to 3 C_{1-4} alkyl,

(3) C_{2-4} alkenyl-carbonylamino optionally having C_{1-4} alkoxy,

(4) C_{2-4} alkynyl-carbonylamino,

(5) C_{3-6} cycloalkyl-carbonylamino optionally substituted by 1 to 4 substituents selected from

(a) a halogen atom,

(b) hydroxy,

(c) C_{1-4} alkyl optionally having hydroxy,

(d) C_{1-4} alkoxy,

(e) C_{1-4} alkoxy-carbonyl, and

(f) C_{1-4} alkyl-carbonyloxy,

(6) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino,

(7) 6-membered heterocyclyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) cyano, and

(c) C_{1-4} alkyl optionally having 1 to 3 halogen atoms,

(8) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from

(a) C_{1-4} alkyl optionally having 1 to 3 C_{1-4} alkoxy optionally having 1 to 3 hydroxy, and

(b) C_{1-4} alkoxy,

(9) C_{1-4} alkoxy-carbonylamino optionally substituted by 1 to 3 halogen atoms,

(10) C_{1-4} alkylsulfonylamino,

(11) C_{3-6} cycloalkylsulfonylamino,

(12) C_{6-10} arylamino, or

(13) heterocyclylamino optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom, and

(b) C_{1-4} alkylamino.

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

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

[7] The compound of the above-mentioned [2], wherein R^{4a} is a hydrogen atom.

[8] The compound of the above-mentioned [2], wherein Xa is -O-, -S- or -NH-.

[9] The compound of the above-mentioned [2], wherein ring Ya is an optionally substituted aromatic hydrocarbon group or an optionally substituted aromatic heterocyclic group.

[10] The compound of the above-mentioned [2], wherein ring Ya is

(1) C_{6-10} aryl optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) C_{1-4} alkyl,

(c) C_{1-4} alkoxy,

(d) amino optionally substituted by the substituents selected from

(i) C_{1-4} alkyl optionally substituted by a 5-membered aromatic heterocyclic group optionally substituted by 1 to 3 C_{1-4} alkyl,

(ii) C_{1-4} alkyl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl, and

(iii') a 6-membered aromatic heterocyclic group,

(iii) C_{2-4} alkenyl-carbonyl optionally substituted by C_{6-10} aryl,

(iv) C_{2-4} alkynyl-carbonyl optionally substituted by C_{6-10} aryl,

(v) C_{3-6} cycloalkyl-carbonyl,

(vi) C_{3-6} cycloalkenyl-carbonyl,

(vii) C_{6-10} aryl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') a halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom, cyano, hydroxy and C_{3-6} cycloalkyl,

(iii') C_{3-6} cycloalkyl optionally substituted by cyano,

(iv') C_{1-4} alkoxy optionally substituted by 1 to 5 halogen atoms,

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

(vi') a 5- or 6-membered heterocyclic group optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by 1 to 3 substituents selected from

(i') a halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom, cyano, hydroxy and C_{1-4} alkoxy,

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

(iv') C_{6-10} aryl-C_{1-4} alkyl,

(v') C_{1-4} alkoxy optionally substituted by C_{1-4} alkoxy,

(vi') C_{1-4} alkylsulfonyl,

(vii') C_{1-4} alkyl-carbonyl, and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl,

(x) C_{1-4} alkyl-aminocarbonyl,

(xi) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4}

alkyl optionally substituted by 1 to 3 halogen atoms,

(xii) C_{1-4} alkoxy-aminocarbonyl,

(xiii) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl, and

(xv) 5-membered aromatic heterocyclyl-sulfonyl optionally substituted by 1 to 3 C_{1-4} alkyl,

(e) C_{1-4} alkyl-aminocarbonyl optionally having C_{6-10} aryl,

(f) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom, and

(b) C_{6-10} aryl-carbonylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms, or

(3) fused aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl, and

(b) C_{6-10} arylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms.

[11] A compound selected from the group consisting of:

N-{3-[(2-{[2-(methylamino)pyrimidin-4-yl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide;

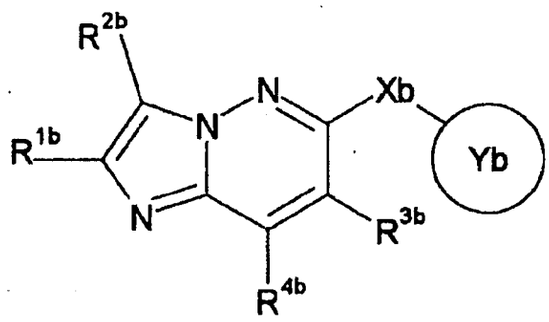
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-

yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;
N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide;
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide;
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-

carboxamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide;
3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]benzamide;
N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide;
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-(trifluoromethyl)benzamide; and
N-{6-[3-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide,
or a salt thereof.

[12] The compound of the above-mentioned [1], which is a compound of the formula (III):



(III)

wherein
ring Yb is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted;
Xb is -O-, -S-, -S(O)-, $-S(O)_2-$ or $-NR^b-$ (wherein R^b is a hydrogen atom or a substituent);
R^{1b} is a hydrogen atom or a substituent (provided that an optionally substituted amino is excluded);
R^{2b} is a hydrogen atom or a substituent;
R^{3b} is a hydrogen atom or a substituent;

R^{4b} is a hydrogen atom or a substituent;
provided that
ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline,
and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof.

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

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

[15] The pharmaceutical agent of the above-mentioned [14], which is a kinase inhibitor.

[16] The pharmaceutical agent of the above-mentioned [14], which is an inhibitor of vascular endothelial growth factor receptor (VEGFR).

[17] The pharmaceutical agent of the above-mentioned [14], which is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 2.

[18] The pharmaceutical agent of the above-mentioned [14], which is an inhibitor of platelet-derived growth factor receptor (PDGFR).

[19] The pharmaceutical agent of the above-mentioned [14], which is a Raf inhibitor.

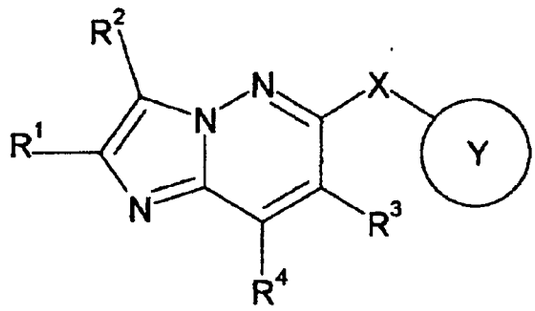
[20] The pharmaceutical agent of the above-mentioned [14], which is an angiogenesis inhibitor.

[21] The pharmaceutical agent of the above-mentioned [14], which is an agent for the prophylaxis or treatment of cancer.

[22] The pharmaceutical agent of the above-mentioned [14], which is a cancer growth inhibitor.

[23] The pharmaceutical agent of the above-mentioned [14], which is a cancer metastasis suppressor.

[24] A method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of a compound of the formula (I):



(I)

wherein

ring Y is an optionally substituted cyclic group;

X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

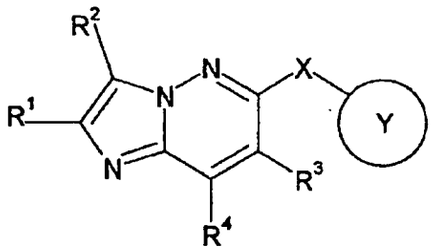
R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;

R^4 is a hydrogen atom or a substituent;

provided that
when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that
methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate,
methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate,
ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline,
and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof or a prodrug thereof to the mammal.

[25] Use of a compound of the formula (I) for the production of an agent for the prophylaxis or treatment of cancer:



(I)

wherein

ring Y is an optionally substituted cyclic group;

X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;

R^4 is a hydrogen atom or a substituent;

provided that

when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that

methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate,

methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate,

ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,

ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

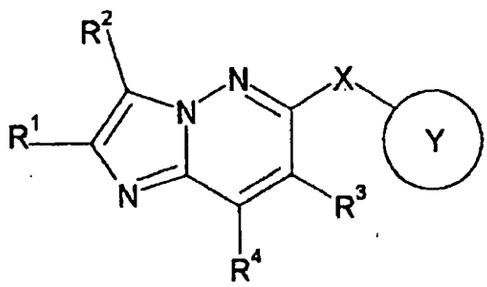
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline,
and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof or a prodrug thereof.

The present invention also includes the following.

[26] A compound of the formula (IV):



(IV)

wherein ring Y is an optionally substituted cyclic group;
X is -O-, -S-, -S(O)-, -$S(O)_2$- or -NR- (wherein R is a hydrogen atom or a substituent);
R^1 is a hydrogen atom or a substituent;
R^2 is a hydrogen atom or a substituent;
R^3 is a hydrogen atom or a substituent;
R^4 is a hydrogen atom or a substituent;
provided that
where R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted,
or a salt thereof.

[27] A kinase inhibitor, which comprises the compound of the above-mentioned [26] or a prodrug thereof.

[28] The kinase inhibitor of the above-mentioned [27], wherein the kinase is a vascular endothelial growth factor receptor (VEGFR).

[29] The kinase inhibitor of the above-mentioned [27], wherein the kinase is a vascular endothelial growth factor receptor (VEGFR) 2.

[30] The kinase inhibitor of the above-mentioned [27], wherein the kinase is a platelet-derived growth factor receptor (PDGFR).

[31] The kinase inhibitor of the above-mentioned [27], wherein the kinase is a Raf.

[32] An angiogenesis inhibitor, which comprises the compound of the above-mentioned [26] or a prodrug thereof.

[33] An agent for the prophylaxis or treatment of cancer, which comprises the compound of the above-mentioned [26] or a prodrug thereof.

[34] A cancer growth inhibitor, which comprises the compound of the above-mentioned [26] or a prodrug thereof.

[35] A cancer metastasis suppressor, which comprises the compound of the above-mentioned [26] or a prodrug thereof.

[36] A method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of the compound of the above-mentioned [26] or a prodrug thereof to the mammal.

[37] Use of the compound of the above-mentioned [26] or a prodrug thereof for the production of an agent for the prophylaxis or treatment of cancer.

Effect of the Invention

The compounds represented by the formulas (I) to (IV) of the present invention or salts thereof or prodrugs thereof have strong inhibitory activity against kinases such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor and the like, and have strong angiogenesis inhibitory activity. Therefore, they can provide a clinically useful agent for the prophylaxis or treatment of cancer, a

cancer growth inhibitor, or a cancer metastasis suppressor. Furthermore, compounds represented by the formulas (I) to (IV) of the present invention or salts thereof or prodrugs thereof can provide clinically useful agents for the prophylaxis or treatment for applications on diseases other than cancer such as chronic rheumatism, diabetic retinopathy and the like, and have excellent efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability.

Hereinafter the present invention is explained in detail.

A compound represented by the formula (I) (hereinafter to be referred to as compound (I)) and a compound represented by the formula (IV) (hereinafter to be referred to as compound (IV)) of the present invention are explained.

In compounds (I) and (IV), examples of the "cyclic group" of the "optionally substituted cyclic group" for ring Y include aromatic hydrocarbon group, aromatic heterocyclic group (e.g., monocyclic aromatic heterocyclic group, fused aromatic heterocyclic group), non-aromatic cyclic hydrocarbon group, non-aromatic heterocyclic group, fused ring group thereof and the like.

Examples of the aromatic hydrocarbon group include C_{6-14} aryl and the like. Specifically, phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, anthryl, phenanthryl, acenaphthylenyl and the like can be mentioned.

Examples of the monocyclic aromatic heterocyclic group include 5- to 7-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like.

Examples of the monocyclic aromatic heterocyclic group specifically include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-

pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), triazinyl and the like.

Examples of the fused aromatic heterocyclic group include a group formed by fusion of 5- to 7-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like, and C_{6-14} aryl and the like; a group formed by fusion of the above-mentioned 5- to 7-membered monocyclic aromatic heterocyclic groups, and the like.

Examples of the fused aromatic heterocyclic group specifically include quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, isoquinolyl), quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl), quinoxalinyl (e.g., 2-quinoxalinyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-5-yl, benzimidazol-6-yl), indolyl (e.g., indol-1-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-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), imidazopyridyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl),

benzisoxazolyl, benzotriazolyl, pyrazolopyridyl, pyrazolothienyl, pyrazolotriazinyl and the like.

Examples of the non-aromatic cyclic hydrocarbon group include cycloalkyl, cycloalkenyl, cycloalkadienyl and the like, each of which is optionally fused with benzene ring.

Examples of the non-aromatic cyclic hydrocarbon group specifically include C_{3-10} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl), C_{3-10} cycloalkenyl (e.g., cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl), C_{4-10} cycloalkadienyl (e.g., cyclobutadienyl, cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, cyclooctadienyl, cyclononadienyl, cyclodecadienyl), fused ring formed by fusion of these groups and benzene ring (e.g., indanyl (e.g., 1-indanyl), tetrahydronaphthyl (e.g., 1,2,3,4-tetrahydronaphthalen-1-yl), fluorenyl (e.g., 9-fluorenyl) etc.), and the like.

Examples of the non-aromatic heterocyclic group include 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group and the like.

Examples of the non-aromatic heterocyclic group specifically include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, thianyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, oxepanyl, thiepanyl, oxazepanyl, thiazepanyl, azocanyl, oxocanyl, thiocanyl, oxazocanyl, thiazocanyl, dioxinyl and the like.

As the "cyclic group" of the "optionally substituted cyclic group" for ring Y, aromatic hydrocarbon group, aromatic heterocyclic group are preferable. As the aromatic hydrocarbon group, C_{6-14} aryl is preferable, C_{6-10} aryl is more preferable, and phenyl is particularly preferable. As the aromatic heterocyclic group, monocyclic heterocyclic group or fused aromatic heterocyclic group is preferable, pyridine ring, or fused

aromatic heterocyclic group formed by fusion of 5-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 or 2 heteroatoms selected from sulfur atom and nitrogen atom, besides carbon atoms, and benzene ring (e.g., benzothiazolyl, benzimidazolyl, indolyl etc.) is more preferable, and benzothiazolyl (e.g., 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-5-yl, benzimidazol-6-yl), indolyl (e.g., indol-4-yl, indol-5-yl, indol-6-yl) and the like are particularly preferable.

The "optionally substituted cyclic group" for ring Y may have 1 to the acceptable maximum number of substituents at any substitutable positions. Where the cyclic group is substituted by two or more substituents, the substituents may be the same or different, and it is preferable to optionally have 1 to 5, more preferably 1 to 3, particularly preferably 1 or 2 substituents.

As the "substituent" of the "optionally substituted cyclic group" for ring Y, for example,

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

(ii) cyano,

(iii) nitro,

(iv) optionally substituted hydrocarbon group,

(v) hydroxy,

(vi) optionally substituted hydrocarbon-oxy,

(vii) optionally substituted aminosulfonyl,

(viii) optionally substituted aminocarbonyl,

(ix) acyl,

(x) optionally substituted amino,

(xi) optionally substituted sulfanyl,

(xii) optionally substituted heterocyclic group,

(xiii) optionally substituted heterocyclyl-oxy,

(xiv) oxo,

(xv) optionally substituted sulfinyl,

(xvi) optionally substituted aminothiocarbonyl,

(xvii) optionally esterified carboxy,

and the like (in the present specification, to be referred to as

Substituent Group (1)) can be mentioned.

Hereinafter the substituents listed in Substituent Group (1) are explained.

As the "optionally substituted hydrocarbon group" in Substituent Group (1)(iv), alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, cycloalkyl-alkyl, cycloalkenyl-alkyl, aryl-alkyl, cycloalkanedienyl and the like, each of which is optionally substituted, can be mentioned.

In the present specification, examples of the "alkyl" may include linear or branched chain alkyl having 1 to 8, preferably 1 to 6, more preferably 1 to 4 carbons and the like, specifically methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, heptyl, octyl and the like. The "alkyl" may have, for example, at any substitutable position thereof, 1 to the acceptable maximum number of the substituents selected from the group of the following substituents (hereinafter abbreviated to as "Substituent Group (2)"):

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

(2) cyano;

(3) nitro;

(4) hydroxy;

(5) C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy etc.) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine) and C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy etc.);

(6) C_{2-6} alkenyloxy (e.g., ethenyloxy, propenyloxy, butenyloxy, pentenyloxy, hexenyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(7) C_{2-6} alkynyloxy (e.g., ethynyloxy, propynyloxy, butynyloxy, pentynyloxy, hexynyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(8) C_{3-6} cycloalkyl-oxy (e.g., cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy) optionally having 1 to 3 halogen

atoms (e.g., fluorine, chlorine, bromine, iodine);
(9) C_{3-6} cycloalkenyloxy (e.g., cyclopropenyloxy, cyclobutenyloxy, cyclopentenyloxy, cyclohexenyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
(10) C_{6-10} aryloxy (e.g., phenyloxy, 1-naphthyloxy, 2-naphthyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
(11) C_{3-6} cycloalkyl-C_{1-6} alkoxy (e.g., cyclopropylmethyloxy, cyclopropylethyloxy, cyclobutylmethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
(12) C_{3-6} cycloalkenyl-C_{1-6} alkoxy (e.g., cyclopentenylmethyloxy, cyclohexenylmethyloxy, cyclohexenylethyloxy, cyclohexenylpropyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
(13) C_{6-10} aryl-C_{1-6} alkoxy (e.g., phenylmethyloxy, phenylethyloxy etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);
(14) C_{1-6} alkyl-aminosulfonyl (e.g., methylaminosulfonyl, ethylaminosulfonyl, propylaminosulfonyl etc.);
(15) di-C_{1-6} alkyl-aminosulfonyl (e.g., dimethylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl etc.);
(16) C_{1-6} alkyl-aminocarbonyl (e.g., methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl etc.);
(17) di-C_{1-6} alkyl-aminocarbonyl (e.g., dimethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl etc.);
(18) formyl;
(19) C_{1-6} alkyl-carbonyl (e.g., acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl etc.);
(20) C_{2-6} alkenyl-carbonyl (e.g., ethenylcarbonyl, propenylcarbonyl, butenylcarbonyl, pentenylcarbonyl, hexenylcarbonyl etc.);
(21) C_{2-6} alkynyl-carbonyl (e.g., ethynylcarbonyl, propynylcarbonyl, butynylcarbonyl, pentynylcarbonyl,

hexynylcarbonyl etc.);

(22) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl);

(23) C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopropenylcarbonyl, cyclobutenylcarbonyl, cyclopentenylcarbonyl, cyclohexenylcarbonyl etc.);

(24) C_{6-10} aryl-carbonyl (e.g., benzoyl, 1-naphthylcarbonyl, 2-naphthylcarbonyl etc.);

(25) C_{3-6} cycloalkyl-C_{1-6} alkyl-carbonyl (e.g., cyclopropylmethylcarbonyl, cyclopropylethylcarbonyl, cyclobutylmethylcarbonyl, cyclopentylmethylcarbonyl, cyclohexylmethylcarbonyl, cyclohexylethylcarbonyl etc.);

(26) C_{3-6} cycloalkenyl-C_{1-6} alkyl-carbonyl (e.g., cyclopentenylmethylcarbonyl, cyclohexenylmethylcarbonyl, cyclohexenylethylcarbonyl, cyclohexenylpropylcarbonyl etc.);

(27) C_{6-10} aryl-C_{1-6} alkyl-carbonyl (e.g., benzylcarbonyl, phenylethylcarbonyl etc.);

(28) 5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl (e.g., furylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, thiazolylcarbonyl, isothiazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, pyrazolylcarbonyl etc.);

(29) 8- to 12-membered fused aromatic heterocyclyl-carbonyl (e.g., benzofurylcarbonyl, isobenzofurylcarbonyl, benzothienylcarbonyl, isobenzothienylcarbonyl, indolylcarbonyl, isoindolylcarbonyl, 1H-indazolylcarbonyl, benzimidazolylcarbonyl, benzoxazolylcarbonyl etc.);

(30) 5- or 6-membered non-aromatic heterocyclyl-carbonyl (e.g., oxiranylcarbonyl, azetidinylcarbonyl, oxetanylcarbonyl, thietanylcarbonyl, pyrrolidinylcarbonyl, tetrahydrofurylcarbonyl, thiolanylcarbonyl, piperidinylcarbonyl etc.);

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

(32) C_{2-6} alkenylsulfonyl (e.g., ethenylsulfonyl, propenylsulfonyl etc.);

(33) C_{2-6} alkynylsulfonyl (e.g., ethynylsulfonyl, propynylsulfonyl, butynylsulfonyl, pentynylsulfonyl, hexynylsulfonyl etc.);

(34) C_{3-6} cycloalkylsulfonyl (e.g., cyclopropylsulfonyl, cyclobutylsulfonyl etc.);

(35) C_{3-6} cycloalkenylsulfonyl (e.g., cyclopropenylsulfonyl, cyclobutenylsulfonyl etc.);

(36) C_{6-10} arylsulfonyl (e.g., phenylsulfonyl etc.);

(37) C_{3-6} cycloalkyl-C_{1-6} alkyl-sulfonyl (e.g., cyclopropylmethylsulfonyl etc.);

(38) C_{3-6} cycloalkenyl-C_{1-6} alkyl-sulfonyl (e.g., cyclopentenylmethylsulfonyl etc.);

(39) C_{6-10} aryl-C_{1-6} alkyl-sulfonyl (e.g., benzylsulfonyl etc.);

(40) 5- or 6-membered monocyclic aromatic heterocyclyl-sulfonyl (e.g., furylsulfonyl, thienylsulfonyl, pyridylsulfonyl etc.);

(41) 8- to 12-membered fused aromatic heterocyclyl-sulfonyl (e.g., benzofurylsulfonyl, isobenzofurylsulfonyl etc.);

(42) 5- or 6-membered non-aromatic heterocyclyl-sulfonyl (e.g., oxiranylsulfonyl, azetidinylsulfonyl etc.);

(43) amino;

(44) mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino etc.);

(45) di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di-tert-butylamino etc.);

(46) mono-(C_{1-6} alkyl-carbonyl)amino (e.g., acetylamino, ethylcarbonylamino, propylcarbonylamino, tert-butylcarbonylamino etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine);

(47) mono-(C_{3-6} cycloalkyl-carbonyl)amino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino etc.);

(48) mono-(C_{6-10} aryl-carbonyl)amino (e.g., benzoylamino etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine,

bromine, iodine);

(49) mono-(5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl)amino (e.g., furylcarbonylamino, thienylcarbonylamino, pyrrolylcarbonylamino, oxazolylcarbonylamino, isoxazolylcarbonylamino, thiazolylcarbonylamino, isothiazolylcarbonylamino, imidazolylcarbonylamino, pyridylcarbonylamino, pyrazolylcarbonylamino etc.);

(50) mono-(8- to 12-membered fused aromatic heterocyclyl-carbonyl)amino (e.g., benzofurylcarbonylamino, isobenzofurylcarbonylamino, benzothienylcarbonylamino, isobenzothienylcarbonylamino etc.);

(51) mono-(5- or 6-membered non-aromatic heterocyclyl-carbonyl)amino (e.g., oxiranylcarbonylamino, azetidinylcarbonylamino, oxetanylcarbonylamino etc.);

(52) thiol;

(53) C_{1-6} alkylsulfanyl (e.g., methylsulfanyl, ethylsulfanyl etc.);

(54) C_{2-6} alkenylsulfanyl (e.g., ethenylsulfanyl, propenylsulfanyl etc.);

(55) C_{2-6} alkynylsulfanyl (e.g., ethynylsulfanyl, propynylsulfanyl, butynylsulfanyl, pentynylsulfanyl, hexynylsulfanyl etc.);

(56) C_{3-6} cycloalkylsulfanyl (e.g., cyclopropylsulfanyl, cyclobutylsulfanyl etc.);

(57) C_{3-6} cycloalkenylsulfanyl (e.g., cyclopropenylsulfanyl, cyclobutenylsulfanyl etc.);

(58) C_{6-10} arylsulfanyl (e.g., phenylsulfanyl etc.);

(59) C_{3-6} cycloalkyl-C_{1-6} alkyl-sulfanyl (e.g., cyclopropylmethylsulfanyl etc.);

(60) C_{3-6} cycloalkenyl-C_{1-6} alkyl-sulfanyl (e.g., cyclopentenylmethylsulfanyl etc.);

(61) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrazolyl etc.) optionally having 1 to 3 C_{1-4} alkyl (e.g., methyl, ethyl etc.);

(62) 8- to 12-membered fused aromatic heterocyclic group (e.g., benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl etc.);

(63) 5- or 6-membered non-aromatic heterocyclic group (e.g., oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl etc.);

(64) 5- or 6-membered monocyclic aromatic heterocyclyl-oxy (e.g., furyloxy, thienyloxy, pyrrolyloxy, oxazolyloxy, isoxazolyloxy, thiazolyloxy, isothiazolyloxy, imidazolyloxy, pyridyloxy, pyrazolyloxy etc.);

(65) 8- to 12-membered fused aromatic heterocyclyl-oxy (e.g., benzofuryloxy, isobenzofuryloxy, benzothienyloxy, isobenzothienyloxy, indolyloxy, isoindolyloxy, 1H-indazolyloxy, benzimidazolyloxy, benzoxazolyloxy etc.);

(66) 5- or 6-membered non-aromatic heterocyclyl-oxy (e.g., oxiranyloxy, azetidinyloxy, oxetanyloxy, thietanyloxy, pyrrolidinyloxy, tetrahydrofuryloxy, thiolanyloxy, piperidinyloxy etc.);

(67) oxo;

(68) C_{1-6} alkylsulfinyl (e.g., methylsulfinyl, ethylsulfinyl etc.);

(69) C_{2-6} alkenylsulfinyl (e.g., ethenylsulfinyl, propenylsulfinyl etc.);

(70) C_{2-6} alkynylsulfinyl (e.g., ethynylsulfinyl, propynylsulfinyl, butynylsulfinyl, pentynylsulfinyl, hexynylsulfinyl etc.);

(71) C_{3-6} cycloalkylsulfinyl (e.g., cyclopropylsulfinyl, cyclobutylsulfinyl etc.);

(72) C_{3-6} cycloalkenylsulfinyl (e.g., cyclopropenylsulfinyl, cyclobutenylsulfinyl etc.);

(73) C_{6-10} arylsulfinyl (e.g., phenylsulfinyl etc.);

(74) C_{3-6} cycloalkyl-C_{1-6} alkyl-sulfinyl (e.g., cyclopropylmethylsulfinyl etc.);

(75) C_{3-6} cycloalkenyl-C_{1-6} alkyl-sulfinyl (e.g.,

cyclopentenylmethylsulfinyl etc.);
(76) aminothiocarbonyl substituted by C_{1-6} alkyl or C_{6-10} aryl-C_{1-4} alkyl-carbonyl (e.g., methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl, benzylcarbonylaminothiocarbonyl etc.);
(77) di-C_{1-6} alkyl-aminothiocarbonyl (e.g., dimethylaminothiocarbonyl, diethylaminothiocarbonyl, dipropylaminothiocarbonyl etc.);
(78) carboxy;
(79) C_{1-6} alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl etc.);
(80) C_{2-6} alkenyloxy-carbonyl (e.g., ethenyloxycarbonyl, propenyloxycarbonyl, butenyloxycarbonyl, pentenyloxycarbonyl, hexenyloxycarbonyl etc.);
(81) C_{2-6} alkynyloxy-carbonyl (e.g., ethynyloxycarbonyl, propynyloxycarbonyl, butynyloxycarbonyl, pentynyloxycarbonyl, hexynyloxycarbonyl etc.);
(82) C_{3-6} cycloalkyl-oxy-carbonyl (e.g., cyclopropyloxycarbonyl, cyclobutyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl etc.);
(83) C_{3-6} cycloalkenyloxy-carbonyl (e.g., cyclopropenyloxycarbonyl, cyclobutenyloxycarbonyl, cyclopentenyloxycarbonyl, cyclohexenyloxycarbonyl etc.);
(84) C_{6-10} aryloxy-carbonyl (e.g., phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl etc.);
(85) C_{3-6} cycloalkyl-C_{1-6} alkoxy-carbonyl (e.g., cyclopropylmethyloxycarbonyl, cyclopropylethyloxycarbonyl, cyclobutylmethyloxycarbonyl, cyclopentylmethyloxycarbonyl, cyclohexylmethyloxycarbonyl, cyclohexylethyloxycarbonyl etc.);
(86) C_{3-6} cycloalkenyl-C_{1-6} alkoxy-carbonyl (e.g., cyclopentenylmethyloxycarbonyl, cyclohexenylmethyloxycarbonyl, cyclohexenylethyloxycarbonyl, cyclohexenylpropyloxycarbonyl etc.); and
(87) C_{6-10} aryl-C_{1-6} alkoxy-carbonyl (e.g., phenylmethyloxycarbonyl,

phenylethyloxycarbonyl etc.).

Where the alkyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, and more preferably 1 to 3.

As the "alkenyl", for example, linear or branched chain alkenyl having 2 to 8, preferably 2 to 4 carbons and the like can be mentioned, and ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, butadienyl and the like can be specifically mentioned. The "alkenyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from the above-mentioned Substituent Group (2) and C_{6-10} aryl (e.g., phenyl etc.). Where the alkenyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "alkynyl", for example, linear or branched chain alkynyl having 2 to 8, preferably 2 to 4 carbons and the like can be mentioned, and ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and the like can be specifically mentioned. The "alkynyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from the above-mentioned Substituent Group (2) and C_{6-10} aryl (e.g., phenyl etc.). Where the alkynyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "cycloalkyl", for example, cycloalkyl having 3 to 8, preferably 3 to 6 carbons and the like can be mentioned, and cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like can be specifically mentioned. The "cycloalkyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from (a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine)

and hydroxy, and (b) substituent selected from the above-mentioned Substituent Group (2). Where the cycloalkyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "cycloalkenyl", for example, cycloalkenyl having 3 to 8, preferably 3 to 6 carbons and the like can be mentioned, and cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and the like can be specifically mentioned. The "cycloalkenyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine), and substituent selected from the above-mentioned Substituent Group (2). Where the cycloalkenyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "aryl", for example, aryl having 6 to 18, preferably 6 to 14, more preferably 6 to 10, particularly preferably 6 carbons and the like can be mentioned, and phenyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-anthryl, phenanthryl, acenaphthylenyl and the like can be specifically mentioned. The "aryl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from (a) C_{1-4} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), cyano, hydroxy and C_{3-6} cycloalkyl (e.g., cyclopropyl etc.), and (b) substituent selected from the above-mentioned Substituent Group (2) (except for oxo). Where the aryl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "cycloalkyl-alkyl", for example, group in which cycloalkyl group having 3 to 8, preferably 3 to 6 carbons and the like, is bonded to linear or branched chain alkyl having 1 to 6, preferably 1 to 4 carbon atoms (e.g., C_{3-8} cycloalkyl-C_{1-4} alkyl) and the like can be mentioned, and cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl and the like can be specifically mentioned. The "cycloalkyl-alkyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and substituent selected from the above-mentioned Substituent Group (2). Where the cycloalkyl-alkyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "cycloalkenyl-alkyl", for example, group in which cycloalkenyl having 3 to 8, preferably 3 to 6 carbons is bonded to linear or branched chain alkyl having 1 to 6, preferably 1 to 4 carbon atoms (e.g., C_{3-8} cycloalkenyl-C_{1-4} alkyl group) can be mentioned, and cyclopentenylmethyl, cyclohexenylmethyl, cyclohexenylethyl, cyclohexenylpropyl, cycloheptenylmethyl, cycloheptenylethyl and the like can be specifically mentioned. The "cycloalkenyl-alkyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and substituent selected from the above-mentioned Substituent Group (2). Where the cycloalkenyl-alkyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "aryl-alkyl", for example, group in which aryl

having 6 to 18, more preferably 6 to 10, particularly preferably 6 carbons is bonded to linear or branched chain alkyl having 1 to 6, preferably 1 to 4 carbon atoms (e.g., C_{6-18} aryl-C_{1-4} alkyl) and the like can be mentioned, and phenylmethyl (benzyl), phenylethyl (phenethyl) and the like can be specifically mentioned. The "aryl-alkyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and substituent selected from the above-mentioned Substituent Group (2). Where the aryl-alkyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "cycloalkanedienyl", for example, C_{4-6} cycloalkanedienyl group such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like, and the like can be mentioned. The "cycloalkanedienyl" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents selected from C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 halogen atoms (e.g., fluorine, chlorine, bromine, iodine) and substituent selected from the above-mentioned Substituent Group (2). Where the cycloalkanedienyl is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

As the "optionally substituted hydrocarbon-oxy" in Substituent Group (1)(vi), alkyl-oxy, alkenyl-oxy, alkynyl-oxy, cycloalkyl-oxy, cycloalkenyl-oxy, aryl-oxy, cycloalkyl-alkyl-oxy, cycloalkenyl-alkyl-oxy, aryl-alkyl-oxy and the like, each of which is optionally substituted, can be mentioned. As the "alkyl" for alkyl-oxy, the "alkenyl" for alkenyl-oxy, the "alkynyl" for alkynyl-oxy, the "cycloalkyl" for cycloalkyl-oxy,

the "cycloalkenyl" for cycloalkenyl-oxy, the "aryl" for aryl-oxy, the "cycloalkyl-alkyl" for cycloalkyl-alkyl-oxy, the "cycloalkenyl-alkyl" for cycloalkenyl-alkyl-oxy, the "aryl-alkyl" for aryl-alkyl-oxy, similar groups to those exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv) can be respectively mentioned.

The "optionally substituted aminosulfonyl" in Substituent Group (1)(vii) may have 1 or 2 substituents. Where the aminosulfonyl is substituted by two substituents, the substituents may be the same or different.

As the "substituent" of the "optionally substituted aminosulfonyl", for example, similar groups to those exemplified as the "hydrocarbon group" of the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv) and the below-mentioned groups as the "optionally substituted heterocyclic group" in the aforementioned Substituent Group (1)(xii) can be mentioned.

The "optionally substituted aminocarbonyl" in Substituent Group (1)(viii) may have 1 or 2 substituents. Where the aminocarbonyl is substituted by two substituents, the substituents may be the same or different.

As the "substituent" of the "optionally substituted aminocarbonyl", for example, those similar to group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv), group exemplified as the "optionally substituted hydrocarbon-oxy" in the aforementioned Substituent Group (1)(vi), and group below-mentioned as "optionally substituted heterocycle" in the aforementioned Substituent Group (1)(xii) can be mentioned.

As the "acyl" in Substituent Group (1)(ix), for example, optionally substituted hydrocarbon-carbonyl, optionally substituted heterocyclyl-carbonyl, optionally substituted hydrocarbon-sulfonyl, optionally substituted heterocyclyl-sulfonyl and the like can be mentioned.

As the "optionally substituted hydrocarbon" of the "optionally substituted hydrocarbon-carbonyl", those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the above-mentioned Substituent Group (1)(iv) can be mentioned.

As the "optionally substituted hydrocarbon" of the "optionally substituted hydrocarbon-sulfonyl", those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the above-mentioned Substituent Group (1)(iv) can be mentioned.

As the "optionally substituted heterocycle" of the "optionally substituted heterocyclyl-carbonyl" and "optionally substituted heterocyclyl-sulfonyl", those similar to the group below-mentioned as the "optionally substituted heterocyclic group" in the aforementioned Substituent Group (1)(xii) can be mentioned.

The "optionally substituted amino" in Substituent Group (1)(x) may have 1 or 2 substituents. Where the amino is substituted by two substituents, the substituents may be the same or different. As the "substituent" of the "optionally substituted amino", for example, those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv), the group exemplified as the "optionally substituted aminocarbonyl" in the aforementioned Substituent Group (1)(viii), the group exemplified as the "acyl" in the aforementioned Substituent Group (1)(ix), the group below-mentioned as the "optionally substituted heterocyclic group" in the aforementioned Substituent Group (1)(xii), and group selected from the "optionally esterified carboxy" in the aforementioned Substituent Group (1)(xviii) can be mentioned.

As the "substituent" of the "optionally substituted sulfanyl" in Substituent Group (1)(xi), for example, those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group

(1)(iv) can be mentioned.

As the "heterocyclic group" of the "optionally substituted heterocyclic group" in Substituent Group (1)(xii), aromatic heterocyclic group (e.g., monocyclic aromatic heterocyclic group, fused aromatic heterocyclic group), non-aromatic heterocyclic group, and the like can be mentioned, and for example, 5- to 12-membered aromatic heterocyclic group (monocyclic aromatic heterocyclic group or fused aromatic heterocyclic group etc.), saturated or unsaturated non-aromatic heterocycle, and the like having, as ring-constituting atom, 1 or more (preferably 1 to 4, more preferably 1 or 2) of 1 to 3, preferably 1 or 2 kinds of heteroatoms selected from oxygen atom, optionally oxidized sulfur atom and nitrogen atom and the like (preferably oxygen atom, sulfur atom and nitrogen atom etc.) besides carbon atoms, can be mentioned.

As the monocyclic aromatic heterocyclic group, for example, 5- or 6-membered monocyclic aromatic heterocyclic group and the like can be mentioned.

As the monocyclic aromatic heterocyclic group, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl (e.g., 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl), furazanyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl), triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl and the like can be specifically mentioned.

As the fused aromatic heterocyclic group, for example, 8- to 12-membered fused aromatic heterocyclic group can be mentioned, and heterocyclic group formed by fusion of the aforementioned 5- or 6-membered monocyclic aromatic heterocyclic group and benzene ring or heterocyclic group formed by fusion of the same or different two of the aforementioned 5- or 6-membered monocyclic aromatic heterocyclic groups can be particularly mentioned.

Examples of fused aromatic heterocyclic group specifically

include benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acrydinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl and the like.

Examples of non-aromatic heterocyclic group include 3- to 8-membered (preferably 5- or 6-membered) saturated or unsaturated (preferably saturated) non-aromatic heterocyclic group and the like.

Examples of non-aromatic heterocyclic group specifically include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, thianyl, morpholinyl, thiomorpholinyl, piperazinyl, azepanyl, oxepanyl, thiepanyl, oxazepanyl, thiazepanyl, azocanyl, oxocanyl, thiocanyl, oxazocanyl, thiazocanyl, dioxinyl and the like.

Alternatively, the non-aromatic heterocyclic group may be fused to benzene ring or the above-mentioned monocyclic aromatic heterocyclic group to form fused non-aromatic heterocyclic group. As the fused non-aromatic heterocyclic group formed by fusion of non-aromatic heterocyclic group and benzene ring, for example, benzodioxinyl, tetrahydroisoquinolyl and the like can be mentioned.

The "optionally substituted heterocyclic group" may have, at any substitutable positions, 1 to the acceptable maximum number of substituents. Where the heterocyclic group is substituted by two or more substituents, the substituents may be the same or different, and preferable number of the substituents is 1 to 5, more preferably 1 to 3.

Examples of the "substituent" of the "optionally substituted heterocyclic group" may include (a) C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl etc.) optionally having 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), cyano, hydroxy and C_{1-4} alkoxy (e.g., methoxy), (b) C_{6-10} aryl (e.g., phenyl), (c) C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl etc.) and (d) those similar to the group selected from the aforementioned Substituent Group (2).

For example, among the heterocyclic groups substituted by oxo in the aforementioned Substituent Group (2), as the specific examples of the non-aromatic heterocyclic group substituted by oxo, 2-oxoazetidinyl, 2-oxopyrrolidinyl, 2-oxopiperidinyl, 2-oxoazepanyl, 2-oxoazocanyl, 2-oxotetrahydrofuryl, 2-oxotetrahydropyranyl, 2-oxothiolanyl, 2-oxothianyl, 2-oxopiperazinyl, 2-oxooxepanyl, 2-oxooxazepanyl, 2-oxothiepanyl, 2-oxothiazepanyl, 2-oxooxocanyl, 2-oxothiocanyl, 2-oxooxazocanyl, 2-oxothiazocanyl, 2-oxodioxinyl and the like can be mentioned.

As the "optionally substituted heterocycle" of the "optionally substituted heterocyclyl-oxy" in Substituent Group (1)(xiii), those similar to the group exemplified as the "optionally substituted heterocycle" in the aforementioned Substituent Group (1)(xii) can be mentioned.

As the "substituent" of the "optionally substituted sulfinyl" in Substituent Group (1)(xv), for example, those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv) can be mentioned.

The "optionally substituted aminothiocarbonyl" in Substituent Group (1)(xvi) may have 1 or 2 substituents. Where the aminothiocarbonyl is substituted by 2 substituents, the substituents may be the same or different.

As the "substituent" of the "optionally substituted aminothiocarbonyl", for example, 1 or 2 groups similar to the group exemplified as the "optionally substituted hydrocarbon

group" in the aforementioned Substituent Group (1)(iv) can be mentioned.

As the "optionally esterified carboxy" in Substituent Group (1)(xvii), for example, carboxy optionally esterified by the group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv) can be mentioned.

The "substituent" of the "optionally substituted cyclic group" for ring Y is preferably

(1) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
(2) optionally substituted alkyl,
(3) optionally substituted alkoxy,
(4) optionally substituted aminocarbonyl,
(5) optionally substituted amino,
(6) optionally esterified carboxy,
(7) nitro,

and the like.

Of these,

(1) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
(2) optionally substituted alkyl,
(3) optionally substituted amino,

and the like are preferable.

Hereinafter the above-mentioned preferable examples of the "substituent" of the "optionally substituted cyclic group" for ring Y are exemplified in detail.

(1) As the halogen atom, fluorine, chlorine, bromine and the like are preferable.

(2) As the optionally substituted alkyl, optionally substituted C_{1-8} alkyl is preferable, optionally substituted C_{1-4} alkyl is more preferable, and unsubstituted C_{1-4} alkyl is much more preferable. Specifically, methyl, ethyl and the like are preferable.

(3) As the optionally substituted alkoxy, optionally substituted C_{1-8} alkoxy is preferable, optionally substituted C_{1-4} alkoxy is more preferable, unsubstituted C_{1-4} alkoxy is much more

preferable. Specifically, methoxy and the like are preferable.

(4) As the "substituent" for the optionally substituted aminocarbonyl, for example, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} cycloalkynyl, C_{6-18} aryl, heterocyclic group and the like, each of which is optionally substituted, are preferable. Of these, optionally substituted C_{1-4} alkyl, optionally substituted C_{6-12} aryl and optionally substituted 5-membered heterocyclic group and the like are preferable. Particularly, (a) C_{1-4} alkyl (e.g., methyl, ethyl) optionally having C_{6-12} aryl (e.g., phenyl) (Specific examples are benzyl, ethyl), (b) 5-membered heterocyclic group (e.g., pyrazolyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl) and C_{6-12} aryl (e.g., phenyl), (c) C_{6-12} aryl optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine) and cyano (specific examples: trifluoromethyl, tert-butyl, 1-cyano-1-methylethyl) are preferable.

(5) As the "substituent" for the optionally substituted amino, optionally substituted alkyl, optionally substituted aminocarbonyl, acyl, optionally substituted aminothiocarbonyl and the like are preferable.

As the optionally substituted amino, amino optionally substituted by 1 or 2 substituents selected from (a) optionally substituted alkyl, (b) optionally substituted aminocarbonyl, (c) acyl and (d) optionally substituted aminothiocarbonyl is preferable.

As the optionally substituted alkyl, optionally substituted C_{1-4} alkyl is preferable. Of these, C_{1-4} alkyl (e.g., methyl) optionally substituted by 5-membered heterocyclic group (e.g., pyrazolyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl) (specific example: 1,3-dimethyl-1H-pyrazol-5-ylmethyl) is preferable.

As the optionally substituted aminocarbonyl, C_{1-8} alkyl-aminocarbonyl, C_{6-18} aryl-aminocarbonyl, C_{6-18} aryl-C_{1-4} alkyl-

aminocarbonyl, heterocyclyl-aminocarbonyl, C_{3-8} cycloalkyl-aminocarbonyl, C_{1-8} alkoxy-aminocarbonyl and the like, each of which is optionally substituted, are preferable. Of these, optionally substituted C_{1-8} alkyl-aminocarbonyl, optionally substituted C_{6-18} aryl-aminocarbonyl, optionally substituted heterocyclyl-aminocarbonyl, optionally substituted C_{1-8} alkoxy-aminocarbonyl and the like are preferable. Particularly, (i) C_{1-4} alkyl-aminocarbonyl (e.g., ethylaminocarbonyl), (ii) C_{6-10} aryl-aminocarbonyl (e.g., phenylaminocarbonyl) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-(trifluoromethyl)phenylcarbonyl), (iii) C_{1-4} alkoxy-aminocarbonyl (e.g., methoxyaminocarbonyl, isobutoxyaminocarbonyl), (iv) 5-membered heterocyclyl-aminocarbonyl (e.g., pyrazolyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl) and C_{6-10} aryl (specific example: 1,3-dimethyl-1H-pyrazol-5-yl-aminocarbonyl) and the like are preferable.

As the acyl, C_{1-8} alkyl-carbonyl, C_{2-8} alkenyl-carbonyl, C_{2-8} alkynyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{3-8} cycloalkenyl-carbonyl, C_{6-18} aryl-carbonyl, C_{6-18} aryl-C_{1-4} alkyl-carbonyl, C_{1-8} alkylsulfonyl, C_{6-18} aryl-sulfonyl, heterocyclyl-carbonyl, heterocyclyl-sulfonyl and the like, each of which is optionally substituted, are preferable. Of these, C_{1-8} alkyl-carbonyl, C_{2-8} alkenyl-carbonyl, C_{2-8} alkynyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{3-8} cycloalkenyl-carbonyl, C_{6-18} aryl-carbonyl, heterocyclyl-carbonyl, each of which is optionally substituted, are preferable.

As the optionally substituted C_{1-8} alkyl-carbonyl, optionally substituted C_{1-4} alkyl-carbonyl is preferable. Particularly, C_{1-4} alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl, 3-methylbutanoyl) optionally substituted by 1 to 3 substituents selected from (a) hydroxy, (b) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl) and (c) 6-membered heterocyclic group (e.g., pyridyl) (specific examples: methylsulfonylmethylcarbonyl,

2-pyridylmethylcarbonyl, tert-butylcarbonyl, 3-hydroxy-3-methylbutanoyl) is preferable.

As the optionally substituted C_{2-8} alkenyl-carbonyl, optionally substituted C_{2-4} alkenyl-carbonyl is preferable. Particularly, C_{2-4} alkenyl-carbonyl (e.g., 3-methyl-2-butenoyl) optionally substituted by C_{6-10} aryl (e.g., phenyl) (specific example: 3-methyl-2-butenoyl) is preferable.

As the optionally substituted C_{2-8} alkynyl-carbonyl, optionally substituted C_{2-4} alkynyl-carbonyl is preferable. Particularly, C_{2-4} alkynyl-carbonyl (e.g., 2-butynoyl) optionally substituted by C_{6-10} aryl (e.g., phenyl) (specific example: 2-butynoyl) is preferable.

As the optionally substituted C_{3-8} cycloalkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl is preferable, and cyclopropylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl are specifically preferable.

As the optionally substituted C_{3-8} cycloalkenyl-carbonyl, C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopentenecarbonyl) (specific example: 1-cyclopentenecarbonyl) is preferable.

As the optionally substituted C_{6-18} aryl-carbonyl, optionally substituted C_{6-10} aryl-carbonyl is preferable. Particularly, C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., fluorine), (b) C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{3-6} cycloalkyl (e.g., cyclopropyl) (specific example: trifluoromethyl), (c) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl) optionally substituted by cyano, (d) C_{1-4} alkoxy (e.g., isopropoxy, tert-butoxy) optionally substituted by 1 to 5 halogen atoms (e.g., fluorine), (e) C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl), and (f) 5 or 6-membered heterocyclic group (e.g., tetrahydropyranyl, pyrrolidinyl) optionally substituted by cyano or oxo is preferable. Specifically, phenylcarbonyl (benzoyl), 3-(trifluoromethyl)phenylcarbonyl, 4-

(trifluoromethyl)phenylcarbonyl, 3-fluorophenylcarbonyl, 3-chlorophenylcarbonyl, 3-(1-cyanocyclopropyl)phenylcarbonyl, 3-(1-cyanocyclobutyl)phenylcarbonyl, 3-(1-cyanocyclohexyl)phenylcarbonyl, 2-fluoro-3-(trifluoromethyl)phenylcarbonyl, 2-fluoro-5-(trifluoromethyl)phenylcarbonyl, 3-fluoro-5-(trifluoromethyl)phenylcarbonyl, 4-chloro-3-(trifluoromethyl)phenylcarbonyl, 2-chloro-3-(trifluoromethyl)phenylcarbonyl, 2-chloro-5-(trifluoromethyl)phenylcarbonyl, 3-isopropoxyphenylcarbonyl, 3-(tert-butoxy)phenylcarbonyl, 3-(1-cyano-1-methylethyl)phenylcarbonyl, 3-methoxyphenylcarbonyl, 3-methoxycarbonylphenylcarbonyl, 3-(trifluoromethoxy)carbonylphenylcarbonyl, 3-(1,1,2,2-tetrafluoroethoxy)phenylcarbonyl, 3-(4-cyanotetrahydropyran-4-yl)phenylcarbonyl, 3,5-di(trifluoromethyl)phenylcarbonyl, 3-(2-oxopyrrolidin-1-yl)phenylcarbonyl, 4-(tert-butyl)phenylcarbonyl, 3-(1-cyanoethyl)phenylcarbonyl, 3-(1-cyano-2-cyclopropyl-1-methylethyl)phenylcarbonyl and the like are preferable.

As the optionally substituted C_{6-18} aryl-C_{1-4} alkyl-carbonyl, C_{6-10} aryl-C_{1-4} alkyl-carbonyl is preferable.

As the optionally substituted C_{1-8} alkylsulfonyl, C_{1-4} alkylsulfonyl are preferable.

As the optionally substituted C_{6-18} aryl-sulfonyl, C_{6-10} aryl-sulfonyl is preferable.

As the "heterocycle" moiety for the optionally substituted heterocyclyl-carbonyl, 5- or 6-membered monocyclic heterocyclic group containing, as ring-constituting atom, 1 to 3 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like are preferable, and pyridyl, furyl, tetrahydrofuryl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, dihydrooxazolyl, pyridazinyl, pyrazinyl, dihydropyrazolyl, pyrrolyl, pyrrolidinyl, pyrimidinyl and the like are specifically preferable. As the "substituent" for the optionally

substituted heterocyclyl-carbonyl, (1) halogen atom (e.g., chlorine), (2) C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{1-4} alkoxy (e.g., methoxy) (specific examples: methyl, trifluoromethyl, ethyl, methoxyethyl, 2,2,2-trifluoroethyl, isopropyl, tert-butyl), (3) C_{6-18} aryl (e.g., phenyl), (4) C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl), (5) C_{1-4} alkoxy (e.g., methoxy, ethoxy) optionally substituted by C_{1-4} alkoxy (e.g., methoxy) (specific examples: methoxy, ethoxy, methoxyethoxy), (6) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl), (7) C_{1-4} alkylcarbonyl (e.g., acetyl), (8) oxo, and the like are preferable.

As the optionally substituted heterocyclyl-carbonyl, 2-pyridylcarbonyl, 3-pyridylcarbonyl, 4-pyridylcarbonyl, 2-methyl-6-pyridylcarbonyl, 3-methyl-2-pyridylcarbonyl, 4-methyl-2-pyridylcarbonyl, 2-methyl-3-pyridylcarbonyl, 2-(trifluoromethyl)-3-pyridylcarbonyl, 2-(trifluoromethyl)-4-pyridylcarbonyl, 2-(trifluoromethyl)-6-pyridylcarbonyl, 2-chloro-6-methyl-4-pyridylcarbonyl, 2,6-dichloro-4-pyridylcarbonyl, 2-furylcarbonyl, 2,5-dimethylfuran-3-carbonyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonyl, 3-methylthiophene-2-carbonyl, 5-acetylsulfonylthiophene-2-carbonyl, 5-ethylsulfonylthiophene-2-carbonyl, 4-methyl-1,2,3-thiadiazole-5-carbonyl, isoxazole-5-carbonyl, 1H-pyrazole-5-carbonyl, 1-methyl-1H-pyrazole-3-carbonyl, 1-methyl-1H-pyrazole-5-carbonyl, 1-ethyl-1H-pyrazole-3-carbonyl, 1-ethyl-1H-pyrazole-5-carbonyl, 3-methyl-1H-pyrazole-5-carbonyl, 3-chloro-1-methyl-1H-pyrazole-5-carbonyl, 4-chloro-1-methyl-1H-pyrazole-3-carbonyl, 1-methyl-3-methoxy-1H-pyrazole-5-carbonyl, 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-4-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-5-carbonyl, 3-ethoxy-1-methyl-1H-pyrazole-5-carbonyl, 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carbonyl, 1-ethyl-3-methyl-1H-pyrazole-4-carbonyl, 1-ethyl-3-methyl-1H-pyrazole-5-carbonyl, 3-methyl-1-phenyl-1H-

pyrazole-5-carbonyl, 5-methyl-1-phenyl-1H-pyrazole-3-carbonyl, 3-ethyl-1-methyl-1H-pyrazole-5-carbonyl, 3-isopropyl-1-methyl-1H-pyrazole-5-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-5-carbonyl, 1-tert-butyl-3-methyl-1H-pyrazole-5-carbonyl, 3-tert-butyl-1-methyl-1H-pyrazole-5-carbonyl, 1-methoxyethyl-3-methyl-1H-pyrazole-5-carbonyl, 1,3-dimethyl-1H-pyrazole-4-carbonyl, 1,3-dimethyl-1H-pyrazole-5-carbonyl, 1,4-dimethyl-1H-pyrazole-3-carbonyl, 1,4-dimethyl-1H-pyrazole-5-carbonyl, 1,5-dimethyl-1H-pyrazole-3-carbonyl, 3-methylisoxazole-4-carbonyl, 3-methylisoxazole-5-carbonyl, 5-methylisoxazole-3-carbonyl, 5-methylisoxazole-4-carbonyl, 3,5-dimethylisoxazole-4-carbonyl, 1,3-thiazole-2-carbonyl, 2-methyl-1,3-thiazole-4-carbonyl, 4-methyl-1,3-thiazole-5-carbonyl, 5-methyl-1,3-thiazole-4-carbonyl, 2,4-dimethyl-1,3-thiazole-5-carbonyl, 2-chloro-4-methyl-1,3-thiazole-5-carbonyl, 4-methoxy-2-methyl-1,3-thiazole-5-carbonyl, 2-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carbonyl, 2-(1-cyano-1-methylethyl)-1,3-thiazole-5-carbonyl, 2-methyl-1,3-oxazole-4-carbonyl, 4-methyl-1,3-oxazole-5-carbonyl, 2-ethyl-4-methyl-1,3-oxazole-5-carbonyl, 2,4-dimethyl-1,3-oxazole-5-carbonyl, 2,5-dimethyl-1,3-oxazole-4-carbonyl, 1-methyl-1H-1,2,3-triazole-5-carbonyl, 1-methyl-1H-1,2,3-triazole-4-carbonyl, 1-methyl-1H-imidazole-2-carbonyl, 1-methyl-1H-imidazole-5-carbonyl, 2-pyrazinylcarbonyl, 1-methylpyrrole-2-carbonyl, 1-benzylpyrrole-3-carbonyl, 1,2,5-trimethylpyrrole-3-carbonyl, 1-methylpyrrolidine-2-carbonyl, 2-(trifluoromethyl)pyrimidine-4-carbonyl and the like are specifically preferable.

As the "heterocycle" moiety for the optionally substituted heterocyclyl-sulfonyl, 5- or 6-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like are preferable, and thiazolyl and the like are specifically preferable. As the "substituent" for the optionally substituted heterocyclyl-carbonyl, C_{1-4} alkyl (e.g., methyl) and the like are preferable.

As the optionally substituted heterocyclyl-sulfonyl, 2,5-

dimethyl-1,3-thiazole-4-sulfonyl and the like are specifically preferable.

As the optionally substituted aminothiocarbonyl, aminothiocarbonyl optionally substituted by C_{6-18} aryl-C_{1-4} alkyl-carbonyl (e.g., benzylcarbonyl) and the like are preferable.

(6) As the optionally esterified carboxy, carboxy and C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl) are preferable.

Preferably, ring Y is

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

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

(b) C_{1-4} alkyl (e.g., methyl, ethyl),

(c) C_{1-4} alkoxy (e.g., methoxy),

(d) amino optionally substituted by substituents selected from

(i) C_{1-4} alkyl (e.g., methyl) optionally substituted by 5-membered aromatic heterocyclic group (e.g., pyrazolyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl),

(ii) C_{1-4} alkyl-carbonyl (e.g., methylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl) optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl (e.g., methylsulfonyl), and

(iii') 6-membered aromatic heterocyclic group (e.g., pyridyl),

(iii) C_{2-4} alkenyl-carbonyl (e.g., 2-methyl-1-propenylcarbonyl, vinylcarbonyl) optionally substituted by C_{6-10} aryl (e.g., phenyl),

(iv) C_{2-4} alkynyl-carbonyl (e.g., acetylenecarbonyl, 1-propynylcarbonyl) optionally substituted by C_{6-10} aryl (e.g., phenyl),

(v) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl),

(vi) C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopentenylcarbonyl),

(vii) C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally substituted by 1 to 3 substituents selected from

(i') halogen atom (e.g., fluorine, chlorine),
(ii') C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{3-6} cycloalkyl (e.g., cyclopropyl),
(iii') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl) optionally substituted by cyano,
(iv') C_{1-4} alkoxy (e.g., methoxy, ethoxy, isopropoxy, tert-butoxy) optionally substituted by 1 to 5 halogen atoms (e.g., fluorine),
(v') C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl), and
(vi') 5- or 6-membered heterocyclic group (e.g., tetrahydropyranyl, pyrrolidinyl) optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms (e.g., furylcarbonyl, tetrahydrofurylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, pyrrolidinylcarbonyl, imidazolylcarbonyl, thiazolylcarbonyl, thiadiazolylcarbonyl, dihydrooxazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, pyrazolylcarbonyl, dihydropyrazolylcarbonyl, triazolylcarbonyl, pyridylcarbonyl, pyrimidinylcarbonyl, pyrazinylcarbonyl, pyridazinylcarbonyl) optionally substituted by 1 to 3 substituents selected from
(i') halogen atom (e.g., chlorine),
(ii') C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{1-4} alkoxy (e.g., methoxy),
(iii') C_{6-10} aryl (e.g., phenyl),
(iv') C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl),
(v') C_{1-4} alkoxy (e.g., methoxy, ethoxy) optionally substituted by C_{1-4} alkoxy (e.g., methoxy),
(vi') C_{1-4} alkylsulfonyl (e.g., methylsulfonyl,

ethylsulfonyl),

(vii') C_{1-4} alkyl-carbonyl (e.g., acetyl), and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl (e.g., benzopyrazolylcarbonyl, indolylcarbonyl),

(x) C_{1-4} alkyl-aminocarbonyl (e.g., ethylaminocarbonyl),

(xi) C_{6-10} aryl-aminocarbonyl (e.g., phenylaminocarbonyl) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(xii) C_{1-4} alkoxy-aminocarbonyl (e.g., methoxyaminocarbonyl, isobutoxyaminocarbonyl),

(xiii) 5-membered heterocyclyl-aminocarbonyl (e.g., isoxazolylaminocarbonyl, pyrazolylaminocarbonyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl, tert-butyl) and C_{6-10} aryl (e.g., phenyl),

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl (e.g., benzylcarbonyl), and

(xv) 5-membered aromatic heterocyclyl-sulfonyl (e.g., thiazolylsulfonyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl),

(e) C_{1-4} alkyl-aminocarbonyl (e.g., methylaminocarbonyl) optionally having C_{6-10} aryl (e.g., phenyl),

(f) 5-membered heterocyclyl-aminocarbonyl (e.g., pyrazolylaminocarbonyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl) and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl (e.g., phenylaminocarbonyl) optionally substituted by C_{1-4} alkyl (e.g., methyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine) and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle (e.g., pyridyl) optionally substituted by 1 to 3 substituents selected from

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

(b) C_{6-10} aryl-carbonylamino (e.g., benzoylamino) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), or

(3) fused aromatic heterocycle (e.g., indolyl, benzothiazolyl, benzimidazolyl) optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl (e.g., methyl), and

(b) C_{6-10} arylamino (e.g., phenylamino) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

and the like.

As ring Y, 3-[(1,3-dimethyl-1H-pyrazol-5-yl)aminocarbonyl]-3-phenyl, 3-aminophenyl, 4-aminophenyl, 3-{[(ethylamino)carbonyl]amino}phenyl, 4-{[(phenylamino)carbonyl]amino}phenyl, 3-{[(phenylamino)carbonyl]amino}phenyl, 3-({[3-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-({[4-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-[(tert-butylcarbonyl)amino]phenyl, 3-[(cyclopropylcarbonyl)amino]phenyl, 3-[(cyclohexylcarbonyl)amino]phenyl, 3-[(phenylcarbonyl)amino]phenyl, 3-{[3-(trifluoromethylphenyl)carbonyl]amino}phenyl, 3-{[3-(fluorophenyl)carbonyl]amino}phenyl, 3-{[3-(chlorophenyl)carbonyl]amino}phenyl, 3-{[3-(pyridyl)carbonyl]amino}phenyl, 3-{[2-(furyl)carbonyl]amino}phenyl, 3-{[3-(2,5-dimethylfuran)carbonyl]amino}phenyl, 3-{[2-(3-methylthiophene)carbonyl]amino}phenyl, 3-{[5-(4-methyl-1,2,3-thiadiazole)carbonyl]amino}phenyl, 3-{[5-(isoxazole)carbonyl]amino}phenyl, 3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[5-(3-methylisoxazole)carbonyl]amino}phenyl, 3-{[3-(5-methylisoxazole)carbonyl]amino}phenyl, 3-({5-[1-methyl-3-(trifluoromethyl)-1H-pyrazole]carbonyl}amino)phenyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonylaminophenyl, 3-{[5-(2,4-

dimethyl-1,3-thiazole)carbonyl]amino}phenyl, 3-{[4-(2,5-dimethyl-1,3-oxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[3-(1,5-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[4-(3,5-dimethylisoxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[4-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[2-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 1H-indol-6-yl, 2-methyl-1H-indol-6-yl, 1,2-dimethyl-1H-benzimidazol-5-yl, 1H-indol-4-yl, 2-methyl-1,3-benzothiazol-5-yl, 2-methyl-1,3-benzothiazol-6-yl, 5-amino-2-methylphenyl, 3-amino-2-methylphenyl, 3-amino-4-methylphenyl, 3-amino-4-chlorophenyl, 5-amino-2-chlorophenyl, 5-amino-2-methoxyphenyl, 6-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 2-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-fluoro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-methoxy-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-(cyclopropylcarbonylamino)phenyl, 3-amino-4-fluorophenyl, 4-fluoro-3-{[4-(1-ethyl-3-methyl-1H-pyrazole)carbonyl]amino}phenyl and the like can be specifically mentioned.

In the compounds (I) and (IV), as the substituent for R of NR defined by X, those similar to the group exemplified as the "optionally substituted hydrocarbon group" in the aforementioned Substituent Group (1)(iv), the group exemplified as the "optionally substituted aminocarbonyl" in the aforementioned Substituent Group (1)(viii), the group exemplified as the "acyl" in the aforementioned Substituent Group (1)(ix) and the group exemplified as the "optionally substituted heterocyclic group" in the aforementioned Substituent Group (1)(xii) can be mentioned.

As the substituent for R, optionally substituted

hydrocarbon group and the like are preferable.

X is preferably -O-, -S- or -NH-, more preferably -O- or -S-, and particularly preferably -O-.

In the compounds (I) and (IV), R^1 is hydrogen atom or substituent (provided that when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted).

As the "substituent" for R^1, those similar to the substituent of the aforementioned Substituent Group (1) can be mentioned. Of these, optionally substituted amino, optionally substituted aminocarbonyl, optionally substituted alkyl and the like are preferable.

Preferable R^1 is

(1) hydrogen atom,
(2) amino,
(3) optionally substituted alkylcarbonylamino,
(4) optionally substituted alkenylcarbonylamino,
(5) optionally substituted alkynylcarbonylamino,
(6) optionally substituted cycloalkylcarbonylamino,
(7) optionally substituted cycloalkyl-alkylcarbonylamino,
(8) optionally substituted 6-membered heterocyclyl-carbonylamino,
(9) optionally substituted aminocarbonylamino,
(10) optionally substituted alkoxycarbonylamino,
(11) optionally substituted alkylsulfonylamino,
(12) optionally substituted cycloalkylsulfonylamino,
(13) optionally substituted arylamino,
(14) optionally substituted heterocyclylamino,
(15) optionally substituted aminocarbonyl,
(16) optionally substituted alkyl,
(17) optionally esterified carboxy, and the like.

Of these, preferable R^1 are

(1) hydrogen atom,
(2) amino,
(3) C_{1-4} alkyl-carbonylamino (e.g., acetylamino,

ethylcarbonylamino, isopropylcarbonylamino, isobutylcarbonylamino, tert-butylcarbonylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., chlorine), (b) hydroxy, (c) C_{1-4} alkoxy (e.g., methoxy), (d) C_{1-4} alkyl-carbonyloxy (e.g., methylcarbonyloxy), (e) C_{1-4} alkylamino (e.g., methylamino), (f) di-C_{1-4} alkylamino (e.g., dimethylamino), (g) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl), and (h) 6-membered heterocyclic group (e.g., piperazinyl, morpholinyl) optionally having 1 to 3 C_{1-4} alkyl (e.g., methyl),

(4) C_{2-4} alkenyl-carbonylamino (e.g., vinylcarbonylamino, 2-methyl-1-propenylcarbonylamino) optionally having C_{1-4} alkoxy (e.g., methoxy),

(5) C_{2-4} alkynyl-carbonylamino (e.g., 1-propenylcarbonylamino),

(6) C_{3-6} cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino) optionally substituted by 1 to 4 substituents selected from (a) halogen atom (e.g., fluorine), (b) hydroxy, (c) C_{1-4} alkyl (e.g., methyl, isopropyl) optionally having hydroxy, (d) C_{1-4} alkoxy (e.g., methoxy), (e) C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl), and (f) C_{1-4} alkyl-carbonyloxy (e.g., acetoxy),

(7) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino (e.g., cyclopropylmethylcarbonylamino),

(8) 6-membered heterocyclyl-carbonylamino (e.g., tetrahydropyranylcarbonylamino, pyridylcarbonylamino, pyrimidinylcarbonylamino, morpholinylcarbonylamino, piperazinylcarbonylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., fluorine, chlorine), (b) cyano, and (c) C_{1-4} alkyl (e.g., methyl) optionally having 1 to 3 halogen atoms (e.g., fluorine),

(9) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from (a) C_{1-4} alkyl (e.g., ethyl) optionally having 1 to 3 C_{1-4} alkoxy (e.g., ethoxy) optionally having 1 to 3 hydroxy, and (b) C_{1-4} alkoxy (e.g., methoxy),

(10) C_{1-4} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, tert-butoxycarbonylamino) optionally substituted by 1 to 3 halogen atoms (e.g., chlorine),
(11) C_{1-4} alkylsulfonylamino (e.g., methylsulfonylamino),
(12) C_{3-6} cycloalkylsulfonylamino (e.g., cyclopropylsulfonylamino),
(13) C_{6-10} arylamino (e.g., phenylamino),
(14) heterocyclylamino (e.g., thiazolylamino, pyrimidinylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., chlorine), and (b) C_{1-4} alkylamino (e.g., methylamino),
(15) aminocarbonyl optionally substituted by C_{1-4} alkyl (e.g., methyl),
(16) C_{1-4} alkyl (e.g., methyl) optionally substituted by hydroxy,
(17) carboxy,
(18) C_{1-6} alkoxy-carbonyl (e.g., ethoxycarbonyl),
and the like.

Specific R^1 may include hydrogen atom, amino, acetylamino, chloroacetylamino, 4-morpholinylacetylamino, methylcarbonyloxymethylcarbonylamino, methylaminomethylcarbonylamino, hydroxymethylcarbonylamino, methoxymethylcarbonylamino, ethylcarbonylamino, isopropylcarbonylamino, dimethylaminomethylcarbonylamino, 4-methylpiperazin-1-ylacetylamino, methylsulfonylmethylcarbonylamino, 3-hydroxy-3-methylbutanoylamino, hydroxyethylcarbonylamino, 3-methyl-2-butenoylamino, 3-methoxy-2-propenoylamino, 2-butynoylamino, (cyclopropylcarbonyl)amino, (1-methoxycarbonylcyclopropylcarbonyl)amino, (1-hydroxycyclopropylcarbonyl)amino, (2-methylcyclopropylcarbonyl)amino, (2-methoxycyclopropylcarbonyl)amino, (2-methylcarbonylcyclopropylcarbonyl)amino, (2-hydroxymethylcarbonylcyclopropylcarbonyl)amino, (2-(1-hydroxy-1-methylethyl)cyclopropyl)carbonylamino, (2,2-

dimethylcyclopropylcarbonyl)amino, (2,2-difluorocyclopropylcarbonyl)amino, (2,2,3,3-tetramethylcyclopropylcarbonyl)amino, (cyclobutylcarbonyl)amino, (cyclopentylcarbonyl)amino, (cyclohexylcarbonyl)amino, cyclopropylmethylcarbonylamino, (tetrahydro-2H-pyran-4-ylcarbonyl)amino, (3-pyridylcarbonyl)amino, (4-pyridylcarbonyl)amino, (6-methyl-3-pyridylcarbonyl)amino, (6-fluoro-3-pyridylcarbonyl)amino, (6-chloro-3-pyridylcarbonyl)amino, (6-cyano-3-pyridylcarbonyl)amino, (6-(trifluoromethyl)-3-pyridylcarbonyl)amino, (5-pyrimidinylcarbonyl)amino, 4-morpholinylcarbonylamino, methoxyureido, ethylureido, 2-hydroxyethoxyethylureido, methoxycarbonylamino, ethoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, tert-butoxycarbonylamino, methylsulfonylamino, (cyclopropylsulfonyl)amino, phenylamino, 2-methylaminopyrimidin-4-ylamino, 2-chloropyrimidin-4-ylamino, 1,3-thiazol-2-ylamino, methylaminocarbonyl, hydroxymethyl, carboxy, ethoxycarbonyl and the like can be mentioned.

In the compounds (I) and (IV), as the "substituent" for R^2, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^2 is hydrogen atom.

In the compounds (I) and (IV), as the "substituent" for R^3, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^3 is hydrogen atom.

In the compounds (I) and (IV), as the "substituent" for R^4, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^4 is hydrogen atom.

As preferable examples of the compounds (I) and (IV), for example, the following compounds can be mentioned.

A compound wherein

ring Y is

(1) C_{6-10} aryl optionally substituted by 1 to 3 substituents

selected from

(a) halogen atom,

(b) C_{1-4} alkyl,

(c) C_{1-4} alkoxy,

(d) amino optionally substituted by the substituents selected from

(i) C_{1-4} alkyl optionally substituted by a 5-membered aromatic heterocyclic group optionally substituted by 1 to 3 C_{1-4} alkyl,

(ii) C_{1-4} alkyl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl, and

(iii') 6-membered aromatic heterocyclic group,

(iii) C_{2-4} alkenyl-carbonyl optionally substituted by C_{6-10} aryl,

(iv) C_{2-6} alkynyl-carbonyl optionally substituted by C_{6-10} aryl,

(v) C_{3-6} cycloalkyl-carbonyl,

(vi) C_{3-6} cycloalkenyl-carbonyl,

(vii) C_{6-10} aryl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom, cyano, hydroxy and C_{3-6} cycloalkyl,

(iii') C_{3-6} cycloalkyl optionally substituted by cyano,

(iv') C_{1-4} alkoxy optionally substituted by 1 to 5 halogen atoms,

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

(vi') 5- or 6-membered heterocyclic group optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by 1 to 3 substituents selected from

(i') halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom, cyano, hydroxy and C_{1-4} alkoxy,

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

(iv') C_{6-10} aryl-C_{1-4} alkyl,

(v') C_{1-4} alkoxy optionally substituted by C_{1-4} alkoxy,

(vi') C_{1-4} alkylsulfonyl,

(vii') C_{1-4} alkyl-carbonyl, and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl,

(x) C_{1-4} alkyl-aminocarbonyl,

(xi) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms,

(xii) C_{1-4} alkoxy-aminocarbonyl,

(xiii) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl, and

(xv) 5-membered aromatic heterocyclyl-sulfonyl optionally substituted by 1 to 3 C_{1-4} alkyl,

(e) C_{1-4} alkyl-aminocarbonyl optionally having C_{6-10} aryl,

(f) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) C_{6-10} aryl-carbonylamino optionally substituted by C_{1-4} alkyl

optionally substituted by 1 to 3 halogen atoms, or

(3) fused aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl, and

(b) C_{6-10} arylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms;

X is -O-, -S- or -NH- (more preferably -O- or -S-, particularly preferably -O-);

R^1 is

(1) hydrogen atom,

(2) amino,

(3) C_{1-4} alkyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) hydroxy,

(c) C_{1-4} alkoxy,

(d) C_{1-4} alkyl-carbonyloxy,

(e) C_{1-4} alkylamino,

(f) di-C_{1-4} alkylamino,

(g) C_{1-4} alkylsulfonyl, and

(h) 6-membered heterocyclic group optionally having 1 to 3 C_{1-4} alkyl,

(4) C_{2-4} alkenyl-carbonylamino optionally having C_{1-4} alkoxy,

(5) C_{2-4} alkynyl-carbonylamino,

(6) C_{3-6} cycloalkyl-carbonylamino optionally substituted by 1 to 4 substituents selected from

(a) halogen atom,

(b) hydroxy,

(c) C_{1-4} alkyl optionally having hydroxy,

(d) C_{1-4} alkoxy,

(e) C_{1-4} alkoxy-carbonyl, and

(f) C_{1-4} alkyl-carbonyloxy,

(7) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino,

(8) 6-membered heterocyclyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) cyano, and

(c) C_{1-4} alkyl optionally having 1 to 3 halogen atom,

(9) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from

(a) C_{1-4} alkyl optionally having 1 to 3 C_{1-4} alkoxy optionally having 1 to 3 hydroxy, and

(b) C_{1-4} alkoxy,

(10) C_{1-4} alkoxy-carbonylamino optionally substituted by 1 to 3 halogen atoms,

(11) C_{1-4} alkylsulfonylamino,

(12) C_{3-6} cycloalkylsulfonylamino,

(13) C_{6-10} arylamino,

(14) heterocyclylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) C_{1-4} alkylamino,

(15) aminocarbonyl substituted by C_{1-4} alkyl (e.g., methyl etc.),

(16) C_{1-4} alkyl (e.g., methyl) optionally substituted by hydroxy,

(17) carboxy, or

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

R^2, R^3 and R^4 are each hydrogen atom.

As specific examples of the compounds (I) and (IV), for example, compounds of Examples 1 to 440, 442 and 445 can be mentioned.

Particularly preferable examples may include the following compounds or salts thereof.

N-{3-[(2-{[2-(methylamino)pyrimidin-4-yl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (Example 70);

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

(Example 111);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148);
N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 149);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208);
N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-

carboxamide (Example 254);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289);
N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (Example 319);
3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]benzamide (Example 330);
N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (Example 398);
N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-(trifluoromethyl)benzamide (Example 427);
N-{6-[3-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 431).

The compound represented by the formula (II) (hereinafter compound (II)) of the present invention is explained.

As the "cyclic group" of the "optionally substituted cyclic group" for ring Ya, those similar to the group exemplified as the "cyclic group" of the "optionally substituted cyclic group" for ring Y of compound (I) can be mentioned.

As the "cyclic group" of the "optionally substituted cyclic group" shown by ring Ya, aromatic hydrocarbon group, aromatic heterocyclic group are preferable. As the aromatic hydrocarbon group, C_{6-14} aryl is preferable, C_{6-10} aryl is more preferable, and phenyl is particularly preferable. As the aromatic heterocyclic group, monocyclic aromatic heterocyclic group, fused aromatic heterocyclic group are preferable,

pyridine ring, and, fused aromatic heterocyclic group formed by fusion of benzene ring and 5-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 or 2 hetero atoms selected from sulfur atom and nitrogen atom besides carbon atoms (e.g., benzothiazolyl, benzimidazolyl, indolyl etc.) is more preferable, and benzothiazolyl (e.g., 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-5-yl, benzimidazol-6-yl), indolyl (e.g., indol-4-yl, indol-5-yl, indol-6-yl) and the like are particularly preferable.

The "optionally substituted cyclic group" for ring Ya may have 1 to the acceptable maximum number of substituents at any substitutable positions. Where the cyclic group is substituted by two or more substituents, the substituents may be the same or different, and the cyclic group optionally has preferably 1 to 5, more preferably 1 to 3 substituents.

As the "substituent" of the "optionally substituted cyclic group" for ring Ya, those similar to the group exemplified as the "substituent" of the "optionally substituted cyclic group" for ring Y of compound (I) can be mentioned.

The "substituent" of the "optionally substituted cyclic group" for ring Ya is preferably

(1) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
(2) optionally substituted alkyl,
(3) optionally substituted alkoxy,
(4) optionally substituted aminocarbonyl,
(5) optionally substituted amino,
(6) carboxyl,

and the like.

Of these,

(1) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
(2) optionally substituted alkyl,
(3) optionally substituted amino,

and the like are preferable.

Hereinafter the above-mentioned preferable examples of the "substituent" of the "optionally substituted cyclic group" for

ring Ya are explained in detail.

(1) As the halogen atom, fluorine, chlorine, bromine and the like are preferable.

(2) As the optionally substituted alkyl, optionally substituted C_{1-8} alkyl is preferable, optionally substituted C_{1-4} alkyl is more preferable, and unsubstituted C_{1-4} alkyl is more preferable. Specifically, methyl, ethyl and the like are preferable.

(3) As the optionally substituted alkoxy, optionally substituted C_{1-8} alkoxy is preferable, optionally substituted C_{1-4} alkoxy is more preferable, unsubstituted C_{1-4} alkoxy is much more preferable. Specifically, methoxy and the like are preferable.

(4) As the "substituent" for the optionally substituted aminocarbonyl, for example, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} cycloalkynyl, C_{6-18} aryl, heterocyclic group and the like, each of which is optionally substituted, are preferable. Of these, optionally substituted C_{1-4} alkyl, optionally substituted C_{6-12} aryl and optionally substituted 5-membered heterocyclic group and the like are preferable. Particularly, C_{6-12} aryl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from (a) C_{1-4} alkyl optionally having C_{6-12} aryl, (b) 5-membered heterocyclic group optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-12} aryl, (c) halogen atom and (d) cyano is preferable.

(5) As the "substituent" for the optionally substituted amino, optionally substituted alkyl, optionally substituted aminocarbonyl, acyl, optionally substituted aminothiocarbonyl, optionally substituted heterocyclyl-sulfonyl and the like are preferable.

As the optionally substituted amino, amino optionally substituted by 1 or 2 substituents selected from (a) optionally substituted alkyl, (b) optionally substituted aminocarbonyl, (c) acyl, (d) optionally substituted aminothiocarbonyl, and (e) optionally substituted heterocyclyl-sulfonyl is preferable.

As the optionally substituted alkyl, optionally

substituted C_{1-4} alkyl is preferable. Of these, C_{1-4} alkyl optionally substituted by 5-membered heterocyclic group optionally substituted by 1 to 3 C_{1-4} alkyl is preferable.

As the optionally substituted aminocarbonyl, C_{1-8} alkyl-aminocarbonyl, C_{6-18} aryl-aminocarbonyl, C_{6-18} aryl-C_{1-4} alkyl-aminocarbonyl, heterocyclyl-aminocarbonyl, C_{3-8} cycloalkyl-aminocarbonyl, C_{1-8} alkoxy-aminocarbonyl and the like, each of which is optionally substituted, are preferable. Of these, optionally substituted C_{1-8} alkyl-aminocarbonyl, optionally substituted C_{6-18} aryl-aminocarbonyl, optionally substituted heterocyclyl-aminocarbonyl, optionally substituted C_{1-8} alkoxy-aminocarbonyl and the like are preferable. Particularly, (i) C_{1-4} alkyl-aminocarbonyl, (ii) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms, (iii) C_{1-4} alkoxy-aminocarbonyl, (iv) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl, and the like are preferable.

As the acyl, C_{1-8} alkyl-carbonyl, C_{2-8} alkenyl-carbonyl, C_{2-8} alkynyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{3-8} cycloalkenyl-carbonyl, C_{6-18} aryl-carbonyl, C_{6-18} aryl-C_{1-4} alkyl-carbonyl, C_{1-8} alkylsulfonyl, C_{6-18} aryl-sulfonyl, heterocyclyl-carbonyl, heterocyclyl-sulfonyl and the like, each of which is optionally substituted, are preferable. Of these, C_{1-8} alkyl-carbonyl, C_{2-8} alkenyl-carbonyl, C_{2-8} alkynyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{3-8} cycloalkenyl-carbonyl, C_{6-18} aryl-carbonyl, heterocyclyl-carbonyl, each of which is optionally substituted, are preferable.

As the optionally substituted C_{1-8} alkyl-carbonyl, optionally substituted C_{1-4} alkyl-carbonyl is preferable. Particularly, C_{1-4} alkyl-carbonyl (e.g., methylcarbonyl, tert-butylcarbonyl, 3-methylbutanoyl) optionally substituted by 1 to 3 substituents selected from (a) hydroxy, (b) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl) and (c) 6-membered heterocyclic group (e.g., pyridyl) (specific examples: methylsulfonylmethylcarbonyl,

2-pyridylmethylcarbonyl, tert-butylcarbonyl, 3-hydroxy-3-methylbutanoyl) is preferable.

As the optionally substituted C_{2-8} alkenyl-carbonyl, optionally substituted C_{2-4} alkenyl-carbonyl is preferable. Particularly, C_{2-4} alkenyl-carbonyl (e.g., 3-methyl-2-butenoyl) optionally substituted by C_{6-10} aryl (e.g., phenyl) (specific examples: 3-methyl-2-butenoyl) is preferable.

As the optionally substituted C_{2-8} alkynyl-carbonyl, optionally substituted C_{2-4} alkynyl-carbonyl is preferable. Particularly, C_{2-4} alkynyl-carbonyl (e.g., 2-butynoyl) optionally substituted by C_{6-10} aryl (e.g., phenyl) (specific example: 2-butynoyl) is preferable.

As the optionally substituted C_{3-8} cycloalkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl is preferable, and cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and the like are specifically preferable.

As the optionally substituted C_{3-8} cycloalkenyl-carbonyl, C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopentenecarbonyl) (specific example: 1-cyclopentenecarbonyl) is preferable.

As the optionally substituted C_{6-18} aryl-carbonyl, optionally substituted C_{6-10} aryl-carbonyl is preferable. Particularly, C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., fluorine), (b) C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{3-6} cycloalkyl (e.g., cyclopropyl) (specific example: trifluoromethyl), (c) C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl) optionally substituted by cyano, (d) C_{1-4} alkoxy (e.g., isopropoxy, tert-butoxy) optionally substituted by 1 to 5 halogen atoms (e.g., fluorine), (e) C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl), and (f) 5 or 6-membered heterocyclic group (e.g., tetrahydropyranyl, pyrrolidinyl) optionally substituted by cyano or oxo is preferable. Specifically, phenylcarbonyl(benzoyl), 3-(trifluoromethyl)phenylcarbonyl, 4-

(trifluoromethyl)phenylcarbonyl, 3-fluorophenylcarbonyl, 3-chlorophenylcarbonyl, 3-(1-cyanocyclopropyl)phenylcarbonyl, 3-(1-cyanocyclobutyl)phenylcarbonyl, 3-(1-cyanocyclohexyl)phenylcarbonyl, 2-fluoro-3-(trifluoromethyl)phenylcarbonyl, 2-fluoro-5-(trifluoromethyl)phenylcarbonyl, 3-fluoro-5-(trifluoromethyl)phenylcarbonyl, 4-chloro-3-(trifluoromethyl)phenylcarbonyl, 2-chloro-3-(trifluoromethyl)phenylcarbonyl, 2-chloro-5-(trifluoromethyl)phenylcarbonyl, 3-isopropoxyphenylcarbonyl, 3-(tert-butoxy)phenylcarbonyl, 3-(1-cyano-1-methylethyl)phenylcarbonyl, 3-methoxyphenylcarbonyl, 3-methoxycarbonylphenylcarbonyl, 3-(trifluoromethoxy)carbonylphenylcarbonyl, 3-(1,1,2,2-tetrafluoroethoxy)phenylcarbonyl, 3-(4-cyanotetrahydropyran-4-yl)phenylcarbonyl, 3,5-di(trifluoromethyl)phenylcarbonyl, 3-(2-oxopyrrolidin-1-yl)phenylcarbonyl, 4-(tert-butyl)phenylcarbonyl, 3-(1-cyanoethyl)phenylcarbonyl, 3-(1-cyano-2-cyclopropyl-1-methylethyl)phenylcarbonyl and the like are preferable.

As the optionally substituted C_{6-18} aryl-C_{1-4} alkyl-carbonyl, C_{6-10} aryl-C_{1-4} alkyl-carbonyl is preferable.

As the optionally substituted C_{1-8} alkylsulfonyl, C_{1-4} alkylsulfonyl are preferable.

As the optionally substituted C_{6-18} aryl-sulfonyl, C_{6-10} aryl-sulfonyl is preferable.

As the "heterocycle" moiety for the optionally substituted heterocyclyl-carbonyl, 5- or 6-membered monocyclic heterocyclic group containing, as ring-constituting atom, 1 to 3 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like are preferable, and pyridyl, furyl, tetrahydrofuryl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, dihydrooxazolyl, pyridazinyl, pyrazinyl, dihydropyrazolyl, pyrrolyl, pyrrolidinyl, pyrimidinyl and the like are specifically preferable. As the "substituent" for the optionally

substituted heterocyclyl-carbonyl, (1) halogen atom (e.g., chlorine), (2) C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{1-4} alkoxy (e.g., methoxy) (specific examples: methyl, trifluoromethyl, ethyl, methoxyethyl, 2,2,2-trifluoroethyl, isopropyl, tert-butyl), (3) C_{6-18} aryl (e.g., phenyl), (4) C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl), (5) C_{1-4} alkoxy (e.g., methoxy, ethoxy) optionally substituted by C_{1-4} alkoxy (e.g., methoxy) (specific examples: methoxy, ethoxy, methoxyethoxy), (6) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl), (7) C_{1-4} alkylcarbonyl (e.g., acetyl), (8) oxo, and the like are preferable.

As the optionally substituted heterocyclyl-carbonyl, the above-mentioned 5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl and the like optionally substituted by optionally halogenated C_{1-4} alkyl and the like are preferable. Specifically, 2-pyridylcarbonyl, 3-pyridylcarbonyl, 4-pyridylcarbonyl, 2-methyl-6-pyridylcarbonyl, 3-methyl-2-pyridylcarbonyl, 4-methyl-2-pyridylcarbonyl, 2-methyl-3-pyridylcarbonyl, 2-(trifluoromethyl)-3-pyridylcarbonyl, 2-(trifluoromethyl)-4-pyridylcarbonyl, 2-(trifluoromethyl)-6-pyridylcarbonyl, 2-chloro-6-methyl-4-pyridylcarbonyl, 2,6-dichloro-4-pyridylcarbonyl, 2-furylcarbonyl, 2,5-dimethylfuran-3-carbonyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonyl, 3-methylthiophene-2-carbonyl, 5-acetylsulfonylthiophene-2-carbonyl, 5-ethylsulfonylthiophene-2-carbonyl, 4-methyl-1,2,3-thiadiazole-5-carbonyl, isoxazole-5-carbonyl, 1H-pyrazole-5-carbonyl, 1-methyl-1H-pyrazole-3-carbonyl, 1-methyl-1H-pyrazole-5-carbonyl, 1-ethyl-1H-pyrazole-3-carbonyl, 1-ethyl-1H-pyrazole-5-carbonyl, 3-methyl-1H-pyrazole-5-carbonyl, 3-chloro-1-methyl-1H-pyrazole-5-carbonyl, 4-chloro-1-methyl-1H-pyrazole-3-carbonyl, 1-methyl-3-methoxy-1H-pyrazole-5-carbonyl, 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-4-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-5-carbonyl, 3-ethoxy-1-

methyl-1H-pyrazole-5-carbonyl, 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carbonyl, 1-ethyl-3-methyl-1H-pyrazole-4-carbonyl, 1-ethyl-3-methyl-1H-pyrazole-5-carbonyl, 3-methyl-1-phenyl-1H-pyrazole-5-carbonyl, 5-methyl-1-phenyl-1H-pyrazole-3-carbonyl, 3-ethyl-1-methyl-1H-pyrazole-5-carbonyl, 3-isopropyl-1-methyl-1H-pyrazole-5-carbonyl, 3-methoxy-1-methyl-1H-pyrazole-5-carbonyl, 1-tert-butyl-3-methyl-1H-pyrazole-5-carbonyl, 3-tert-butyl-1-methyl-1H-pyrazole-5-carbonyl, 1-methoxyethyl-3-methyl-1H-pyrazole-5-carbonyl, 1,3-dimethyl-1H-pyrazole-4-carbonyl, 1,3-dimethyl-1H-pyrazole-5-carbonyl, 1,4-dimethyl-1H-pyrazole-3-carbonyl, 1,4-dimethyl-1H-pyrazole-5-carbonyl, 1,5-dimethyl-1H-pyrazole-3-carbonyl, 3-methylisoxazole-4-carbonyl, 3-methylisoxazole-5-carbonyl, 5-methylisoxazole-3-carbonyl, 5-methylisoxazole-4-carbonyl, 3,5-dimethylisoxazole-4-carbonyl, 1,3-thiazole-2-carbonyl, 2-methyl-1,3-thiazole-4-carbonyl, 4-methyl-1,3-thiazole-5-carbonyl, 5-methyl-1,3-thiazole-4-carbonyl, 2,4-dimethyl-1,3-thiazole-5-carbonyl, 2-chloro-4-methyl-1,3-thiazole-5-carbonyl, 4-methoxy-2-methyl-1,3-thiazole-5-carbonyl, 2-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carbonyl, 2-(1-cyano-1-methylethyl)-1,3-thiazole-5-carbonyl, 2-methyl-1,3-oxazole-4-carbonyl, 4-methyl-1,3-oxazole-5-carbonyl, 2-ethyl-4-methyl-1,3-oxazole-5-carbonyl, 2,4-dimethyl-1,3-oxazole-5-carbonyl, 2,5-dimethyl-1,3-oxazole-4-carbonyl, 1-methyl-1H-1,2,3-triazole-5-carbonyl, 1-methyl-1H-1,2,3-triazole-4-carbonyl, 1-methyl-1H-imidazole-2-carbonyl, 1-methyl-1H-imidazole-5-carbonyl, 2-pyrazinylcarbonyl, 1-methylpyrrole-2-carbonyl, 1-benzylpyrrole-3-carbonyl, 1,2,5-trimethylpyrrole-3-carbonyl, 1-methylpyrrolidine-2-carbonyl, 2-(trifluoromethyl)pyrimidine-4-carbonyl and the like are preferable.

As the "heterocycle" moiety for the optionally substituted heterocyclyl-sulfonyl, 5- or 6-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, and the like are preferable, and thiazolyl and the like are specifically preferable. As the

"substituent" for the optionally substituted heterocyclyl-carbonyl, C_{1-4} alkyl (e.g., methyl) and the like are preferable.

As the optionally substituted heterocyclyl-sulfonyl, 2,5-dimethyl-1,3-thiazole-4-sulfonyl and the like are specifically preferable.

As the optionally substituted aminothiocarbonyl, aminothiocarbonyl optionally substituted by C_{6-18} aryl-C_{1-4} alkyl-carbonyl (e.g., benzylcarbonyl) and the like are preferable.

Preferably, ring Ya is

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

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

(b) C_{1-4} alkyl (e.g., methyl, ethyl),

(c) C_{1-4} alkoxy (e.g., methoxy),

(d) amino optionally substituted by substituents selected from

(i) C_{1-4} alkyl (e.g., methyl) optionally substituted by 5-membered aromatic heterocyclic group (e.g., pyrazolyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl),

(ii) C_{1-4} alkyl-carbonyl (e.g., methylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl) optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl (e.g., methylsulfonyl), and

(iii') 6-membered aromatic heterocyclic group (e.g., pyridyl),

(iii) C_{2-4} alkenyl-carbonyl (e.g., 2-methyl-1-propenylcarbonyl, vinylcarbonyl) optionally substituted by C_{6-10} aryl (e.g., phenyl),

(iv) C_{2-4} alkynyl-carbonyl (e.g., acetylenecarbonyl, 1-propynylcarbonyl) optionally substituted by C_{6-10} aryl (e.g., phenyl),

(v) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl),

(vi) C_{3-6} cycloalkenyl-carbonyl (e.g., cyclopentenylcarbonyl),

(vii) C_{6-10} aryl-carbonyl (e.g., benzoyl) optionally

substituted by 1 to 3 substituents selected from

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

(ii') C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{3-6} cycloalkyl (e.g., cyclopropyl),

(iii') C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclohexyl) optionally substituted by cyano,

(iv') C_{1-4} alkoxy (e.g., methoxy, ethoxy, isopropoxy, tert-butoxy) optionally substituted by 1 to 5 halogen atoms (e.g., fluorine),

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

(vi') 5- or 6-membered heterocyclic group (e.g., tetrahydropyranyl, pyrrolidinyl) optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms (e.g., furylcarbonyl, tetrahydrofurylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl, pyrrolidinylcarbonyl, imidazolylcarbonyl, thiazolylcarbonyl, thiadiazolylcarbonyl, dihydrooxazolylcarbonyl, oxazolylcarbonyl, isoxazolylcarbonyl, pyrazolylcarbonyl, dihydropyrazolylcarbonyl, triazolylcarbonyl, pyridylcarbonyl, pyrimidinylcarbonyl, pyrazinylcarbonyl) optionally substituted by 1 to 3 substituents selected from

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

(ii') C_{1-4} alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine), cyano, hydroxy and C_{1-4} alkoxy (e.g., methoxy),

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

(iv') C_{6-10} aryl-C_{1-4} alkyl (e.g., benzyl),

(v') C_{1-4} alkoxy (e.g., methoxy, ethoxy) optionally substituted by C_{1-4} alkoxy (e.g., methoxy),

(vi') C_{1-4} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl),

(vii') C_{1-4} alkyl-carbonyl (e.g., acetyl), and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl (e.g., benzopyrazolylcarbonyl, indolylcarbonyl),

(x) C_{1-4} alkyl-aminocarbonyl (e.g., ethylaminocarbonyl),

(xi) C_{6-10} aryl-aminocarbonyl (e.g., phenylaminocarbonyl) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine),

(xii) C_{1-4} alkoxy-aminocarbonyl (e.g., methoxyaminocarbonyl, isobutoxyaminocarbonyl),

(xiii) 5-membered heterocyclyl-aminocarbonyl (e.g., isoxazolylaminocarbonyl, pyrazolylaminocarbonyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl, tert-butyl) and C_{6-10} aryl (e.g., phenyl),

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl (e.g., benzylcarbonyl), and

(xv) 5-membered aromatic heterocyclyl-sulfonyl (e.g., thiazolylsulfonyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl),

(e) C_{1-4} alkyl-aminocarbonyl (e.g., methylaminocarbonyl) optionally having C_{6-10} aryl (e.g., phenyl),

(f) 5-membered heterocyclyl-aminocarbonyl (e.g., pyrazolylaminocarbonyl) optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl (e.g., methyl) and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl (e.g., phenylaminocarbonyl) optionally substituted by C_{1-4} alkyl (e.g., methyl, isopropyl, tert-butyl) optionally substituted by 1 to 3 substituents selected from halogen atom (e.g., fluorine) and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle (e.g., pyridyl) optionally substituted by 1 to 3 substituents selected from

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

(b) C_{6-10} aryl-carbonylamino (e.g., benzoylamino) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine), or

(3) fused aromatic heterocycle (e.g., indolyl, benzothiazolyl, benzimidazolyl) optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl (e.g., methyl), and,

(b) C_{6-10} arylamino (e.g., phenylamino) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally substituted by 1 to 3 halogen atoms (e.g., fluorine).

As ring Ya, (1,3-dimethyl-1H-pyrazol-5-yl)aminocarbonyl-3-phenyl, 3-aminophenyl, 4-aminophenyl, 3-{[(ethylamino)carbonyl]amino}phenyl, 4-{[(phenylamino)carbonyl]amino}phenyl, 3-{[(phenylamino)carbonyl]amino}phenyl, 3-({[3-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-({[4-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-[(tert-butylcarbonyl)amino]phenyl, 3-[(cyclopropylcarbonyl)amino]phenyl, 3-[(cyclohexylcarbonyl)amino]phenyl, 3-[(phenylcarbonyl)amino]phenyl, 3-{[3-(trifluoromethylphenyl)carbonyl]amino}phenyl, 3-{[3-(fluorophenyl)carbonyl]amino}phenyl, 3-{[3-(chlorophenyl)carbonyl]amino}phenyl, 3-{[3-(pyridyl)carbonyl]amino}phenyl, 3-{[2-(furyl)carbonyl]amino}phenyl, 3-{[3-(2,5-dimethylfuran)carbonyl]amino}phenyl, 3-{[2-(3-methylthiophene)carbonyl]amino}phenyl, 3-{[5-(4-methyl-1,2,3-thiadiazole)carbonyl]amino}phenyl, 3-{[5-(isoxazole)carbonyl]amino}phenyl, 3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[5-(3-methylisoxazole)carbonyl]amino}phenyl, 3-{[3-(5-methylisoxazole)carbonyl]amino}phenyl, 3-({5-[1-methyl-3-(trifluoromethyl)-1H-pyrazole]carbonyl}amino)phenyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonylaminophenyl, 3-{[5-(2,4-

dimethyl-1,3-thiazole)carbonyl]amino}phenyl, 3-{[4-(2,5-dimethyl-1,3-oxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[3-(1,5-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[4-(3,5-dimethylisoxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[4-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[2-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 1H-indol-6-yl, 2-methyl-1H-indol-6-yl, 1,2-dimethyl-1H-benzimidazol-5-yl, 1H-indol-4-yl, 2-methyl-1,3-benzothiazol-5-yl, 2-methyl-1,3-benzothiazol-6-yl, 5-amino-2-methylphenyl, 3-amino-2-methylphenyl, 3-amino-4-methylphenyl, 3-amino-4-chlorophenyl, 5-amino-2-chlorophenyl, 5-amino-2-methoxyphenyl, 6-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 2-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-fluoro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-methoxy-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-(cyclopropylcarbonylamino)phenyl, 3-amino-4-fluorophenyl, 4-fluoro-3-{[4-(1-ethyl-3-methyl-1H-pyrazole)carbonyl]amino}phenyl and the like can be specifically mentioned.

In the compound (II), as the substituent for R^a of NR^a defined by Xa, those similar to the substituent selected from the group exemplified as the "optionally substituted hydrocarbon group" for the aforementioned Substituent Group (1)(iv), the group exemplified as the "optionally substituted aminocarbonyl" for the aforementioned Substituent Group (1)(viii), the group exemplified as the "acyl" for the aforementioned Substituent Group (1)(ix) and the group exemplified as the "optionally substituted heterocyclic group" for the aforementioned Substituent Group (1)(xii) can be mentioned.

As the substituent for R^a, optionally substituted

hydrocarbon group and the like are preferable.

Xa is preferably -O-, -S- or -NH-, more preferably -O- or -S-, and particularly preferably -O-.

As the "optionally substituted amino" for R^{1a} in the compound (II), those similar to the "optionally substituted amino" exemplified in the aforementioned Substituent Group (1)(x) can be mentioned.

As the "optionally substituted amino" for R^{1a}, (1) amino, (2) optionally substituted alkylcarbonylamino, (3) optionally substituted alkenylcarbonylamino, (4) optionally substituted alkynylcarbonylamino, (5) optionally substituted cycloalkylcarbonylamino, (6) optionally substituted cycloalkyl-alkylcarbonylamino, (7) optionally substituted 6-membered heterocyclyl-carbonylamino, (8) optionally substituted aminocarbonylamino, (9) optionally substituted alkoxycarbonylamino, (10) optionally substituted alkylsulfonylamino, (11) optionally substituted cycloalkylsulfonylamino, (12) optionally substituted arylamino and (13) optionally substituted heterocyclylamino are preferable.

Of these, preferable R^{1a} are

(1) amino,

(2) C_{1-4} alkyl-carbonylamino (e.g., acetylamino, ethylcarbonylamino, isopropylcarbonylamino, isobutylcarbonylamino, tert-butylcarbonylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., chlorine), (b) hydroxy, (c) C_{1-4} alkoxy (e.g., methoxy), (d) C_{1-4} alkyl-carbonyloxy (e.g., methylcarbonyloxy), (e) C_{1-4} alkylamino (e.g., methylamino), (f) di-C_{1-4} alkylamino (e.g., dimethylamino), (g) C_{1-4} alkylsulfonyl (e.g., methylsulfonyl), and (h) 6-membered heterocyclic group (e.g., piperazinyl, morpholinyl) optionally substituted by 1 to 3 C_{1-4} alkyl (e.g., methyl),

(3) C_{2-4} alkenyl-carbonylamino (e.g., vinylcarbonylamino, 2-methyl-1-propenylcarbonylamino) optionally having C_{1-4} alkoxy (e.g., methoxy),

(4) C_{2-4} alkynyl-carbonylamino (e.g., 1-propenylcarbonylamino),
(5) C_{3-6} cycloalkyl-carbonylamino (e.g., cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino) optionally substituted by 1 to 4 substituents selected from (a) halogen atom (e.g., fluorine), (b) hydroxy, (c) C_{1-4} alkyl (e.g., methyl, isopropyl) optionally having hydroxy, (d) C_{1-4} alkoxy (e.g., methoxy), (e) C_{1-4} alkoxy-carbonyl (e.g., methoxycarbonyl), and (f) C_{1-4} alkyl-carbonyloxy (e.g., acetoxy),
(6) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino (e.g., cyclopropylmethylcarbonylamino),
(7) 6-membered heterocyclyl-carbonylamino (e.g., tetrahydropyranylcarbonylamino, pyridylcarbonylamino, pyrimidinylcarbonylamino, morpholinylcarbonylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., fluorine, chlorine), (b) cyano, and (c) C_{1-4} alkyl (e.g., methyl) optionally having 1 to 3 halogen atom (e.g., fluorine),
(8) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from (a) C_{1-4} alkyl (e.g., ethyl) optionally having 1 to 3 C_{1-4} alkoxy (e.g., ethoxy) optionally having 1 to 3 hydroxy, and (b) C_{1-4} alkoxy (e.g., methoxy),
(9) C_{1-4} alkoxy-carbonylamino (e.g., methoxycarbonylamino, ethoxycarbonylamino, tert-butoxycarbonylamino) optionally substituted by 1 to 3 halogen atom (e.g., chlorine),
(10) C_{1-4} alkylsulfonylamino (e.g., methylsulfonylamino),
(11) C_{3-6} cycloalkylsulfonylamino (e.g., cyclopropylsulfonylamino),
(12) C_{6-10} arylamino (e.g., phenylamino), and
(13) heterocyclylamino (e.g., thiazolylamino, pyrimidinylamino) optionally substituted by 1 to 3 substituents selected from (a) halogen atom (e.g., chlorine), and (b) C_{1-4} alkylamino (e.g., methylamino), and the like.

As R^{1a}, amino, acetylamino, chloroacetylamino, 4-morpholinylacetylamino, methylcarbonyloxymethylcarbonylamino,

methylaminomethylcarbonylamino, hydroxymethylcarbonylamino, methoxymethylcarbonylamino, ethylcarbonylamino, isopropylcarbonylamino, dimethylaminomethylcarbonylamino, 4-methylpiperazin-1-ylacetylamino, methylsulfonylmethylcarbonylamino, 3-hydroxy-3-methylbutanoylamino, hydroxyethylcarbonylamino, 3-methyl-2-butenoylamino, 3-methoxy-2-propenoylamino, 2-butynoylamino, (cyclopropylcarbonyl)amino, (1-methoxycarbonylcyclopropylcarbonyl)amino, (1-hydroxycyclopropylcarbonyl)amino, (2-methylcyclopropylcarbonyl)amino, (2-methoxycyclopropylcarbonyl)amino, (2-methylcarbonylcyclopropylcarbonyl)amino, (2-hydroxymethylcarbonylcyclopropylcarbonyl)amino, (2-(1-hydroxy-1-methylethyl)cyclopropyl)carbonylamino, (2,2-dimethylcyclopropylcarbonyl)amino, (2,2-difluorocyclopropylcarbonyl)amino, (2,2,3,3-tetramethylcyclopropylcarbonyl)amino, (cyclobutylcarbonyl)amino, (cyclopentylcarbonyl)amino, (cyclohexylcarbonyl)amino, cyclopropylmethylcarbonylamino, (tetrahydro-2H-pyran-4-ylcarbonyl)amino, (3-pyridylcarbonyl)amino, (4-pyridylcarbonyl)amino, (6-methyl-3-pyridylcarbonyl)amino, (6-fluoro-3-pyridylcarbonyl)amino, (6-chloro-3-pyridylcarbonyl)amino, (6-cyano-3-pyridylcarbonyl)amino, (6-(trifluoromethyl)-3-pyridylcarbonyl)amino, (5-pyrimidinylcarbonyl)amino, 4-morpholinylcarbonylamino, methoxyureido, ethylureido, 2-hydroxyethoxyethylureido, methoxycarbonylamino, ethoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, tert-butoxycarbonylamino, methylsulfonylamino, (cyclopropylsulfonyl)amino, phenylamino, 2-methylaminopyrimidin-4-ylamino, 2-chloropyrimidin-4-ylamino, 1,3-thiazol-2-ylamino and the like can be specifically mentioned.

In the compound (II), as the "substituent" for R^{2a}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{2a} is hydrogen atom.

In the compound (II), as the "substituent" for R^{3a}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{3a} is hydrogen atom.

In the compound (II), as the "substituent" for R^{4a}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{4a} is hydrogen atom.

As preferable examples of the compound (II), for example, the following compounds can be mentioned.

A compound wherein

ring Ya is

(1) C_{6-10} aryl optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) C_{1-4} alkyl,

(c) C_{1-4} alkoxy,

(d) amino optionally substituted by the substituents selected from

(i) C_{1-4} alkyl optionally substituted by a 5-membered aromatic heterocyclic group optionally substituted by 1 to 3 C_{1-4} alkyl,

(ii) C_{1-4} alkyl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl, and

(iii') 6-membered aromatic heterocyclic group,

(iii) C_{2-4} alkenyl-carbonyl optionally substituted by C_{6-10} aryl,

(iv) C_{2-4} alkynyl-carbonyl optionally substituted by C_{6-10} aryl,

(v) C_{3-6} cycloalkyl-carbonyl,

(vi) C_{3-6} cycloalkenyl-carbonyl,

(vii) C_{6-10} aryl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom, cyano, hydroxy and C_{3-6} cycloalkyl,

(iii') C_{3-6} cycloalkyl optionally substituted by cyano,

(iv') C_{1-4} alkoxy optionally substituted by 1 to 5 halogen atoms,

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

(vi') 5- or 6-membered heterocyclic group optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by 1 to 3 substituents selected from

(i') halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom, cyano, hydroxy and C_{1-4} alkoxy,

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

(iv') C_{6-10} aryl-C_{1-4} alkyl,

(v') C_{1-4} alkoxy optionally substituted by C_{1-4} alkoxy,

(vi') C_{1-4} alkylsulfonyl,

(vii') C_{1-4} alkyl-carbonyl, and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl,

(x) C_{1-4} alkyl-aminocarbonyl,

(xi) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms,

(xii) C_{1-4} alkoxy-aminocarbonyl,

(xiii) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl, and

(xv) 5-membered aromatic heterocyclyl-sulfonyl optionally

substituted by 1 to 3 C_{1-4} alkyl,

(e) C_{1-4} alkyl-aminocarbonyl optionally having C_{6-10} aryl,

(f) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from halogen atom and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) halogen, and

(b) C_{6-10} aryl-carbonylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms, or

(3) fused aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl, and

(b) C_{6-10} arylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms;

Xa is -O-, -S- or -NH- (more preferably -O- or -S-, particularly preferably -O-);

R^{1a} is

(1) amino,

(2) C_{1-4} alkyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) hydroxy,

(c) C_{1-4} alkoxy,

(d) C_{1-4} alkyl-carbonyloxy,

(e) C_{1-4} alkylamino,

(f) di-C_{1-4} alkylamino,

(g) C_{1-4} alkylsulfonyl, and

(h) 6-membered heterocyclic group optionally having 1 to 3 C_{1-4} alkyl,

(3) C_{2-4} alkenyl-carbonylamino optionally having C_{1-4} alkoxy,

(4) C_{2-4} alkynyl-carbonylamino,

(5) C_{3-6} cycloalkyl-carbonylamino optionally substituted by 1 to 4 substituents selected from

(a) halogen atom,

(b) hydroxy,

(c) C_{1-4} alkyl optionally having hydroxy,

(d) C_{1-4} alkoxy, and

(e) C_{1-4} alkoxy-carbonyl,

(6) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino,

(7) 6-membered heterocyclyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom,

(b) cyano, and

(c) C_{1-4} alkyl optionally having 1 to 3 halogen atoms,

(8) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from

(a) C_{1-4} alkyl optionally having 1 to 3 C_{1-4} alkoxy optionally having 1 to 3 hydroxy, and

(b) C_{1-4} alkoxy,

(9) C_{1-4} alkoxy-carbonylamino optionally substituted by 1 to 3 halogen atoms,

(10) C_{1-4} alkylsulfonylamino,

(11) C_{3-6} cycloalkylsulfonylamino,

(12) C_{6-10} arylamino, and

(13) heterocyclylamino optionally substituted by 1 to 3 substituents selected from

(a) halogen atom, and

(b) C_{1-4} alkylamino; and

R^{2a}, R^{3a} and R^{4a} are each hydrogen atom.

As the specific examples of the compound (II), for example, compounds of Examples 1 to 60, 64, 66 to 72, 74 to 123, 126 to 138 and 147 to 439 can be mentioned.

Of these, the following compounds or salts thereof are preferable.

N-{3-[(2-{[2-(methylamino)pyrimidin-4-yl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (Example 70);

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 97);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 111);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide (Example 114);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide (Example 117);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 148);

N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 149);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (Example 150);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 161);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide (Example 165);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide (Example 173);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide (Example 174);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide (Example 180);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide (Example 208);

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide (Example 254);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide (Example 287);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide (Example 289);

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide (Example 314);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (Example 319);

3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]benzamide (Example 330);

N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (Example 398);

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-(trifluoromethyl)benzamide (Example 427);

N-{6-[3-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (Example 431).

The compound represented by the formula (III) (hereinafter compound (III)) of the present invention is explained below.

As the "cyclic group" of the "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted", for ring Yb, those similar to

the groups exemplified as the "cyclic group" of the "optionally substituted cyclic group" for ring Y of compound (I) can be mentioned.

As the "cyclic group" of the "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted" for ring Yb, aromatic hydrocarbon group, aromatic heterocyclic group are preferable. As the aromatic hydrocarbon group, C_{6-14} aryl is preferable, C_{6-10} aryl is more preferable, and phenyl is particularly preferable. As the aromatic heterocyclic group, fused aromatic heterocyclic group is preferable, fused aromatic heterocyclic group formed by fusion of 5-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 or 2 heteroatoms selected from sulfur atom and nitrogen atom, besides carbon atoms, and benzene ring (e.g., benzothiazolyl, benzimidazolyl, indolyl etc.) is more preferable, and benzothiazolyl (e.g., 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-5-yl, benzimidazol-6-yl), indolyl (e.g., indol-4-yl, indol-5-yl, indol-6-yl) and the like are particularly preferable.

The "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted" for ring Yb is substituted, at its any substitutable position, by optionally substituted amino that may further have 1 to the acceptable maximum number, preferably 1 to 5, more preferably 1 to 3, substituents at any substitutable position(s). Where the cyclic group is substituted by two or more substituents, the substituents may be the same or different.

As the "optionally substituted amino" of the "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted" for ring Yb, those similar to the group exemplified as the "optionally substituted amino" (Substituent Group (1)(x)) among the groups exemplified as the "substituent" of the "optionally substituted cyclic group" for ring Y of compound (I). As the substituent that may be used for the further substitution, those similar to

the group exemplified as the "substituent" of the "optionally substituted cyclic group" for ring Y of compound (I) can be mentioned.

As the "substituent" of the "optionally substituted amino" in the "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted" for ring Yb, the "optionally substituted aminocarbonyl" of the aforementioned Substituent Group (1)(viii), and the "acyl" of the aforementioned Substituent Group (1)(ix) are preferable among the substituents referenced and exemplified above. Of these, (1) C_{6-18} aryl-aminocarbonyl (e.g., phenylaminocarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-trifluoromethylphenylaminocarbonyl, 4-trifluoromethylphenylaminocarbonyl etc.), (2) C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylcarbonyl, 3-trifluoromethylphenylcarbonyl etc.) and (3) 5- or 6-membered monocyclic aromatic heterocycle (e.g., pyrazolyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) and the like (specific examples: 1,3-dimethyl-1H-pyrazole-5-carbonyl etc.), and the like are preferable.

Of the substituents referenced and exemplified above, the "substituent" by which the "cyclic group" is optionally substituted is preferably

(1) halogen atom (e.g., fluorine, chlorine, bromine, iodine),
(2) optionally substituted alkyl,
(3) optionally substituted alkoxy,
(4) optionally substituted aminocarbonyl,
(5) optionally substituted amino,

and the like.

Of these,

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

(2) optionally substituted alkyl,

(3) optionally substituted amino,

and the like are preferable.

Hereinafter the above-mentioned preferable examples of the substituent by which the cyclic group is further substituted of the "cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted" for ring Yb are exemplified in detail.

(1) As the halogen atom, fluorine, chlorine, bromine and the like are preferable.

(2) As the optionally substituted alkyl, optionally substituted C_{1-8} alkyl is preferable, optionally substituted C_{1-4} alkyl is more preferable, and unsubstituted C_{1-4} alkyl is much more preferable. Specifically, methyl, ethyl and the like are preferable.

(3) As the optionally substituted alkoxy, optionally substituted C_{1-8} alkoxy is preferable, optionally substituted C_{1-4} alkoxy is more preferable, and unsubstituted C_{1-4} alkoxy is more preferable. Specifically methoxy and the like are preferable.

(4) As the "substituent" for the optionally substituted aminocarbonyl, for example, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{3-8} cycloalkynyl, C_{6-18} aryl, heterocyclic group and the like, each of which is optionally substituted, are preferable, optionally substituted heterocyclic group and the like are more preferable, and optionally substituted aromatic heterocyclic group is particularly preferable. As the optionally substituted aminocarbonyl, aminocarbonyl optionally substituted by aromatic heterocyclic group optionally substituted C_{1-4} alkyl and the like are preferable, and 1,3-dimethyl-1H-pyrazol-5-yl-aminocarbonyl and the like are specifically preferable.

(5) As the "substituent" for the optionally substituted amino, optionally substituted aminocarbonyl, acyl and the like are

preferable.

As the optionally substituted amino, unsubstituted amino; amino optionally substituted by optionally substituted aminocarbonyl; amino optionally substituted by acyl and the like are preferable.

As the optionally substituted aminocarbonyl, C_{1-8} alkyl-aminocarbonyl, C_{6-18} aryl-aminocarbonyl, C_{6-18} aryl-C_{1-4} alkyl-aminocarbonyl, heterocyclyl-aminocarbonyl, C_{3-8} cycloalkyl-aminocarbonyl and the like, each of which is optionally substituted, are preferable. Of these, optionally substituted C_{1-8} alkyl-aminocarbonyl and the like are preferable, and optionally substituted C_{1-4} alkyl-aminocarbonyl is more preferable. Specifically, ethylaminocarbonyl and the like are preferable. Alternatively, optionally substituted C_{6-18} aryl-aminocarbonyl and the like are preferable, optionally substituted C_{6-10} aryl-aminocarbonyl is more preferable, and those wherein the aryl moiety is unsubstituted phenyl; phenyl optionally substituted by halogen atom (e.g., fluorine, chlorine), optionally halogenated C_{1-4} alkyl (e.g., trifluoromethyl) and the like, and the like are particularly preferable. Specifically, phenylaminocarbonyl (anilinocarbonyl), 3-trifluoromethylphenylaminocarbonyl (3-trifluoromethylanilinocarbonyl), 4-trifluoromethylphenylaminocarbonyl (4-trifluoromethylanilinocarbonyl) and the like are preferable.

As the acyl, C_{1-8} alkyl-carbonyl, C_{6-18} aryl-carbonyl, C_{6-18} aryl-C_{1-4} alkyl-carbonyl, C_{1-8} alkylsulfonyl, C_{6-18} aryl-sulfonyl, heterocyclyl-carbonyl, heterocyclyl-sulfonyl, C_{3-8} cycloalkyl-carbonyl and the like, each of which is optionally substituted, are preferable. Of these, C_{1-8} alkyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{6-18} aryl-carbonyl, heterocyclyl-carbonyl, each of which is optionally substituted, are preferable.

As the optionally substituted C_{1-8} alkyl-carbonyl, C_{1-4} alkyl-carbonyl is preferable, and tert-butylcarbonyl and the like are specifically preferable.

As the optionally substituted C_{3-8} cycloalkyl-carbonyl, C_{3-6} cycloalkyl-carbonyl is preferable, and cyclopropylcarbonyl, cyclohexylcarbonyl and the like are specifically preferable.

As the optionally substituted C_{6-18} aryl-carbonyl, optionally substituted C_{6-10} aryl-carbonyl is preferable, and optionally substituted phenyl-carbonyl is more preferable. As the "substituent" for the optionally substituted C_{6-18} aryl-carbonyl, halogen atom (e.g., fluorine, chlorine), optionally halogenated C_{1-4} alkyl (e.g., trifluoromethyl) and the like are preferable. As the optionally substituted C_{6-18} aryl-carbonyl, those wherein the "aryl" moiety is unsubstituted phenyl; phenyl optionally substituted by halogen atom (e.g., fluorine, chlorine), optionally halogenated C_{1-4} alkyl (e.g., trifluoromethyl) and the like, and the like are preferable. Specifically, phenylcarbonyl(benzoyl), 3-trifluoromethylphenylcarbonyl, 3-fluorophenylcarbonyl, 3-chlorophenylcarbonyl and the like are preferable.

As the "heterocycle" moiety for the optionally substituted heterocyclyl-carbonyl, 5- or 6-membered monocyclic aromatic heterocyclic group containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms and the like are preferable, and pyridyl, furyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, pyridazinyl and the like are specifically preferable. As the "substituent" for the optionally substituted heterocyclyl-carbonyl, optionally halogenated C_{1-4} alkyl (e.g., methyl, trifluoromethyl) and the like are preferable.

As the optionally substituted heterocyclyl-carbonyl, the above-mentioned 5- or 6-membered monocyclic aromatic heterocyclyl-carbonyl and the like optionally substituted by optionally halogenated C_{1-4} alkyl and the like are preferable. specifically, 3-pyridylcarbonyl, 2-furylcarbonyl, 2,5-dimethylfuran-3-carbonyl, 3-methylthiophene-2-carbonyl, 4-methyl-1,2,3-thiadiazole-5-carbonyl, isoxazole-5-carbonyl, 1,3-

dimethyl-1H-pyrazole-5-carbonyl, 3-methylisoxazole-5-carbonyl, 5-methylisoxazole-3-carbonyl, 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbonyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonyl, 2,4-dimethyl-1,3-thiazole-5-carbonyl, 2,5-dimethyl-1,3-oxazole-4-carbonyl, 1-methyl-1H-pyrazole-5-carbonyl, 1,5-dimethyl-1H-pyrazole-3-carbonyl, 3,5-dimethylisoxazole-4-carbonyl, 1-methyl-1H-1,2,3-triazole-5-carbonyl, 1-methyl-1H-1,2,3-triazole-4-carbonyl, 1-methyl-1H-imidazole-2-carbonyl, 1-methyl-1H-imidazole-5-carbonyl and the like are preferable.

Preferably, ring Yb is

(1) C_{6-14} aryl (e.g., phenyl etc.) substituted by amino optionally substituted by substituent selected from (1') C_{6-18} aryl-aminocarbonyl (e.g., phenylaminocarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-trifluoromethylphenylaminocarbonyl, 4-trifluoromethylphenylaminocarbonyl etc.), (2') C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylcarbonyl, 3-trifluoromethylphenylcarbonyl etc.), and (3') 5- or 6-membered monocyclic aromatic heterocycle (e.g., pyrazolyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) and the like (specific examples: 1,3-dimethyl-1H-pyrazole-5-carbonyl etc.), wherein said C_{6-14} aryl is optionally further substituted by 1 or 2 substituents selected from

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

(ii) C_{1-4} alkyl (e.g., methyl etc.),

(iii) C_{1-4} alkoxy (e.g., methoxy etc.),

(iv) aminocarbonyl substituted by aromatic heterocyclic group (e.g., pyrazolyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl etc.), and

(v) amino optionally substituted by substituent selected from

(a) C_{1-4} alkyl-carbonyl (e.g., tert-butylcarbonyl etc.),

(b) C_{3-6} cycloalkyl-carbonyl (e.g., cyclopropylcarbonyl, cyclohexylcarbonyl etc.),

(c) C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by substituent selected from halogen atom (e.g., fluorine, chlorine) and optionally halogenated C_{1-4} alkyl (e.g., trifluoromethyl) (specific examples: phenylcarbonyl (benzoyl), 3-trifluoromethylphenylcarbonyl, 3-fluorophenylcarbonyl, 3-chlorophenylcarbonyl etc.), and

(d) 5- or 6-membered monocyclic aromatic heterocyclic group (e.g., pyridyl, furyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, pyridazinyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) and the like (specific examples: 3-pyridylcarbonyl, 2-furylcarbonyl, 2,5-dimethylfuran-3-carbonyl, 3-methylthiophene-2-carbonyl, 4-methyl-1,2,3-thiadiazole-5-carbonyl, isoxazole-5-carbonyl, 1,3-dimethyl-1H-pyrazole-5-carbonyl, 3-methylisoxazole-5-carbonyl, 5-methylisoxazole-3-carbonyl, 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carbonyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonyl, 2,4-dimethyl-1,3-thiazole-5-carbonyl, 2,5-dimethyl-1,3-oxazole-4-carbonyl, 1-methyl-1H-pyrazole-5-carbonyl, 1,5-dimethyl-1H-pyrazole-3-carbonyl, 3,5-dimethylisoxazole-4-carbonyl, 1-

methyl-1H-1,2,3-triazole-5-carbonyl, 1-methyl-1H-1,2,3-triazole-4-carbonyl, 1-methyl-1H-imidazole-2-carbonyl, 1-methyl-1H-imidazole-5-carbonyl etc.), and the like,

(2) fused aromatic heterocycle (e.g., benzothiazolyl (e.g., 5-benzothiazolyl, 6-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-5-yl, benzimidazol-6-yl), indolyl (e.g., indol-4-yl, indol-5-yl, indol-6-yl) etc.) substituted by amino optionally substituted by (1') C_{6-18} aryl-aminocarbonyl (e.g., phenylaminocarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-trifluoromethylphenylaminocarbonyl, 4-trifluoromethylphenylaminocarbonyl etc.), (2') C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylcarbonyl, 3-trifluoromethylphenylcarbonyl etc.), and (3') 5- or 6-membered monocyclic aromatic heterocycle (e.g., pyrazolyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) and the like (specific examples: 1,3-dimethyl-1H-pyrazole-5-carbonyl etc.), wherein said fused aromatic heterocycle further has 1 or 2 C_{1-4} alkyl (e.g., methyl etc.), and the like.

Particularly, C_{6-14} aryl (e.g., phenyl etc.) substituted by amino optionally substituted by (1) C_{6-18} aryl-aminocarbonyl (e.g., phenylaminocarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-trifluoromethylphenylaminocarbonyl, 4-trifluoromethylphenylaminocarbonyl etc.), (2) C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine)

(specific examples: phenylcarbonyl, 3-trifluoromethylphenylcarbonyl etc.), and (3) 5- or 6-membered monocyclic aromatic heterocycle (e.g., pyrazolyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) and the like (specific examples: 1,3-dimethyl-1H-pyrazole-5-carbonyl etc.), wherein said C_{6-14} aryl does not have further substituent, is preferable.

As ring Yb, 3-aminophenyl, 4-aminophenyl, 3-{[(ethylamino)carbonyl]amino}phenyl, 4-{[(phenylamino)carbonyl]amino}phenyl, 3-{[(phenylamino)carbonyl]amino}phenyl, 3-({[3-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-({[4-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-[(tert-butylcarbonyl)amino]phenyl, 3-[(cyclopropylcarbonyl)amino]phenyl, 3-[(cyclohexylcarbonyl)amino]phenyl, 3-[(phenylcarbonyl)amino]phenyl, 3-{[3-(trifluoromethylphenyl)carbonyl]amino}phenyl, 3-{[3-(fluorophenyl)carbonyl]amino}phenyl, 3-{[3-(chlorophenyl)carbonyl]amino}phenyl, 3-{[3-(pyridyl)carbonyl]amino}phenyl, 3-{[2-(furyl)carbonyl]amino}phenyl, 3-{[3-(2,5-dimethylfuran)carbonyl]amino}phenyl, 3-{[2-(3-methylthiophene)carbonyl]amino}phenyl, 3-{[5-(4-methyl-1,2,3-thiadiazole)carbonyl]amino}phenyl, 3-{[5-(isoxazole)carbonyl]amino}phenyl, 3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[5-(3-methylisoxazole)carbonyl]amino}phenyl, 3-{[3-(5-methylisoxazole)carbonyl]amino}phenyl, 3-({5-[1-methyl-3-(trifluoromethyl)-1H-pyrazole]carbonyl}amino)phenyl, 5-methyl-2-(trifluoromethyl)-3-furancarbonylaminophenyl, 3-{[5-(2,4-dimethyl-1,3-thiazole)carbonyl]amino}phenyl, 3-{[4-(2,5-dimethyl-1,3-oxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-pyrazole)carbonyl]amino}phenyl, 3-{[3-(1,5-dimethyl-1H-

pyrazole)carbonyl]amino}phenyl, 3-{[4-(3,5-dimethylisoxazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[4-(1-methyl-1H-1,2,3-triazole)carbonyl]amino}phenyl, 3-{[2-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 3-{[5-(1-methyl-1H-imidazole)carbonyl]amino}phenyl, 5-amino-2-methylphenyl, 3-amino-2-methylphenyl, 3-amino-4-methylphenyl, 3-amino-4-chlorophenyl, 5-amino-2-chlorophenyl, 5-amino-2-methoxyphenyl, 6-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 2-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-methyl-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-chloro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-fluoro-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 6-methoxy-3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-chloro-3-(cyclopropylcarbonylamino)phenyl, 3-amino-4-fluorophenyl and the like can be specifically mentioned. Of these, 3-aminophenyl, 4-aminophenyl, 4-{[(phenylamino)carbonyl]amino}phenyl, 3-{[(phenylamino)carbonyl]amino}phenyl, 3-({[3-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-({[4-(trifluoromethylphenyl)amino]carbonyl}amino)phenyl, 3-{[5-(1,3-dimethyl-1H-pyrazole)carbonyl]amino}phenyl, 4-fluoro-3-{[4-(1-ethyl-3-methyl-1H-pyrazole)carbonyl]amino}phenyl and the like are preferable.

In the compound (III), as the substituent for R^b of NR^b defined by Xb, those similar to the substituent selected from the aforementioned Substituent Group (1) can be mentioned.

As the substituent for R^b, optionally substituted hydrocarbon group and the like are preferable.

Xb is preferably -O-, -S- or -NH-, and particularly preferably -O-.

As the "substituent (except for optionally substituted amino)" for R^{1b}, those similar to the group of the substituents of the aforementioned Substituent Group (1) except for the

"optionally substituted amino" can be mentioned. Of these, optionally substituted aminocarbonyl and the like are preferable.

Preferable R^{1b} are

(1) hydrogen atom,

(2) optionally substituted aminocarbonyl,

(3) optionally substituted alkyl,

(4) optionally esterified carboxy,

and the like.

Of these, more preferable R^{1b} are

(1) hydrogen atom,

(2) aminocarbonyl optionally substituted by optionally substituted alkyl,

(3) alkyl optionally substituted by hydroxy,

(4) carboxy,

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

and the like.

Hereinafter the preferable examples of the "substituent" for R^{1b} are explained in detail.

As the "alkyl" of the "optionally substituted alkyl" of the above-mentioned (2), C_{1-8} alkyl and the like are preferable, C_{1-4} alkyl and the like are more preferable, and methyl and the like are specifically preferable.

As the "alkyl" of the "alkyl optionally substituted hydroxy" of the above-mentioned (3), C_{1-8} alkyl and the like are preferable, C_{1-4} alkyl and the like are more preferable, and methyl and the like are specifically preferable.

As R^{1b}, hydroxymethyl, $-C(O)NH-CH_3$, hydrogen atom, carboxy, ethoxycarbonyl and the like can be specifically mentioned.

In the compound (III), as the "substituent" for R^{2b}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{2b} is hydrogen atom.

In the compound (III), as the "substituent" for R^{3b}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{3b} is hydrogen atom.

In the compound (III), as the "substituent" for R^{4b}, those similar to the substituents of the aforementioned Substituent Group (1) can be mentioned.

Of these, preferable R^{4b} is hydrogen atom.

As the preferable example of the compound (III), for example, the following compound can be mentioned.

A compound wherein

ring Yb is C_{6-14} aryl (e.g., phenyl etc.) substituted by amino optionally substituted by (1) C_{6-18} aryl-aminocarbonyl (e.g., phenylaminocarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylaminocarbonyl, 3-trifluoromethylphenylaminocarbonyl, 4-trifluoromethylphenylaminocarbonyl etc.), (2) C_{6-18} aryl-carbonyl (e.g., phenylcarbonyl etc.) optionally substituted by C_{1-4} alkyl (e.g., methyl) optionally having halogen atom (e.g., fluorine) (specific examples: phenylcarbonyl, 3-trifluoromethylphenylcarbonyl etc.), and (3) 5- or 6-membered monocyclic aromatic heterocycle (e.g., pyrazolyl etc.)-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by C_{1-4} alkyl (e.g., methyl) and the like (specific examples: 1,3-dimethyl-1H-pyrazole-5-carbonyl etc.), wherein said C_{6-14} aryl does not have further substituent;

Xb is -O-, -S- or -NH- (preferably -O-);

R^{1b} is

(1) hydrogen atom,

(2) $-C(O)NH-CH_3$, or

(3) hydroxymethyl; and

R^{2b}, R^{3b} and R^{4b} are each hydrogen atom.

Specific examples of the compound (III) include Examples 61 to 63, 65, 73, 124, 125, 139 to 146, 440, 442 and 445.

Examples of the salt of compounds (I) - (IV) include a

metal salt, an ammonium salt, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid and the like. Preferable examples of the metal salt include alkali metal salt such as sodium salt, potassium salt and the like; alkaline earth metal salt such as calcium salt, magnesium salt, barium salt and the like; aluminum salt and the like. Preferable examples of the salt with the organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine and the like. Preferable examples of the salt with the 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 the 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 the basic amino acid include a salt with arginine, lysine, ornithine and the like. Preferable examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid and the like.

Of these, pharmaceutically acceptable salt is preferable. For example, where the compound has an acidic functional group, inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt etc.) and the like, ammonium salt and the like can be mentioned. Alternatively, where the compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like, or a salt with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, p-

toluenesulfonic acid and the like can be mentioned.

Hereinafter, the production methods of compounds (I) - (IV) of the present invention are explained.

The compounds (I) - (IV) of the present invention can be obtained, for example, according to the methods shown in the following Schemes or a method analogous thereto and the like (while the production methods of compounds (II) and (III) are exemplarily shown below, compounds (I) and (IV) can also be obtained according to a method shown by a similar Scheme or a method analogous thereto and the like).

Each compound in the following Schemes includes salts, and as such salts, for example, those similar to the salts of the compounds (I) - (IV) and the like can be used.

The compound obtained in each step can be used in the form of a reaction mixture or a crude product for the next reaction. In addition, the compound can be isolated from a reaction mixture according to a conventional method, and can be easily purified by a separation means such as recrystallization, distillation, chromatography and the like.

Schematic reaction formulas are shown in the following, wherein each symbol in the compounds is as defined above.

Moreover, the respective terms in the production methods mean the following.

The "halogen atom" means fluorine, chlorine, bromine or iodine.

The "optionally substituted alkylsulfonyl" means C_{1-6} alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl etc.) optionally substituted by substituent(s) selected from halogen atom, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, trifluoromethyl) and nitro.

The "optionally substituted alkylsulfonyloxy" means C_{1-6} alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy etc.) optionally substituted by substituent(s) selected from halogen atom, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, trifluoromethyl) and nitro.

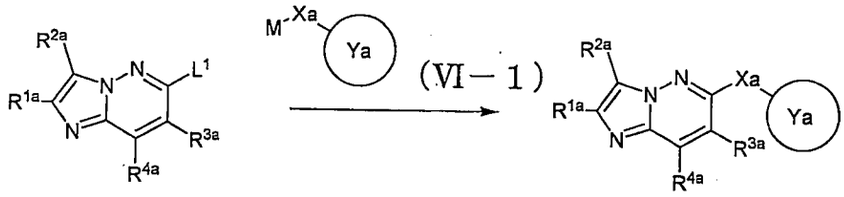
The "optionally substituted arylsulfonyloxy" means C_{6-14} arylsulfonyloxy (e.g., phenylsulfonyloxy etc.) optionally substituted by substituent(s) selected from halogen atom, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, trifluoromethyl) and nitro.

The "optionally substituted aryloxy" means C_{6-14} aryloxy (e.g., phenyloxy etc.) optionally substituted by substituent(s) selected from halogen atom, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, trifluoromethyl) and nitro.

The "optionally substituted alkoxy" means C_{1-6} alkoxy (e.g., methoxy, ethoxy etc.) optionally substituted by substituent(s) selected from halogen atom, optionally halogenated C_{1-6} alkyl (e.g., methyl, ethyl, trifluoromethyl) and nitro.

[Production Method 1]

(Scheme 1)



(V−1) (II)

wherein L^1 is a leaving group, M is a hydrogen atom or a metal atom, and other symbols are as defined above.

As the leaving group for L^1, for example, a halogen atom, optionally substituted alkylsulfonyl, optionally substituted alkylsulfonyloxy, optionally substituted arylsulfonyloxy and the like can be used.

M is mainly a hydrogen atom, but may be an alkali metal such as lithium, sodium, potassium, cesium and the like, or an alkaline earth metal such as magnesium, calcium and the like.

Compound (II) can be produced by reacting compound (V-1) with compound (VI-1). Compound (VI-1) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-1). A base may be added as necessary. As the base,

inorganic base or organic base and the like can be used. Specifically, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium diisopropylamide and the like can be mentioned. The base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-1). This reaction is advantageously carried out using a solvent inert to the reaction. While the solvent is not particularly limited as long as the reaction proceeds, for example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like, hydrocarbons such as benzene, toluene, cyclohexane, hexane and the like, esters such as ethyl acetate and the like, ketones such as acetone, methyl ethyl ketone and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone and the like, halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane and the like, nitriles such as acetonitrile and the like, sulfoxides such as dimethylsulfoxide and the like, pyridine, water and the like can be used alone or in mixture. While the reaction time varies depending on the kind of reagent and solvent to be used, it is generally 1 min to 200 hr, preferably 10 min to 100 hr. While the reaction temperature varies depending on the kind of reagent and solvent to be used, it is generally -100 to 250°C, preferably -78 to 200°C. The reaction can be carried out using a microwave synthesizer.

A compound within the scope of the present invention can also be produced by applying a means known *per se* to the obtained compound (II) of the present invention for introduction of substituents and conversion of functional groups. For

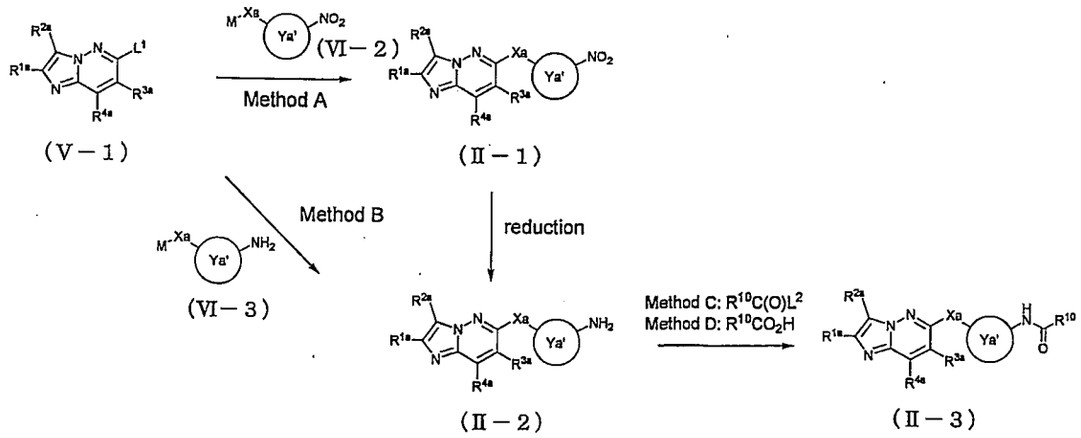
conversion of substituents, a known conventional method can be used. For example, conversion to carboxy by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination of nitro by reduction, alkylation of hydroxy, substitution and amination of hydroxy and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can also be produced.

Compound (VI-1) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 2]

Compound (II) wherein Ya is substituted by optionally substituted amide, which is further optionally substituted, can also be produced for example, according to a method shown in Scheme 2. Compounds (II-1), (II-2) and (II-3) are encompassed in compound (II).

(Scheme 2)



wherein L^2 is a leaving group, Ya' is a cyclic group of Ya, R^{10} is a group shown by the moiety of acyl except for carbonyl moiety, which acyl is exemplified as the substituent of the "optionally substituted amino" which is one of the substituents of the "optionally substituted cyclic group" for ring Y of compound (I), and other symbols are as defined above.

As the leaving group for L^2, for example, halogen atom, optionally substituted aryloxy, optionally substituted alkoxy, 1-imidazolyl and the like can be used.

In Method A, compound (II-2) is produced by reacting compound (V-1) and compound (VI-2) in the presence of a base, and reducing the nitro of compound (II-1). Compound (VI-2) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-1). As the base, those similar to the base exemplified in Scheme 1 can be used. The base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-1). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-2) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a

method analogous thereto. The obtained compound (II-1) can be used as a reaction mixture or as a crude product in the next reaction. It can be isolated from a reaction mixture according to a conventional method. The reduction of nitro can be carried out according to a method known *per se*, for example, the methods described in the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

In Method B, compound (II-2) is produced by reacting compound (V-1) with compound (VI-3) in the presence of a base. Compound (VI-3) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-1). As the base, those similar to the base exemplified in Scheme 1 can be used. The base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-1). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-3) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method C, compound (II-3) is produced by reacting compound (II-2) with a compound represented by the formula $R^{10}C(O)L^2$. The compound represented by the formula $R^{10}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-2). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to

200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $R^{10}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

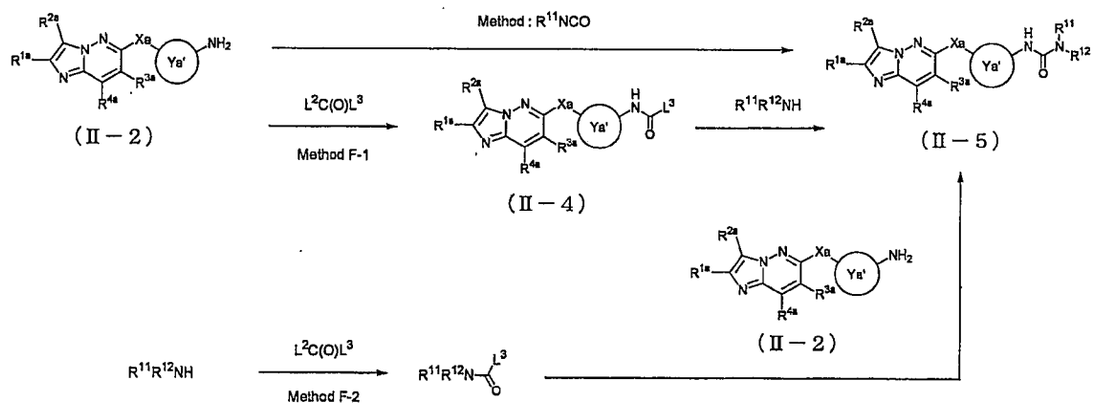
In Method D, (II-3) is produced by reacting compound (II-2) with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent. When Compound (II-2) is reacted with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{10}CO_2H$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. The condensing agent is used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound (II-2). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. The condensation promoter is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). This reaction may proceed more smoothly when a base is added. As the base, those similar to the bases exemplified in Scheme 1 can be used. The base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is

generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{10}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 3]

In compound (II), when Ya is substituted by optionally substituted ureido, and optionally further substituted, for example, the compound can also be produced by the method shown in Scheme 3. Compounds (II-2), (II-4) and (II-5) are encompassed in compound (II).

(Scheme 3)



wherein L^3 is a leaving group, $-NR^{11}R^{12}$ is a group shown by the moiety of optionally substituted aminocarbonyl except for carbonyl moiety, which optionally substituted aminocarbonyl is exemplified as the substituent of the "optionally substituted amino" which is one of the substituents of the "optionally substituted cyclic group" for ring Y of compound (I), and other symbols are as defined above.

As the leaving group for L^3, for example, a halogen atom,

optionally substituted aryloxy, optionally substituted alkoxy, 1-imidazolyl and the like can be used.

In Method E, compound (II-5) is produced by reacting compound (II-2) with the isocyanate derivative ($R^{11}NCO$). Isocyanate derivative ($R^{11}NCO$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). A base may be used in 0.01 to 10 equivalents, preferably 0.01 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Isocyanate derivative ($R^{11}NCO$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method F-1, compound (II-5) is produced by first reacting compound (II-2) with a compound represented by the formula $L^2C(O)L^3$ to give compound (II-4), and then reacting compound (II-4) with amine derivative ($R^{11}R^{12}NH$). The compound represented by the formula $L^2C(O)L^3$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $L^2C(O)L^3$ may be commercially available, or can be produced by a method known *per se*. The

obtained compound (II-4) can be used in the form of a reaction mixture or a crude product for the next reaction. It can also be used for the next reaction after isolation and purification from a reaction mixture according to a conventional method. The amine derivative ($R^{11}R^{12}NH$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-4). In addition, a base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The amine derivative ($R^{11}R^{12}NH$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

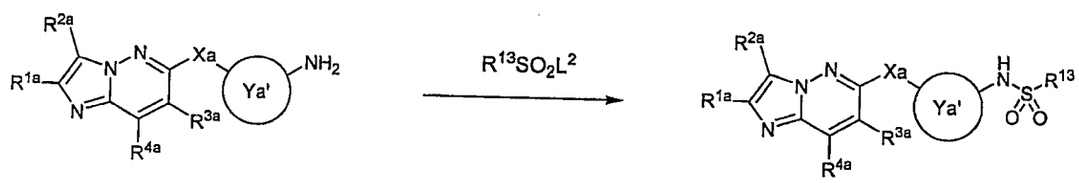
In Method F-2, compound (II-5) is produced by first reacting a compound represented by the formula $R^{11}R^{12}NH$ with a compound represented by the formula $L^2C(O)L^3$, successively compound (II-2) to give compound (II-5). The compound represented by the formula $L^2C(O)L^3$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to amine derivative ($R^{11}R^{12}NH$). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The amine derivative ($R^{11}R^{12}NH$) and the compound represented by the formula $L^2C(O)L^3$ may be commercially available,

or can be produced by a method known *per se* for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto. The obtained compound represented by the formula $R^{11}R^{12}NC(O)L^3$ can be used in the form of a reaction mixture or a crude product for the next reaction. It can also be used for the next reaction after isolation and purification from a reaction mixture according to a conventional method. The compound (II-2) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to the compound represented by the formula $R^{11}R^{12}NC(O)L^3$. In addition, a base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C.

[Production Method 4]

In compound (II), when Ya is substituted by optionally substituted sulfonamide, and optionally further substituted, for example, the compound can also be produced by the method shown in Scheme 4. Compound (II-6) is encompassed in compound (II).

(Scheme 4)



(II − 2) (II − 6)

wherein R^{13} is a group shown by the moiety of acyl except for carbonyl moiety, which acyl is exemplified as the substituent of the "optionally substituted amino" which is one of the substituents of the "optionally substituted cyclic group" for

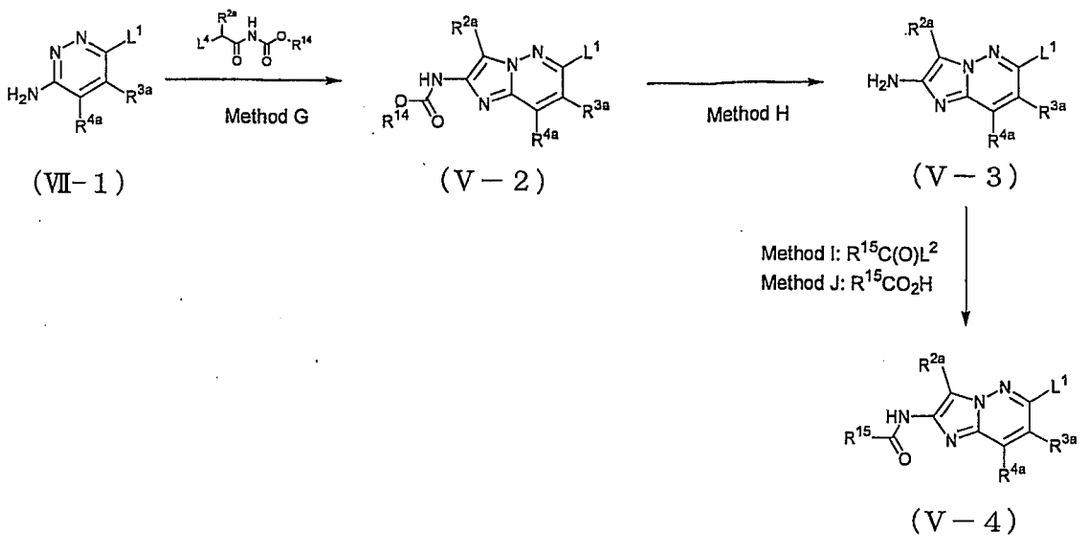
ring Y of compound (I), and other symbols are as defined above.

Compound (II-6) can be produced by reacting compound (II-2) with a reactive derivative of sulfonic acid ($R^{13}SO_2L^2$). The reactive derivative of sulfonic acid ($R^{13}SO_2L^2$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-2). In the present method, the reaction is generally carried out in the presence of a base, though it is not always essential. As the base, those similar to the base exemplified in Scheme 1 can be used. A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The reactive derivative of sulfonic acid ($R^{13}SO_2L^2$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 5]

Compound (V-1) shown in Schemes 1 and 2 can be obtained, for example, by the method shown in the following Scheme or a method analogous thereto and the like. Compounds (V-2), (V-3) and (V-4) are encompassed in compound (V-1).

(Scheme 5)



(VII-1) (V-2) (V-3) (V-4)

wherein L^4 is a leaving group, R^{14} is an optionally substituted hydrocarbon group, R^{15} is an optionally substituted hydrocarbon group or optionally substituted cyclic group, and other symbols are as defined above.

As the leaving group for L^4, chlorine, bromine, iodine and the like can be used.

Examples of the optionally substituted hydrocarbon group for R^{14} include methyl, ethyl, propyl, isopropyl, tert-butyl and the like.

Examples of the optionally substituted hydrocarbon group, optionally substituted cyclic group for R^{15} include a group shown by the moiety of acyl except for carbonyl group, which acyl is exemplified as the substituent of the "optionally substituted amino" for R^{1a} of compound (II) and the like.

In Method G, compound (V-2) is produced by reacting compound (VII-1) with an acetylcarbamic acid derivative ($L^4CHR^{2a}C(O)NHC(O)OR^{14}$). The acetylcarbamic acid derivative is used in 0.1 to 10 equivalents, preferably 0.3 to 5 equivalents, relative to compound (VII-1). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 5 equivalents, relative to compound (VII-1). As the base, inorganic base or organic base and the like can be used, specifically, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, disodium hydrogenphosphate, dipotassium

hydrogenphosphate, calcium hydrogenphosphate, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline and the like can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The acetylcarbamic acid derivative ($L^4CHR^{2a}C(O)NHC(O)OR^{14}$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Journal of Organic Chemistry, 50, 2480-2499 (1985)" and the like or a method analogous thereto.

In Method H, compound (V-3) is produced by treating compound (V-2) with a base or acid. As the base, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide, barium hydroxide and the like can be mentioned. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (V-2). As the acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, trifluoroacetic acid and the like can be used. An acid is used in 0.1 to 20 equivalents, preferably 0.3 to 10 equivalents, relative to compound (V-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used.

In Method I, compound (V-4) is produced by reacting compound (V-3) with a compound represented by the formula $R^{15}C(O)L^2$. The compound represented by the formula $R^{15}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-3). As the base, those similar to the base exemplified in Scheme 1 can be used. A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (V-3). This reaction is advantageously

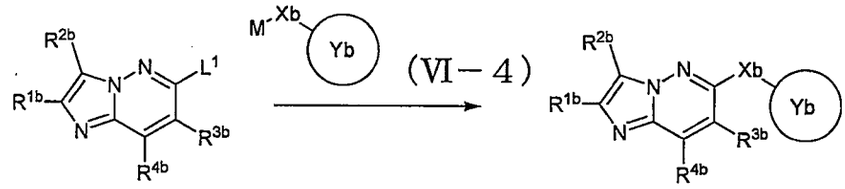
carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $R^{15}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method J, (V-4) is produced by reacting compound (V-3) with carboxylic acid ($R^{15}CO_2H$) in the presence of a condensing agent. When compound (V-3) is reacted with carboxylic acid ($R^{15}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{15}CO_2H$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-3). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound (V-3). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-3). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. These bases are used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (V-3).

This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{15}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 6]

(Scheme 6)



(V−5) (III)

wherein each symbol is as defined above.

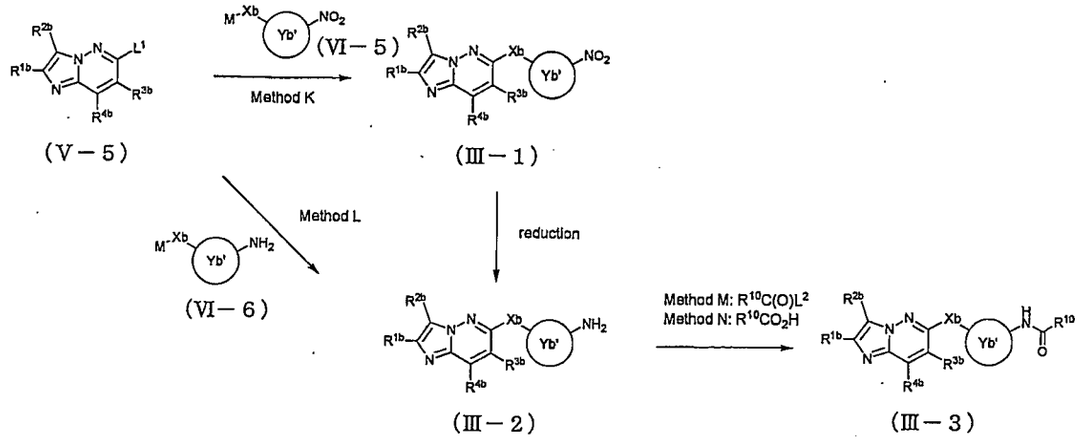
Compound (III) can be produced by reacting compound (V-5) with compound (VI-4). Compound (VI-4) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to Compound (V-5). Where necessary, a base may be added. As the base, those similar to the base exemplified in Scheme 1 can be used. These bases are used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-5). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time varies depending on the kind of reagent and solvent to be used, and is generally 1 min to 200 hr, preferably 10 min to 100 hr. While the reaction temperature varies depending on the kind of reagent and solvent to be used, generally -100°C to 250°C, preferably -78°C to 200°C. The reaction may be carried out using a microwave synthesizer.

A compound within the scope of the present invention can also be produced by applying a means known *per se* to the obtained compound (III) of the present invention for introduction of substituents and conversion of functional groups. For conversion of substituents, a known conventional method can be used. For example, conversion to carboxy by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, alkylation of hydroxy, substitution and amination of hydroxy and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby the compound within the scope of the present invention can also be produced.

Compound (VI-4) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production method 7]

In compound (III), when the substituent of optionally substituted amino for Yb is acyl, for example, the compound can also be produced by the method shown in Scheme 7. Compounds (III-1), (III-2) and (III-3) are encompassed in compound (III). (Scheme 7)



wherein Yb' is a cyclic group of Yb, and other symbols are as defined above.

In Method K, compound (III-2) is produced by first reacting compound (V-5) with compound (VI-5) in the presence of a base to give compound (III-1), and then reducing nitro of compound (III-1). Compound (VI-5) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-5). As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-5). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-5) may be commercially available, or can be produced according to a method known *per se*, for example, the method described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto. The obtained compound (III-1) can be used in the form of a reaction mixture or a crude product for the next reaction. Alternatively, it may be used for the next reaction after isolation and purification from the reaction mixture according to a conventional method. The reduction of nitro can be carried out by a method known *per se*, for example, the method described

in the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

In Method L, compound (III-2) is produced by reacting compound (V-5) with compound (VI-6) in the presence of a base. Compound (VI-6) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-5). As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 1 to 5 equivalents, preferably 1 to 2 equivalents, relative to compound (V-5). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-6) may be commercially available, or can be produced according to a method known *per se*, for example, the method described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like, or a method analogous thereto.

In Method M, compound (III-3) is produced by reacting compound (III-2) with a compound represented by the formula $R^{10}C(O)L^2$. The compound represented by the formula $R^{10}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (III-2). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $R^{10}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic

Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

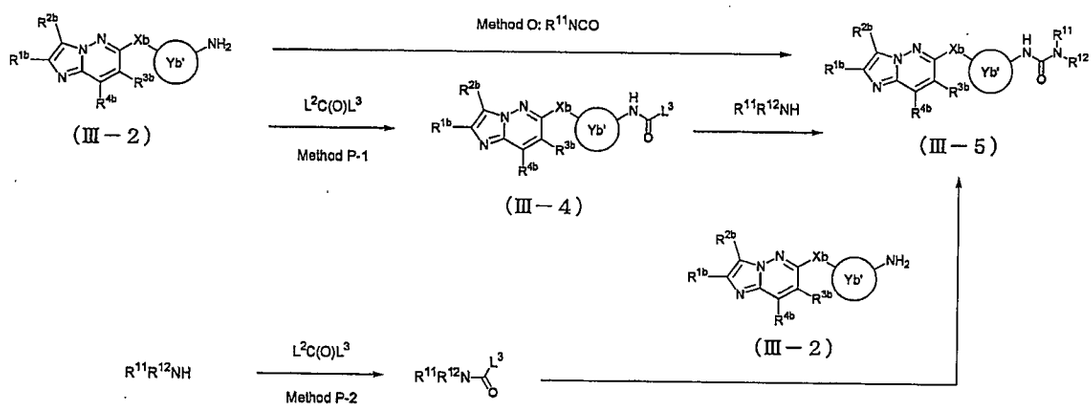
In Method N, compound (III-3) is produced by reacting compound (III-2) with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent. When Compound (III-2) is reacted with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{10}CO_2H$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound (III-2). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (III-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{10}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic

Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 8]

Compound (III) wherein Yb is substituted by optionally substituted ureido, and optionally further substituted can also be produced, for example, by the method shown in Scheme 8. Compounds (III-2), (III-4) and (III-5) are encompassed in compound (III).

(Scheme 8)



wherein each symbol is as defined above.

In Method O, compound (III-5) is produced by reacting compound (III-2) with an isocyanate derivative ($R^{11}NCO$). The isocyanate derivative ($R^{11}NCO$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). In addition, a base may be used in 0.01 to 10 equivalents, preferably 0.01 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. An isocyanate derivative ($R^{11}NCO$) may be commercially available, or can be produced according to a method known *per se*, for example,

the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method P-1, compound (III-5) is produced by first reacting compound (III-2) with a compound represented by the formula $L^2C(O)L^3$ to give compound (III-4), and then reacting compound (III-4) with an amine derivative ($R^{11}R^{12}NH$). The compound represented by the formula $L^2C(O)L^3$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $L^2C(O)L^3$ may be commercially available, or can be produced by a method known *per se*. The obtained compound (III-4) can be used in the form of a reaction mixture or a crude product for the next reaction. It may be used for the next reaction after isolation and purification from the reaction mixture according to a conventional method. An amine derivative ($R^{11}R^{12}NH$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-4). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The amine derivative ($R^{11}R^{12}NH$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced

Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

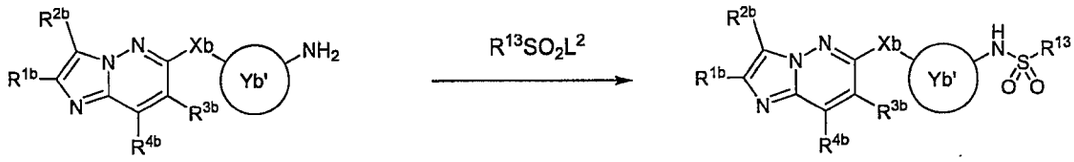
In Method P-2, compound (III-5) is produced by reacting amine derivative ($R^{11}R^{12}NH$) with a compound represented by the formula $L^2C(O)L^3$ successively with compound (III-2). The compound represented by the formula $L^2C(O)L^3$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to the amine derivative ($R^{11}R^{12}NH$). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The amine derivative ($R^{11}R^{12}NH$) and the compound represented by the formula $L^2C(O)L^3$ may be commercially available, or can be produced by a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto. The obtained compound represented by the formula $R^{11}R^{12}NC(O)L^3$ can be used in the form of a reaction mixture or a crude product for the next reaction. It may be used for the next reaction after isolation and purification from the reaction mixture according to a conventional method. The compound (III-2) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to the compound represented by the formula $R^{11}R^{12}NC(O)L^3$. A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents. As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr.

The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C.

[Production Method 9]

Compound (III) wherein the substituent of the optionally substituted amino for Yb is sulfonyl can also be produced, for example, by the method shown in Scheme 9. Compound (III-6) is encompassed in compound (III).

(Scheme 9)



(III − 2) (III − 6)

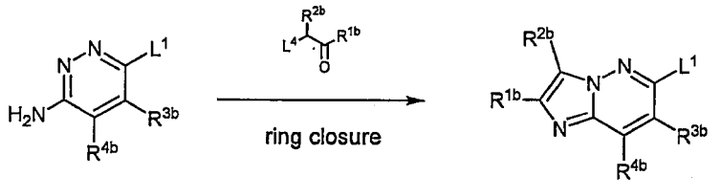
wherein each symbol is as defined above.

Compound (III-6) can be produced by reacting compound (III-2) with a reactive derivative of sulfonic acid ($R^{13}SO_2L^2$). The reactive derivative of sulfonic acid ($R^{13}SO_2L^2$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (III-2). In the present method, the reaction is generally carried out in the presence of a base, which is not always essential. As the base, those similar to the base exemplified in Scheme 1 can be used. A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to Compound (III-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The reactive derivative of sulfonic acid ($R^{13}SO_2L^2$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 10]

Compound (V-5) shown in Schemes 6 and 7 can be obtained, for example, by the method described in WO00/23450 or a method analogous thereto and the like.

(Scheme 10)



(VII－2) (V－5)

wherein each symbol is as defined above.

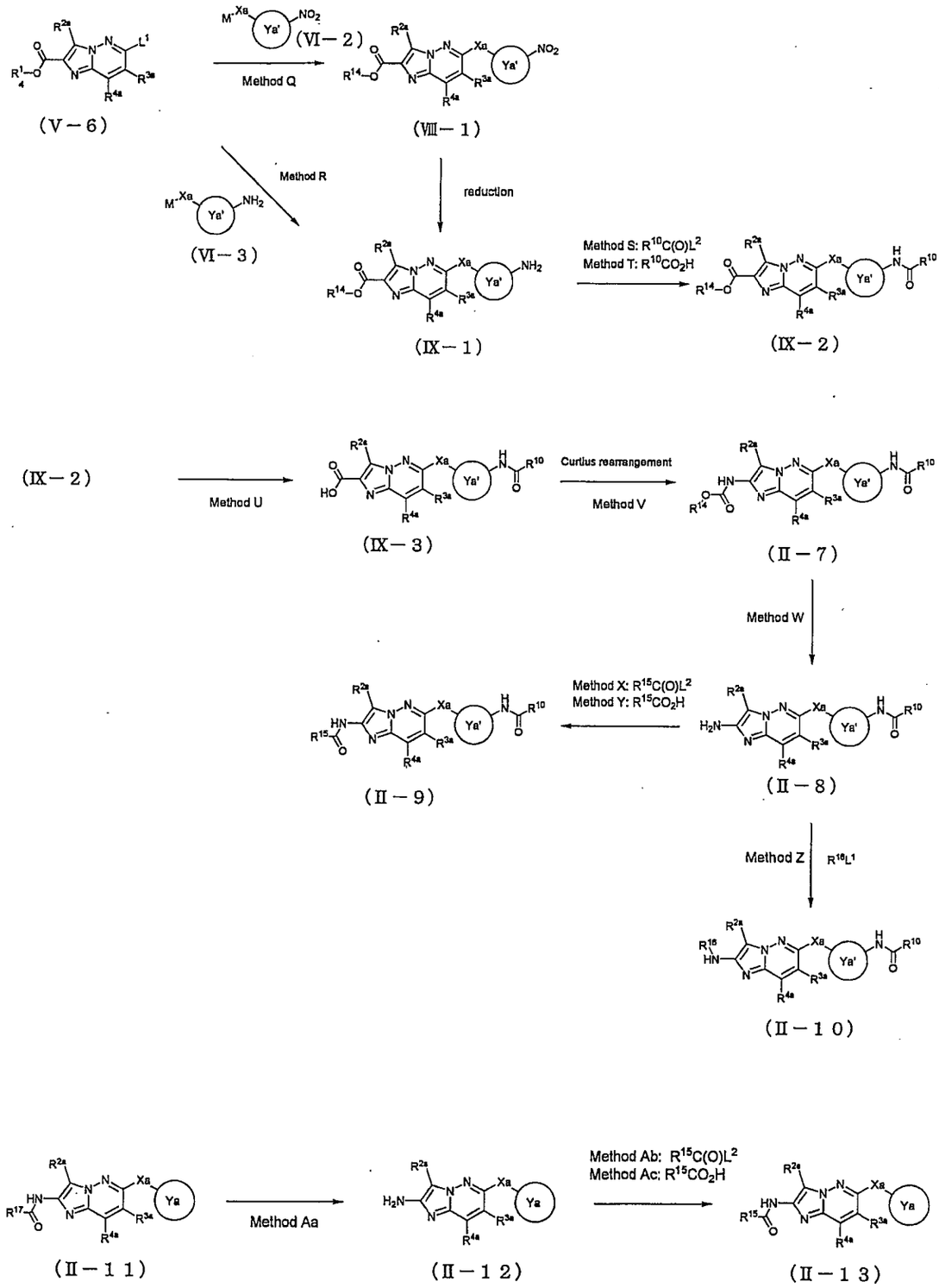
Compound (V-5) can be produced by reacting compound (VII-2) with carbonyl derivative ($L^4CHR^{2b}C(O)R^{1b}$). A carbonyl derivative is used in 0.1 to 10 equivalents, preferably 0.3 to 5 equivalents, relative to compound (VII-2). A base may be used in 0.1 to 10 equivalents, preferably 0.3 to 5 equivalents, relative to compound (VII-2). As the base, those similar to the bases exemplified in Scheme 5 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The carbonyl derivative ($L^4CHR^{2b}C(O)R^{1b}$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 11]

Compound (II) can also be produced by the method shown in Scheme 11. Compounds (IX-1), (IX-2) and (IX-3) are encompassed in compound (III), and compounds (II-7), (II-8), (II-9), (II-10),

(II-11), (II-12) and (II-13) are encompassed in compound (II).

(Scheme 11)



wherein R^{16} is an optionally substituted aryl or optionally substituted heterocyclic group, R^{17} is an optionally substituted

alkyl or optionally substituted cycloalkyl, and other symbols are as defined above.

R^{16} is a group to be, as $R^{16}NH$-, the "optionally substituted arylamino" or "optionally substituted heterocyclylamino" exemplified as a preferable substituent for the aforementioned R^1.

R^{17} is a group to be, as $R^{17}CONH$-, the "optionally substituted alkylcarbonylamino" or "optionally substituted cycloalkylcarbonylamino" exemplified as a preferable substituent for the aforementioned R^1.

In Method Q, compound (IX-1) is produced by first reacting compound (V-6) with compound (VI-2) in the presence of a base to give compound (VIII-1), and then reducing the nitro group of compound (VIII-1). Compound (VI-2) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-6). As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-6). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-2) may be commercially available, or can be produced by a method known *per se*. The obtained compound (VIII-1) can be used in the form of a reaction mixture or a crude product for the next reaction. It may be used for the next reaction after isolation and purification from the reaction mixture according to a conventional method. The nitro group can be reduced according to a method known *per se*, for example, the method described in the fourth series of experimental chemistry, vol. 20, 279-280 and the like, or a method analogous thereto.

In Method R, compound (IX-1) is produced by reacting compound (V-6) with compound (VI-3) in the presence of a base. Compound (VI-3) is used in 0.1 to 10 equivalents, preferably 0.3

to 3 equivalents, relative to compound (V-6). As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-6). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-3) may be commercially available, or can be produced by a method known *per se*.

In Method S, compound (IX-2) is produced by reacting compound (IX-1) with a compound represented by the formula $R^{10}C(O)L^2$. The compound represented by the formula $R^{10}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (IX-1). A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (IX-1). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C preferably -78°C to 200°C. The compound represented by the formula $R^{10}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method T, compound (IX-2) is produced by reacting compound (IX-1) with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent. When compound (IX-1) is reacted with carboxylic acid ($R^{10}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{10}CO_2H$) is used in 0.1 to 10 equivalents,

preferably 0.3 to 3 equivalents, relative to compound (IX-1). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate , O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound (IX-1). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (IX-1). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to Compound (IX-1). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{10}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method U, compound (IX-3) is produced by treating compound (IX-2) with a base or acid. As the base, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide, barium hydroxide and the like can be mentioned. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to

compound (IX-2). As the acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, trifluoroacetic acid and the like can be used. An acid is used in 0.1 to 20 equivalents, preferably 0.3 to 10 equivalents, relative to compound (IX-2). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used.

In Method V, compound (II-7) is produced by reacting compound (IX-3) with diphenylphosphoryl azide in the presence of a base. Diphenylphosphoryl azide is used in 0.1 to 10 equivalents, preferably 0.3 to 5 equivalents, relative to compound (IX-3). As the base, those similar to the bases exemplified in Scheme 1 can be used. As the base for this method, for example, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine, pyridine and the like are preferable. As the solvent for this reaction, those similar to the solvents exemplified in Scheme 1 can be used. For example, alcohols such as methanol, ethanol, 2-propanol, 2-methyl-2-propanol and the like are preferable. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C.

In Method W, compound (II-8) is produced by treating compound (II-7) with a base or acid. As the base, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide, barium hydroxide and the like can be mentioned. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-7). As the acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, trifluoroacetic acid and the like can be used. An acid is used in 0.1 to 20 equivalents, preferably 0.3 to 10 equivalents, relative to compound (II-7). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used.

In Method X, compound (II-9) is produced by reacting compound (II-8) with a compound represented by the formula $R^{15}C(O)L^2$. The compound represented by the formula $R^{15}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-8). The base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-8). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $R^{15}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method Y, compound (II-9) is produced by reacting compound (II-8) with carboxylic acid ($R^{15}CO_2H$) in the presence of a condensing agent. When compound (II-8) is reacted with carboxylic acid ($R^{15}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{15}CO_2H$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-8). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate , O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound

(II-8). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-8). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. The base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-8). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{15}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

In Method Z, compound (II-10) is produced by reacting compound (II-8) with a compound represented by the formula $R^{16}L^1$ in the presence of a base. The compound represented by the formula $R^{16}L^1$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-8). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The compound represented by the formula $R^{16}L^1$ may be commercially available, or can be produced according to a method known *per se*, for example, the method described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C.

Larock) and the like, or a method analogous thereto.

In Method Aa, compound (II-12) is produced by treating compound (II-11) with a base or acid. As the base, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide, barium hydroxide and the like can be mentioned. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-11). As the acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, trifluoroacetic acid and the like can be used. An acid is used in 0.1 to 20 equivalents, preferably 0.3 to 10 equivalents, relative to compound (II-11). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used.

In Method Ab, compound (II-13) is produced by reacting compound (II-12) with a compound represented by the formula $R^{15}C(O)L^2$. The compound represented by the formula $R^{15}C(O)L^2$ is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-12). A base may be used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-12). As the base, those similar to the base exemplified in Scheme 1 can be used. This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. a compound represented by the formula $R^{15}C(O)L^2$ may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

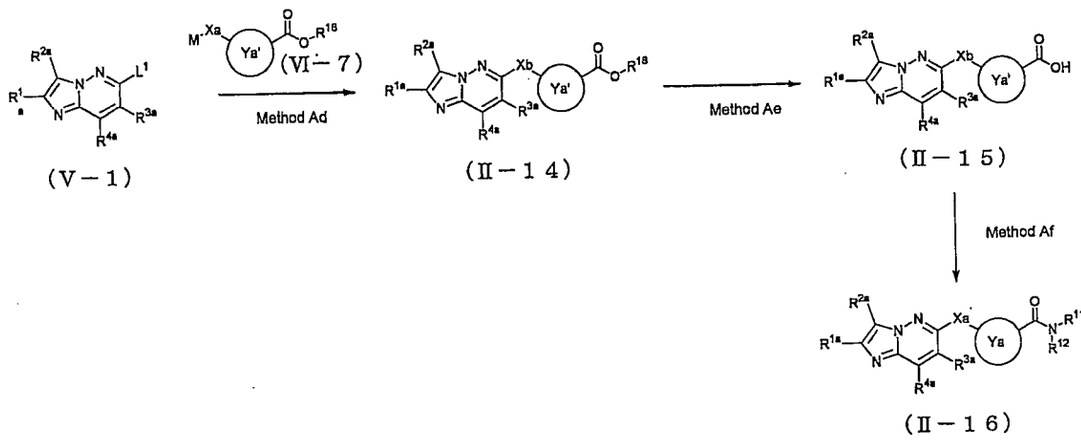
In Method Ac, (II-13) is produced by reacting compound (II-12) with carboxylic acid ($R^{15}CO_2H$) in the presence of a

condensing agent. When compound (II-12) is reacted with carboxylic acid ($R^{15}CO_2H$) in the presence of a condensing agent, carboxylic acid ($R^{15}CO_2H$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-12). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10 equivalents, preferably 1 to 5 equivalents, relative to compound (II-12). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-12). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. The base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-12). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Carboxylic acid ($R^{15}CO_2H$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 12]

Compound (II) wherein Ya is substituted by an optionally substituted aminocarbonyl group, and optionally further substituted can also be produced, for example, by the method shown in Scheme 12. Compounds (II-14), (II-15) and (II-16) are encompassed in compound (II).

(Scheme 12)



wherein R^{18} is an alkyl group, and other symbols are as defined above.

As the alkyl for R^{18}, for example, methyl, ethyl, propyl, isopropyl, tert-butyl and the like can be mentioned.

In Method Ad, compound (II-14) can be produced by reacting compound (V-1) with compound (VI-7). Compound (VI-7) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-1). Where necessary, a base may be added. As the base, inorganic base or organic base and the like can be used. Specifically, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium diisopropylamide and the like can be used. These bases are used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-1). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in

Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-7) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto. The reaction may be carried out using a microwave synthesizer.

In Method Ae, compound (II-15) is produced by treating compound (II-14) with a base or acid. As the base, for example, sodium hydroxide, potassium hydroxide, cesium hydroxide, barium hydroxide and the like can be mentioned. A base is used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-14). As the acid, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, trifluoroacetic acid and the like can be used. An acid is used in 0.1 to 20 equivalents, preferably 0.3 to 10 equivalents, relative to compound (II-14). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used.

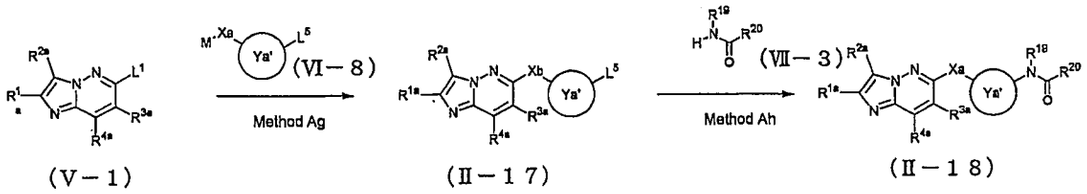
In Method Af, compound (II-16) is produced by reacting compound (II-15) with an amine derivative ($R^{11}R^{12}NH$) under a condensing agent. The amine derivative ($R^{11}R^{12}NH$) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-15). As the condensing agent, for example, 1-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphoryl azide, 1,1'-carbonyldiimidazole, benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like can be used. These condensing agents are used in 1 to 10

equivalents, preferably 1 to 5 equivalents, relative to compound (II-15). Where necessary, a suitable condensation promoter (e.g., 1-hydroxybenzotriazole, N-hydroxysuccinimide etc.) can be used. These condensation promoters are used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (II-15). This reaction may proceed more smoothly when a base is added. As the base, those similar to the base exemplified in Scheme 1 can be used. These bases are used in 0.01 to 10 equivalents, preferably 0.03 to 5 equivalents, relative to compound (II-15). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The amine derivative ($R^{11}R^{12}NH$) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 13]

Compound (II) wherein Ya is substituted by optionally substituted amide, and is optionally further substituted, can also be produced by the method shown in Production Method 2, as well as, for example, Scheme 13. Compounds (II-17) and (II-18) are encompassed in compound (II).

(Scheme 13)



(V−1) (II−17) (II−18)

wherein L^5 is a leaving group, R^{19} and R^{20} are, as $-NR^{19}C(O)R^{20}$, each a group to be amino substituted by the "C_{1-8} alkyl-carbonyl,

C_{2-8} alkenyl-carbonyl, C_{2-8} alkynyl-carbonyl, C_{3-8} cycloalkyl-carbonyl, C_{3-8} cycloalkenyl-carbonyl, C_{6-18} aryl-carbonyl, C_{6-18} aryl-C_{1-4} alkyl-carbonyl or heterocyclyl-carbonyl, each of which is optionally substituted" as the substituent on the aforementioned ring Y, and other symbols are as defined above.

As the leaving group for L^5, a halogen atom can be used.

In Method Ag, compound (II-17) can be produced by reacting compound (V-1) with compound (VI-8). Compound (VI-8) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (V-1). Where necessary, a base may be added. As the base, inorganic base or organic base and the like can be used. Specifically, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene, pyridine, 4-(dimethylamino)pyridine, N,N-dimethylaniline, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium diisopropylamide and the like can be mentioned. These bases are used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (V-1). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VI-8) may be commercially available, or can be produced according to a method known *per se*, for example, the method described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.
The reaction may be carried out using a microwave synthesizer.

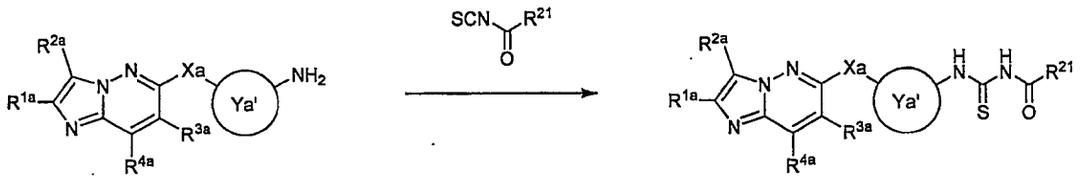
In Method Ah, compound (II-18) can be produced by reacting compound (II-17) with compound (VII-3) under a copper catalyst. Compound (II-3) is used in 0.1 to 10 equivalents, preferably 0.3 to 3 equivalents, relative to compound (VII-17). As the copper

catalyst, for example, copper iodide and copper (II) trifluoromethanesulfonate can be used. Where necessary, a base may be added. As the base, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium tert-butoxide, potassium phosphate tribasic, trans-1,2-cyclohexanediamine, 1,10-phenanthrolin, N,N-dimethylethylenediamine and the like can be used. These bases are used in 1 to 30 equivalents, preferably 1 to 10 equivalents, relative to compound (II-17). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. Compound (VII-3) may be commercially available, or can be produced according to a method known *per se*, for example, the methods described in "Advanced Organic Chemistry, 4th Ed." (Jerry March), "Comprehensive Organic Transformations, 2nd Ed." (Richard C. Larock) and the like or a method analogous thereto.

[Production Method 14]

Compound (II) wherein Ya is substituted by optionally substituted acylthioureido and optionally further substituted can also be produced, for example, by the method shown in Scheme 14. Compound (II-19) is encompassed in compound (II).

(Scheme 14)



(II－2) (II－19)

wherein R^{21} is, as $-C(S)NHC(O)R^{21}$, a group that becomes the "amino substituted by optionally substituted aminothiocarbonyl" as the substituent on the aforementioned ring Y, and other symbols are

as defined above.

Compound (II-19) can be produced by reacting compound (II-2) with an acylthiocyanate derivative ($R^{21}C(O)NCS$). The acylthiocyanate derivative ($R^{21}C(O)NCS$) is used in 0.1 to 10 equivalents, preferably 0.5 to 5 equivalents, relative to compound (II-19). This reaction is advantageously carried out using a solvent inert to the reaction. As the solvent, those similar to the solvents exemplified in Scheme 1 can be used. The reaction time is generally 1 min to 200 hr, preferably 10 min to 100 hr. The reaction temperature is generally -100°C to 250°C, preferably -78°C to 200°C. The acylthiocyanate derivative ($R^{21}C(O)NCS$) may be commercially available, or can be produced according to a method known *per se*.

It is also possible to produce a compound encompassed in the scope of the present invention by subjecting compounds (I) - (IV) (e.g., compound (II) and compound (III) obtained by the above-mentioned method) to introduction of substituents and functional group conversion by a means known *per se*. For the substituent conversion, a known conventional method can be used. For example, conversion to carboxy by hydrolysis of ester, conversion to carbamoyl by amidation of carboxy, conversion to hydroxymethyl by reduction of carboxy, conversion to alcohol compound by reduction or alkylation of carbonyl, reductive amination of carbonyl, oximation of carbonyl, acylation, ureation, sulfonylation or alkylation of amino, substitution and amination of active halogen by amine, amination by reduction of nitro, alkylation of hydroxy, substitution and amination of hydroxy and the like can be mentioned. When a reactive substituent that causes non-objective reaction is present during the introduction of substituents and conversion of functional groups, a protecting group is introduced in advance as necessary into the reactive substituent by a means known *per se*, and the protecting group is removed by a means known *per se* after the objective reaction, whereby a compound within the scope of the present invention can also be produced.

Compounds (I) - (IV) (e.g., compound (II) and compound (III) obtained by the above-mentioned method) can be isolated and purified by a means known *per se*, such as phase transfer, concentration, solvent extraction, fractionation, liquid conversion, crystallization, recrystallization, chromatography and the like. When compounds (I) - (IV) are obtained as free compounds, they can be converted to desired salts by a method known *per se* or a modification thereof; conversely, when the compounds are obtained as salts, they can be converted to free forms or other desired salts by a method known *per se* or a modification thereof.

Compounds (I) - (IV) (hereinafter to be also referred to as compound (I) and the like) may be used as prodrugs. A prodrug of compound (I) and the like means a compound which is converted to compound (I) and the like by a reaction due to an enzyme, a gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to compound (I) and the like by oxidation, reduction, hydrolysis, etc. due to an enzyme; a compound which is converted to compound (I) and the like by hydrolysis etc. due to gastric acid, and the like.

A prodrug of compound (I) and the like may be a compound obtained by subjecting an amino in compound (I) and the like to an acylation, alkylation or phosphorylation (e.g., a compound obtained by subjecting an amino in compound (I) and the like to an eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation); a compound obtained by subjecting a hydroxy in compound (I) and the like to an acylation, alkylation, phosphorylation or boration (e.g., a compound obtained by subjecting an hydroxy in compound (I) and the like to an acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation); a compound

obtained by subjecting a carboxy in compound (I) and the like to an esterification or amidation (e.g., a compound obtained by subjecting a carboxy in compound (I) and the like to an ethyl esterification, phenyl esterification, carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification or methylamidation) and the like. Any one of these compounds can be produced from compound (I) and the like by a method known *per se*.

A prodrug of compound (I) and the like may also be one which is converted into compound (I) and the like under a physiological condition, such as those described in *IYAKUHIN no KAIHATSU* (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p.163-198, Published by HIROKAWA SHOTEN (1990).

When compound (I) and the like has isomers such as optical isomer, stereoisomer, positional isomer, rotational isomer and the like, and any isomers and mixtures are encompassed in compound (I) and the like. For example, when compound (I) and the like has an optical isomer, an optical isomer separated from a racemate is also encompassed in compound (I) and the like. These isomers can be obtained as independent products by a synthesis means or a separation means (concentration, solvent extraction, column chromatography, recrystallization and the like) known *per se*.

The compound (I) and the like may be a crystal, and both a single crystal and crystal mixtures are encompassed in compound (I) and the like. Crystals can be produced by crystallization according to crystallization methods known *per se*.

The compound (I) and the like may be a co-crystal.

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

A compound labeled with an isotope (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I

etc.) is also encompassed in compound (I) and the like.

Compounds (I) - (IV) of the present invention, a salt thereof and a prodrug thereof (hereinafter sometimes to be abbreviated as the compound of the present invention) have, for example, phosphorylation-inhibitory activity against a kinase having such phosphorylating action. As used herein, kinase encompasses not only a substance having a phosphorylating action by itself as a whole, but also a substance a part of which has a phosphorylating action. The phosphorylating action possessed by kinases encompasses both a phosphorylating action on its own and that on other substances.

Examples of kinase include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Raf and the like. Examples of vascular endothelial growth factor receptor (VEGFR) include vascular endothelial growth factor receptor 1 (VEGFR1, Flt-1), vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1), vascular endothelial growth factor receptor 3 (VEGFR3, Flt-4) and the like. Of these, vascular endothelial growth factor receptor 2 (VEGFR2) is preferable. Examples of platelet-derived growth factor receptor (PDGFR) include platelet-derived growth factor receptor α (PDGFRα), platelet-derived growth factor receptor β (PDGFRβ) and the like. Examples of Raf include A-Raf, B-Raf, C-Raf and the like. Particularly, as kinase, vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR) and Raf are preferable.

Besides these, as kinase, tyrosine Kinase with Ig and EGF homology domains 2 (TIE2), fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), fibroblast growth factor receptor 3 (FGFR3), fibroblast growth factor receptor 4 (FGFR4), stem cell factor receptor (c-Kit), Aurora A, Aurora B, CDK, MEK1, MEK2, Akt, ERK, MAPK, Src, MET, epithelial cell growth factor receptor (EGFR), human epithelial growth factor receptor 2 (HER2), human epithelial growth factor receptor 4 (HER4), Abl, Fgr, Fms and the like can also be used.

For example, the vascular endothelial growth factor receptor 2 inhibitory activity of the compound of the present invention can be determined according to Test Example 1, the vascular endothelial cell growth inhibitory activity can be determined according to Test Example 2, the antitumor activity can be determined according to Test Example 3, the platelet-derived growth factor receptor α inhibitory activity can be determined according to Test Example 4, the platelet-derived growth factor receptor β inhibitory activity can be determined according to Test Example 5, and the B-Raf inhibitory activity can be determined according to Test Example 6.

The compound of the present invention particularly shows potent inhibitory activity for vascular endothelial growth factor receptor (VEGFR), and specifically high selectivity for vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) and potent kinase inhibitory activity for VEGFR1, PDGFR, and Raf. In addition, since the compound of the present invention is also superior in the efficacy, pharmacokinetics (absorption, distribution, metabolism, excretion etc.), solubility (water-solubility etc.), interaction with other pharmaceutical products, safety (acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiotoxicity, carcinogenicity etc.) and stability (chemical stability, stability to enzyme etc.), it is useful as a pharmaceutical agent.

Accordingly, the compound of the present invention is useful as a kinase inhibitor, preferably a vascular endothelial growth factor receptor (VEGFR) inhibitor, a platelet-derived growth factor receptor (PDGFR) inhibitor, a Raf inhibitor, more preferably a vascular endothelial growth factor receptor 2 (VEGFR2, KDR, Flk-1) inhibitor for a mammal (e.g., mouse, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human etc.). In addition, the compound of the present invention is useful as an angiogenesis inhibitor or a vascular endothelial cell growth inhibitor. The compound of the present invention is used as a pharmaceutical agent such as an agent for the prophylaxis or

treatment of diseases possibly affected by a vascular endothelial growth factor, for example, cancer [e.g., colorectal cancer (e.g., familial colorectal cancer, hereditary nonpolyposis colorectal cancer, gastrointestinal stromal tumor, etc.), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, malignant mesothelioma, etc.), mesothelioma, pancreatic cancer (e.g., pancreatic duct cancer, etc.), gastric cancer (e.g., papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous cancer, etc.), breast cancer (e.g., invasive ductal carcinoma, ductal cancer in situ, inflammatory breast cancer, etc.), ovarian cancer (e.g., ovarian epithelial cancer, extragonadal germ cell tumor, ovarian germ cell tumor, ovarian low malignant potential tumor, etc.), prostate cancer (e.g., hormone-dependent prostate cancer, non-hormone dependent prostate cancer, etc.), liver cancer (e.g., primary liver cancer, extrahepatic bile duct cancer, etc.), thyroid cancer (e.g., medullary thyroid cancer, etc.), kidney cancer (e.g., renal cell carcinoma, renal pelvis and ureter transitional cell cancer, etc.), uterine cancer, brain tumor (e.g., pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, etc.), melanoma, sarcoma, bladder cancer, blood cancer including multiple myeloma etc.], diabetic retinopathy, rheumatoid arthritis, psoriasis, atherosclerosis, Kaposi's sarcoma, COPD, pain, asthma, endometriosis, nephritis, inflammation such as osteoarthritis and the like and hypertension, a cancer growth inhibitor, a cancer metastasis suppressor, an apoptosis promoter and the like. Of these, it is effective, for example, for colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, breast cancer, ovary cancer, prostate cancer, liver cancer, thyroid cancer, kidney cancer, cerebral tumor, melanoma, bladder cancer and blood cancer. Particularly, the compound of the present invention is effective for patients with lung cancer, colorectal cancer, ovary cancer, prostate cancer or kidney cancer.

The compound of the present invention can be administered

orally or parenterally as it is or in a mixture with a pharmacologically acceptable carrier.

The dosage form of the compound of the present invention for oral administration is, for example, tablet (including sugar-coated tablet, film-coated tablet), pill, granule, powder, capsule (including soft capsule, microcapsule), syrup, emulsion, suspension and the like, and the dosage form for parenteral administration is, for example, injection, injecting agent, instillation, suppository and the like. In addition, it is effective to make a sustained release preparation by combining the compound with a suitable base (e.g., polymer of butyric acid, polymer of glycolic acid, copolymer of butyric acid-glycolic acid, a mixture of a polymer of butyric acid and a polymer of glycolic acid, polyglycerol fatty acid ester etc.).

As a method to produce the compound of the present invention in the above-mentioned dosage form, a known production method generally used in the pertinent field can be employed. When the above-mentioned dosage form is produced, suitable amounts of additives such as excipient, binder, disintegrant, lubricant, sweetening agent, surfactant, suspending agent, emulsifier and the like, generally used in the pertinent field, are appropriately added as necessary for production.

When the compound of the present invention is prepared into a tablet, for example, it can be produced by adding an excipient, a binder, a disintegrant, a lubricant and the like, and when a pill or a granule is to be prepared, it can be produced by adding an excipient, a binder, a disintegrant and the like. When a powder or a capsule is to be prepared, it can be produced by adding an excipient and the like, when a syrup is to be prepared, it can be produced by adding a sweetener and the like, and when an emulsion or a suspension is to be prepared, it can be produced by adding a suspending agent, a surfactant, an emulsifier and the like.

Examples of the excipient include lactose, sucrose, glucose, starch, sucrose, microcrystalline cellulose, powdered

glycyrrhiza, mannitol, sodium hydrogencarbonate, calcium phosphate, calcium sulfate and the like.

Examples of the binder include 5 - 10 wt% starch liquid paste, 10 - 20 wt% gum arabic solution or gelatin solution, 1 - 5 wt% tragacanth solution, carboxymethyl cellulose solution, sodium alginate solution, glycerin and the like.

Examples of the disintegrant include starch, calcium carbonate and the like.

Examples of the lubricant include magnesium stearate, stearic acid, calcium stearate, purified talc and the like.

Examples of the sweetener include glucose, fructose, invert sugar, sorbitol, xylitol, glycerin, simple syrup and the like.

Examples of the surfactant include sodium lauryl sulfate, polysorbate 80, sorbitan monofatty acid ester, polyoxyl 40 stearate and the like.

Examples of the suspending agent include gum arabic, sodium alginate, sodium carboxymethyl cellulose, methyl cellulose, bentonite and the like.

Examples of the emulsifier include gum arabic, tragacanth, gelatin, polysorbate 80 and the like.

Furthermore, when the compound of the present invention is produced in the above-mentioned dosage form, a suitable amount of a coloring agent, a preservative, an aromatic, a corrigent, a stabilizer, a thickening agent and the like typically used in the field of preparation can be added on demand.

As the injection, intravenous injection as well as subcutaneous injection, intracutaneous injection, intramuscular injection, instillation and the like are mentioned, and as the sustained release preparation, an iontophoresis transdermal agent and the like are mentioned.

Such injections are prepared by methods known *per se*, or by dissolving, suspending or emulsifying the compound of the present invention in a sterilized aqueous or oily liquid. As an aqueous liquid for injection, physiological saline, isotonic

solutions containing glucose or other auxiliary drugs (e.g., D-sorbitol, D-mannitol, sodium chloride and the like) and the like can be mentioned, and they can be used in combination with suitable dissolution aids, such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol), nonionic surfactants (e.g., polysorbate 80, HCO-50) and the like. As an oily liquid, sesame oil, soybean oil and the like can be mentioned, which may be used in combination with dissolution aids such as benzyl benzoate, benzyl alcohol and the like. In addition, buffers (e.g., phosphate buffer, sodium acetate buffer), soothing agents (e.g., benzalkonium chloride, procaine hydrochloride and the like), stabilizers (e.g., human serum albumin, polyethylene glycol and the like), preservatives (e.g., benzyl alcohol, phenol and the like) and the like can be mentioned. A prepared injection is generally filled in an ampoule.

While the content of the compound of the present invention in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 0.01 to 100 wt%, preferably about 2 to 85 wt%, more preferably about 5 to 70 wt%, relative to the entire preparation.

While the content of the additive in the pharmaceutical agent of the present invention varies depending on the form of the pharmaceutical preparation, it is generally about 1 to 99.9 wt%, preferably about 10 to 90 wt%, relative to the entire preparation.

The compound of the present invention is stable and low toxic, and can be used safely. While the daily dose varies depending on the condition and body weight of patients, the kind of compound, administration route and the like, in the case of, for example, oral administration to patients for the treatment of cancer, the daily dose to an adult (body weight about 60 kg) is about 1 to 1000 mg, preferably about 3 to 300 mg, more preferably about 10 to 200 mg, as an active ingredient (the

compound of the present invention), which can be given in a single administration or administered in 2 or 3 portions a day.

When the compound of the present invention is administered parenterally, it is generally administered in the form of a liquid (e.g., injection). While the dose varies depending on the subject of administration, target organ, symptom, administration method and the like, it is, for example, about 0.01 mg to about 100 mg, preferably about 0.01 to about 50 mg, more preferably about 0.01 to about 20 mg, in the form of an injection, relative to 1 kg body weight, which is preferably given by intravenous injection.

The compound of the present invention can be used concurrently with other drugs. To be specific, the compound of the present invention can be used together with medicaments such as hormonal therapeutic agents, chemotherapeutic agents, immunotherapeutic agents, pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors and the like. In the following, the drugs that can be used in combination with the compound of the present invention are abbreviated as concomitant drugs.

Examples of the "hormonal therapeutic agents" include fosfestrol, diethylstylbestrol, chlorotrianisene, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate, danazol, allylestrenol, gestrinone, mepartricin, raloxifene, ormeloxifene, levormeloxifene, anti-estrogens (e.g., tamoxifen citrate, toremifene citrate, and the like), pill preparations, mepitiostane, testrolactone, aminoglutethimide, LH-RH agonists (e.g., goserelin acetate, buserelin, leuprorelin, and the like), droloxifene, epitiostanol, ethinylestradiol sulfonate, aromatase inhibitors (e.g., fadrozole hydrochloride, anastrozole, retrozole, exemestane, vorozole, formestane, and the like), anti-androgens (e.g., flutamide, bicartamide, nilutamide, and the like), 5α-reductase inhibitors (e.g., finasteride, epristeride, and the like), aderenal cortex

hormone drugs (e.g., dexamethasone, prednisolone, betamethasone, triamcinolone, and the like), androgen synthesis inhibitors (e.g., abiraterone, and the like), retinoid and drugs that retard retinoid metabolism (e.g., liarozole, and the like), and the like.

Examples of the "chemotherapeutic agents" include alkylating agents, antimetabolites, anticancer antibiotics, plant-derived anticancer agents, and the like.

Examples of the "alkylating agents" include nitrogen mustard, nitrogen mustard-N-oxide hydrochloride, chlorambutyl, cyclophosphamide, ifosfamide, thiotepa, carboquone, improsulfan tosylate, busulfan, nimustine hydrochloride, mitobronitol, melphalan, dacarbazine, ranimustine, sodium estramustine phosphate, triethylenemelamine, carmustine, lomustine, streptozocin, pipobroman, etoglucid, carboplatin, cisplatin, miboplatin, nedaplatin, oxaliplatin, altretamine, ambamustine, dibrospidium hydrochloride, fotemustine, prednimustine, pumitepa, ribomustin, temozolomide, treosulphan, trophosphamide, zinostatin stimalamer, adozelesin, cystemustine, bizelesin, DDS preparations thereof, and the like.

Examples of the "antimetabolites" include mercaptopurine, 6-mercaptopurine riboside, thioinosine, methotrexate, pemetrexed, enocitabine, cytarabine, cytarabine ocfosfate, ancitabine hydrochloride, 5-FU drugs (e.g., fluorouracil, tegafur, UFT, doxifluridine, carmofur, gallocitabine, emmitefur, capecitabine, and the like), aminopterine, nelzarabine, leucovorin calcium, tabloid, butocine, folinate calcium, levofolinate calcium, cladribine, emitefur, fludarabine, gemcitabine, hydroxycarbamide, pentostatin, piritrexim, idoxuridine, mitoguazone, thiazophrine, ambamustine, bendamustine, DDS preparations thereof, and the like.

Examples of the "anticancer antibiotics" include actinomycin-D, actinomycin-C, mitomycin-C, chromomycin-A3, bleomycin hydrochloride, bleomycin sulfate, peplomycin sulfate,

daunorubicin hydrochloride, doxorubicin hydrochloride, aclarubicin hydrochloride, pirarubicin hydrochloride, epirubicin hydrochloride, neocarzinostatin, mithramycin, sarcomycin, carzinophilin, mitotane, zorubicin hydrochloride, mitoxantrone hydrochloride, idarubicin hydrochloride, DDS preparations thereof, and the like.

Examples of the "plant-derived anticancer agents" include etoposide, etoposide phosphate, vinblastine sulfate, vincristine sulfate, vindesine sulfate, teniposide, paclitaxel, docetaxel, vinorelbine, DDS preparations thereof, and the like.

Examples of the "immunotherapeutic agents (BRM)" include picibanil, krestin, sizofiran, lentinan, ubenimex, interferons, interleukins, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, lymphotoxin, BCG vaccine, *Corynebacterium parvum*, levamisole, polysaccharide K, procodazole, anti-CTLA4 antibody, and the like.

Example of the "cell growth factor" in the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors" include any substances that promote cell proliferation, which are normally peptides having not more than 20,000 molecular weight that are capable of exhibiting their activity at low concentrations by binding to a receptor, including (1) EGF (epidermal growth factor) or substances possessing substantially the same activity as EGF [e.g., TGFα, and the like], (2) insulin or substances possessing substantially the same activity as insulin [e.g., insulin, IGF (insulin-like growth factor)-1, IGF-2, and the like], (3) FGF (fibroblast growth factor) or substances possessing substantially the same activity as FGF [e.g., acidic FGF, basic FGF, KGF (keratinocyte growth factor), FGF-10, and the like], (4) other cell growth factors [e.g., CSF (colony stimulating factor), EPO (erythropoietin), IL-2 (interleukin-2), NGF (nerve growth factor), PDGF (platelet-derived growth factor), TGFβ (transforming growth factorβ), HGF

(hepatocyte growth factor), VEGF (vascular endothelial growth factor), heregulin, angiopoietin, and the like].

Examples of the "cell growth factor receptors" include any receptors capable of binding to the aforementioned growth factors, including EGF receptor, heregulin receptor (HER3, etc.), insulin receptor, IGF receptor-1, IGF receptor-2, FGF receptor-1 or FGF receptor-2, VEGF receptor, angiopoietin receptor (Tie2 etc.), PDGF receptor, and the like.

As the "pharmaceutical agents inhibiting the action of cell growth factors or cell growth factor receptors", EGF inhibitor, TGFα inhibitor, haregulin inhibitor, insulin inhibitor, IGF inhibitor, FGF inhibitor, KGF inhibitor, CSF inhibitor, EPO inhibitor, IL-2 inhibitor, NGF inhibitor, PDGF inhibitor, TGFβ inhibitor, HGF inhibitor, VEGF inhibitor, angiopoietin inhibitor, EGF receptor inhibitor, HER2 inhibitor, HER4 inhibitor, insulin receptor, IGF-1 receptor inhibitor, IGF-2 receptor inhibitor, FGF receptor-1 inhibitor, FGF receptor-2 inhibitor, FGF receptor-3 inhibitor, FGF receptor-4 inhibitor, VEGF receptor inhibitor, Tie-2 inhibitor, PDGF receptor inhibitor, Abl inhibitor, Raf inhibitor, FLT3 inhibitor, c-Kit inhibitor, Src inhibitor, PKC inhibitor, Trk inhibitor, Ret inhibitor, mTOR inhibitor, Aurora inhibitor, PLK inhibitor, MEK(MEK1/2) inhibitor, MET inhibitor, CDK inhibitor, Akt inhibitor, ERK inhibitor and the like are used. More specifically, anti-VEGF antibody (Bevacizumab etc.), anti-HER2 antibody (Trastuzumab, Pertuzumab etc.), anti-EGFR antibody (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anti-VEGFR antibody, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib, Lapatinib, Vatalanib, 4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxy-7-[3-(1-pyrrolidinyl)propoxy]quinazoline (AZD-2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3-(4-bromo-2,6-difluorobenzyloxy)-5-[3-[4-(1-pyrrolidinyl)butyl]ureido]isothiazole-4-carboxamide (CP-547632), Axitinib, N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(pyridin-

4-ylmethylamino)pyridine-3-carboxamide (AMG-706), Nilotinib, 6-[4-(4-ethylpiperazin-1-ylmethyl)phenyl]-N-[1(R)-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine (AEE-788), Vandetanib, Temsirolimus, Everolimus, Enzastaurin, N-[4-[4-(4-methylpiperazin-1-yl)-6-(3-methyl-1H-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide (VX-680), phosphoric acid 2-[N-[3-[4-[5-[N-(3-fluorophenyl)carbamoylmethyl]-1H-pyrazol-3-ylamino]quinazolin-7-yloxy]propyl]-N-ethylamino]ethyl ester (AZD-1152), 4-[9-chloro-7-(2,6-difluorophenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-ylamino]benzoic acid (MLN-8054), N-[2-methoxy-5-[(E)-2-(2,4,6-trimethoxyphenyl)vinylsulfonylmethyl]phenyl]glycine sodium salt (ON-1910Na), 4-[8-cyclopentyl-7(R)-ethyl-5-methyl-6-oxo-5,6,7,8-tetrahydropteridin-2-ylamino]-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide (BI-2536), 5-(4-bromo-2-chlorophenylamino)-4-fluoro-1-methyl-1H-benzimidazole-6-carbohydroxamic acid 2-hydroxyethyl ester (AZD-6244), N-[2(R),3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzamide (PD-0325901) and the like are used.

In addition to the aforementioned drugs, L-asparaginase, aceglatone, procarbazine hydrochloride, protoporphyrin-cobalt complex salt, mercuric hematoporphyrin-sodium, topoisomerase I inhibitors (e.g., irinotecan, topotecan, and the like), topoisomerase II inhibitors (e.g., sobuzoxane, and the like), differentiation inducers (e.g., retinoid, vitamin D, and the like), other angiogenesis inhibitors (e.g., humagillin, shark extract, COX-2 inhibitor, and the like), α-blockers (e.g., tamsulosin hydrochloride, and the like), bisphosphonic acids (pamidronate, zoledronate, and the like), thalidomide, 5 azacytidine, decitabine, bortezomib, antitumor antibody such as anti-CD20 antibody and the like, toxin labeled antibody and the like can also be used.

By combining the compound of the present invention and a concomitant drug, a superior effect such as

(1) the dose can be reduced as compared to single administration

of the compound of the present invention or a concomitant drug, (2) the drug to be combined with the compound of the present invention can be selected according to the condition of patients (mild case, severe case and the like), (3) the period of treatment can be set longer, (4) a sustained treatment effect can be designed, (5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, and the like, can be achieved.

In the present specification, the compound of the present invention and a concomitant drug used in combination are referred to as the "combination agent of the present invention".

For use of the combination agent of the present invention, the administration time of the compound of the present invention and the concomitant drug is not restricted, and the compound of the present invention and the concomitant drug can be administered to an administration subject simultaneously, or may be administered at different times. The dosage of the concomitant drug may be determined according to the administration amount clinically set, and can be appropriately selected depending on the administration subject, administration route, disease, combination and the like.

Examples of the administration mode of the combined use of the compound of the present invention and the concomitant drug include the following methods: (1) The compound of the present invention and the concomitant drug are simultaneously produced to give a single preparation, which is then administered. (2) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered simultaneously by the same administration route. (3) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by the same administration route at different times. (4) The compound of the present invention and the concomitant

drug are separately produced to give two kinds of preparations which are administered simultaneously by different administration routes. (5) The compound of the present invention and the concomitant drug are separately produced to give two kinds of preparations which are administered by different administration routes at different times (for example, the compound of the present invention and the concomitant drug are administered in this order, or in the reverse order). The dose of the concomitant drug is determined in accordance with its clinical dose. And the ratio of the compound of the present invention and the concomitant drug is determined depending on the subject, administration route, disease, symptom, combination, and the like. For example, when the subject is human, the concomitant drug is used in 0.01 to 100 (w/w), relative to the compound of the present invention.

The combination agent of the present invention has low toxicity and, for example, the compound of the present invention and/or the above-mentioned concomitant drug can be mixed, according to a method known *per se*, with a pharmacologically acceptable carrier to give pharmaceutical compositions, such as tablets (including sugar-coated tablet, film-coated tablet), powders, granules, capsules (including soft capsule), solutions, injections, suppositories, sustained release agents and the like, which can be safely administered orally or parenterally (e.g., local, rectum, venous, and the like). An injection can be administered directly to the lesion by intravenous, intramuscular, subcutaneous or intra-tissue administration.

As a pharmacologically acceptable carrier which may be used for preparing a preparation of the combination agent of the present invention, those similar to the aforementioned pharmacologically acceptable carriers, that can be used for the production of the pharmaceutical agent of the present invention, can be mentioned. Where necessary, the aforementioned additives that can be used for the production of the pharmaceutical agent of the present invention, such as preservatives, antioxidants,

coloring agents, sweetening agents, adsorbents, wetting agents and the like can also be used in appropriate amounts.

The compounding ratio of the compound of the present invention to the concomitant drug in the combination agent of the present invention can be appropriately set depending on the administration subject, administration route, diseases and the like.

For example, the content of the compound of the present invention in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 100% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of the concomitant drug in the combination agent of the present invention varies depending on the dosage form, and is usually from about 0.01 to 90% by weight, preferably from about 0.1 to 50% by weight, further preferably from about 0.5 to 20% by weight, based on the preparation.

The content of additives in the combination agent of the present invention varies depending on the dosage form, and is usually from about 1 to 99.99% by weight, preferably from about 10 to 90% by weight, based on the preparation.

When the compound of the present invention and the concomitant drug are separately prepared, the same content may be adopted.

These preparations can be produced by a method known *per se*, which is generally employed in the preparation process.

For example, the compound of the present invention and the concomitant drug can be made into an aqueous injection together with a dispersing agent (e.g., Tween 80 (manufactured by Atlas Powder, US), HCO 60 (manufactured by Nikko Chemicals), polyethylene glycol, carboxymethylcellulose, sodium alginate, hydroxypropylmethylcellulose, dextrin and the like), a stabilizer (e.g., ascorbic acid, sodium pyrosulfite, and the like), a surfactant (e.g., Polysorbate 80, macrogol and the

like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride, mannitol, sorbitol, glucose and the like), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl p-oxybenzoate, benzoic acid, methylparaben, propylparaben, benzyl alcohol and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a dissolution aid (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol and the like), and the like, or can be dissolved, suspended or emulsified in a vegetable oil such as olive oil, sesame oil, cotton seed oil, corn oil and the like or a dissolution aid such as propylene glycol and the like and prepared into an oily injection, whereby an injection is afforded.

In addition, an excipient (e.g., lactose, sucrose, starch and the like), a disintegrating agent (e.g., starch, calcium carbonate and the like), a binder (e.g., starch, gum Arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like may be added to the compound of the present invention or the concomitant drug according to a method known *per se*, and the mixture can be compression-molded, then if desirable, the molded product can be coated by a method known *per se* for the purpose of masking of taste, enteric property or durability, to give a preparation for oral administration. As the coating agent, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudoragit (methacrylic acid·acrylic acid copolymer, manufactured by Rohm, DE), pigment (e.g., iron oxide red, titanium dioxide, etc.) and the like can be used. The

preparation for oral administration may be any of an immediate-release preparation and a sustained release preparation.

Moreover, the compound of the present invention and the concomitant drug can be made into an oily or aqueous solid, semisolid or liquid suppository according to a method known *per se*, by mixing them with an oily substrate, aqueous substrate or aqueous gel substrate. As the above-mentioned oily substrate, for example, glycerides of higher fatty acids [e.g., cacao butter, Witepsols (manufactured by Dynamit Nobel, Germany), etc.], glycerides of medium chain fatty acid [e.g., Miglyols (manufactured by Dynamit Nobel, Germany), etc.], or vegetable oils (e.g., sesame oil, soybean oil, cotton seed oil and the like), and the like are mentioned. Furthermore, as the aqueous substrate, for example, polyethylene glycol, propylene glycol and the like are mentioned, and as the aqueous gel substrate, for example, natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers and the like are mentioned.

As the above-mentioned sustained release preparation, sustained release microcapsules and the like are mentioned. The sustained release microcapsule can be produced by a method known *per se*, such as the method shown in the following [2].

The compound of the present invention is preferably molded into a preparation for oral administration such as a solid preparation (e.g., powder, granule, tablet, capsule) and the like, or molded into a preparation for rectal administration such as a suppository and the like. Particularly, a preparation for oral administration is preferable.

The concomitant drug can be made into the above-mentioned drug form depending on the kind of the drug.

[1] An injection of the compound of the present invention or the concomitant drug, and preparation thereof, [2] a sustained release preparation or immediate-release preparation of the compound of the present invention or the concomitant drug, and preparation thereof, [3] a sublingual, buccal or intraoral quick integrating agent of the compound of the present invention

or the concomitant drug, and preparation thereof, will be specifically described below.

[1] Injection and preparation thereof

An injection prepared by dissolving the compound of the present invention or the concomitant drug in water is preferable. This injection may contain a benzoate and/or salicylate.

The injection is obtained by dissolving the compound of the present invention or the concomitant drug, and if desirable, a benzoate and/or salicylate, in water.

As the above-mentioned salts of benzoic acid and salicylic acid, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, meglumine salts, salts with organic bases such as tromethamol and the like, etc. are mentioned.

The concentration of the compound of the present invention or the concomitant drug in an injection is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%. The concentration of a benzoate and/or salicylate is from 0.5 to 50 w/v%, preferably from about 3 to 20 w/v%.

The injection of the present invention can be appropriately mixed with an additive conventionally used for injection, such as a stabilizer (e.g., ascorbic acid, sodium pyrosulfite and the like), a surfactant (e.g., Polysorbate 80, macrogol and the like), a solubilizer (e.g., glycerin, ethanol and the like), a buffer (e.g., phosphoric acid and alkali metal salt thereof, citric acid and alkali metal salt thereof, and the like), an isotonizing agent (e.g., sodium chloride, potassium chloride and the like), a dispersing agent (e.g., hydroxypropylmethylcellulose, dextrin), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide and the like), a preservative (e.g., ethyl p-oxybenzoate, benzoic acid and the like), a dissolving agent (e.g., conc. glycerin, meglumine and the like), a dissolution aid (e.g., propylene glycol, sucrose and the like), a soothing agent (e.g., glucose, benzyl alcohol

and the like), and the like. These additives are generally blended in a proportion usually used for injections.

The pH of an injection is advantageously adjusted to pH 2 to 12, preferably pH 2.5 to 8.0, by addition of a pH adjusting agent.

An injection is obtained by dissolving, in water, the compound of the present invention or the concomitant drug and, if desirable, a benzoate and/or a salicylate, and if necessary, the above-mentioned additives. They may be dissolved in any order, and can be appropriately dissolved in the same manner as in a conventional production method of an injection.

An aqueous solution for injection may be advantageously heated, alternatively, for example, subjected to filter sterilization, high pressure heat sterilization and the like to give an injection, in the same manner as for usual injections.

An aqueous solution for injection may be advantageously subjected to high pressure heat sterilization at 100°C to 121°C for 5 to 30 min.

Furthermore, a preparation conferred with antibacterial property of a solution may also be produced to permit multiple administration in portions.

[2] Sustained release preparation or immediate-release preparation, and preparation thereof

A sustained release preparation is preferable, which is obtained, if desirable, by coating a nucleus containing the compound of the present invention or the concomitant drug with a film agent such as a water-insoluble substance, a swellable polymer and the like. For example, a sustained release preparation for oral administration of a one-day-one-time administration type is preferable.

As the water-insoluble substance used in a film agent, there are listed, for example, cellulose ethers such as ethylcellulose, butylcellulose and the like, cellulose esters such as cellulose acetate, cellulose propionate and the like, polyvinyl esters such as polyvinyl acetate, polyvinyl butyrate

and the like, acrylic acid/methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylate/cinnamoethyl methacrylate/aminoalkyl methacrylate copolymers, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamide copolymers, poly(methyl methacrylate), polymethacrylate, polymethacrylamide, aminoalkyl methacrylate copolymers, poly(methacrylic anhydride), glycidyl methacrylate copolymer, particularly, acrylic acid-based polymers such as Eudoragit (Rohm Pharma) such as Eudoragit RS-100, RL-100, RS-30D, RL-30D, RL-PO, RS-PO (ethyl acrylate/methyl methacrylate/trimethyl methacryloyl chloride/ammoniumethyl copolymer), Eudoragit NE-30D (methyl methacrylate/ethyl acrylate copolymer), and the like, hydrogenated oils such as hydrogenated castor oil (e.g., Lubri wax (Freund Corporation) and the like), waxes such as carnauba wax, glycerin fatty acid ester, paraffin and the like, polyglycerin fatty acid esters, and the like.

As the swellable polymer, polymers having an acidic dissociating group and showing pH dependent swell are preferable, and polymers having an acidic dissociating group, which manifest small swelling in acidic regions such as in stomach and large swelling in neutral regions such as in small intestine and large intestine, are preferable.

As such a polymer having an acidic dissociating group and showing pH dependent swell, cross-linkable polyacrylic acid copolymers such as Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all of which are manufactured by BF Goodrich), Hiviswako 103, 104, 105, 304 (all are manufactured by Wako Pure Chemical Industries, Ltd.), and the like, can be used.

The film agent used in a sustained release preparation may further contain a hydrophilic substance.

As the hydrophilic substance, for example, polysaccharides which may contain a sulfate group such as pullulan, dextrin, alkali metal alginate and the like, polysaccharides having a hydroxyalkyl or carboxyalkyl such as hydroxypropylcellulose,

hydroxypropylmethylcellulose, carboxymethylcellulose sodium and the like, methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like can be mentioned.

The content of a water-insoluble substance in the film agent of a sustained release preparation is from about 30 to about 90% (w/w), preferably from about 35 to about 80% (w/w), further preferably from about 40 to about 75% (w/w), the content of a swellable polymer is from about 3 to about 30% (w/w), preferably from about 3 to about 15% (w/w). The film agent may further contain a hydrophilic substance, and in which case, the content of a hydrophilic substance in the film agent is about 50% (w/w) or less, preferably about 5 to 40% (w/w), further preferably from about 5 to 35% (w/w). This % (w/w) indicates % by weight based on a film agent composition which is obtained by removing a solvent (e.g., water, lower alcohols such as methanol, ethanol and the like) from a film agent solution.

The sustained release preparation is produced by preparing a nucleus containing a drugs as exemplified below, then, coating the resulted nucleus with a film agent solution prepared by heat-solving a water-insoluble substance, swellable polymer and the like or by dissolving or dispersing it in a solvent.

I. Preparation of nucleus containing drug

The form of nucleus containing a drug to be coated with a film agent (hereinafter, sometimes simply referred to as nucleus) is not particularly restricted, and preferably, the nucleus is formed into particles such as a granule or fine particle.

When the nucleus is composed of granules or fine particles, the average particle size thereof is preferably from about 150 to about 2000 μm, further preferably, from about 500 to about 1400 μm.

Preparation of the nucleus can be effected by a usual production method. For example, a suitable excipient, binding agent, disintegrating agent, lubricant, stabilizer and the like are mixed with a drug, and the mixture is subjected to a wet

extrusion granulating method, fluidized bed granulating method or the like, to prepare a nucleus.

The content of drugs in a nucleus is from about 0.5 to about 95% (w/w), preferably from about 5.0 to about 80% (w/w), further preferably from about 30 to about 70% (w/w).

As the excipient contained in the nucleus, for example, saccharides such as sucrose, lactose, mannitol, glucose and the like, starch, crystalline cellulose, calcium phosphate, corn starch and the like are used. Among them, crystalline cellulose, corn starch are preferable.

As the binding agent, for example, polyvinyl alcohol, hydroxypropylcellulose, polyethylene glycol, polyvinyl pyrrolidone, Pluronic F68, gum Arabic, gelatin, starch and the like are used. As the disintegrating agent, for example, carboxymethylcellulose calcium (ECG505), croscarmelose sodium (Ac-Di-Sol), crosslinked polyvinylpyrrolidone (Crospovidone), low substituted hydroxypropylcellulose (L-HPC) and the like are used. Among them, hydroxypropylcellulose, polyvinylpyrrolidone, lower substituted hydroxypropylcellulose are preferable. As the lubricant and coagulation inhibitor, for example, talc, magnesium stearate and inorganic salts thereof are used, and as the lubricant, polyethylene glycol and the like are used. As the stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, are used.

A nucleus can also be prepared by, in addition to the above-mentioned, for example, a rolling granulation method in which a drug or a mixture of a drug with an excipient, lubricant and the like is added portionwise onto an inert carrier particle which is the core of the nucleus while spraying a binder dissolved in a suitable solvent such as water, lower alcohol (e.g., methanol, ethanol and the like) and the like, a pan coating method, a fluidized bed coating method or a melt granulating method. As the inert carrier particle, for example, those made of sucrose, lactose, starch, crystalline cellulose or waxes can be used, and the average particle size thereof is

preferably from about 100 μm to about 1500 μm.

For separating a drug contained in a nucleus and a film agent, the surface of the nucleus may be coated with a protective agent. As the protective agent, for example, the above-mentioned hydrophilic substances, water-insoluble substances and the like are used. As the protective agent, preferably polyethylene glycol, and polysaccharides having a hydroxyalkyl or carboxyalkyl are used, more preferably, hydroxypropylmethylcellulose and hydroxypropylcellulose are used. The protective agent may contain, as stabilizer, acids such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like, and lubricants such as talc and the like. When the protective agent is used, the coating amount is from about 1 to about 15% (w/w), preferably from about 1 to about 10% (w/w), further preferably from about 2 to about 8% (w/w), based on the nucleus.

The protective agent can be coated by a usual coating method, and specifically, the protective agent can be coated by spray-coating the nucleus, for example, by a fluidized bed coating method, pan coating method and the like.

II. Coating of nucleus with film agent

A nucleus obtained in the above-mentioned step I is coated with a film agent solution obtained by heat-solving the above-mentioned water-insoluble substance and pH-dependent swellable polymer, and a hydrophilic substance, or by dissolving or dispersing them in a solvent, to give a sustained release preparation.

As the method for coating a nucleus with a film agent solution, for example, a spray coating method and the like are listed.

The composition ratio of a water-insoluble substance, swellable polymer or hydrophilic substance in a film agent solution is appropriately selected so that the contents of these components in a coated film are the above-mentioned contents, respectively.

The coating amount of a film agent is from about 1 to about 90% (w/w), preferably from about 5 to about 50% (w/w), further preferably from about 5 to about 35% (w/w), based on a nucleus (not including coating amount of protective agent).

As the solvent in a film agent solution, water or an organic solvent can be used alone or in admixture thereof. In the case of use in admixture, the mixing ratio of water to an organic solvent (water/organic solvent: by weight) can be varied in the range from 1 to 100%, and preferably from 1 to about 30%. The organic solvent is not particularly restricted providing it dissolves a water-insoluble substance, and for example, lower alcohols such as methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, lower alkanone such as acetone and the like, acetonitrile, chloroform, methylene chloride and the like are used. Among them, lower alcohols are preferable, and ethyl alcohol and isopropyl alcohol are particularly preferable. Water, and a mixture of water with an organic solvent are preferably used as a solvent for a film agent. In this case, if necessary, an acid such as tartaric acid, citric acid, succinic acid, fumaric acid, maleic acid and the like may also be added into a film agent solution for stabilizing the film agent solution.

An operation of coating by spray coating can be effected by a usual coating method, and specifically, it can be effected by spray-coating a film agent solution onto a nucleus by a fluidized bed coating method, pan coating method and the like. In this case, if necessary, talc, titanium oxide, magnesium stearate, calcium stearate, light anhydrous silicic acid and the like may also be added as a lubricant, and glycerin fatty acid ester, hydrogenated castor oil, triethyl citrate, cetyl alcohol, stearyl alcohol and the like may also be added as a plasticizer.

After coating with a film agent, if necessary, an antistatic agent such as talc and the like may be mixed.

The immediate-release preparation may be liquid (solution, suspension, emulsion and the like) or solid (particle, pill,

tablet and the like). As the immediate-release preparation, oral agents and parenteral agents such as an injection and the like are used, and oral agents are preferable.

The immediate-release preparation, usually, may contain, in addition to an active component drug, also carriers, additives and excipients conventionally used in the production field (hereinafter, sometimes abbreviated as excipient). The excipient used is not particularly restricted providing it is an excipient ordinarily used as a preparation excipient. For example, as the excipient for an oral solid preparation, lactose, starch, corn starch, crystalline cellulose (Avicel PH101, manufactured by Asahi Kasei Corporation, and the like), powder sugar, granulated sugar, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine and the like are listed, and preferably, corn starch and mannitol and the like are listed. These excipients can be used alone or in combination of two or more. The content of the excipient is, for example, from about 4.5 to about 99.4 w/w%, preferably from about 20 to about 98.5 w/w%, further preferably from about 30 to about 97 w/w%, based on the total amount of the immediate-release preparation.

The content of a drug in the immediate-release preparation can be appropriately selected in the range from about 0.5 to about 95%, preferably from about 1 to about 60% based on the total amount of the immediate-release preparation.

When the immediate-release preparation is an oral solid preparation, it usually contains, in addition to the above-mentioned components, also an integrating agent. As this integrating agent, for example, carboxymethylcellulose calcium (ECG-505, manufactured by Gotoku Yakuhin), croscarmelose sodium (for example, Actisol, manufactured by Asahi Kasei Corporation), crospovidone (for example, Kollidon CL, manufactured by BASF), low substituted hydroxypropylcellulose (manufactured by Shin-Etsu Chemical Co., Ltd.), carboxymethylstarch (manufactured by Matsutani Kagaku K.K.), carboxymethylstarch sodium (Exprotab,

manufactured by Kimura Sangyo), partially pregelatinized starch (PCS, manufactured by Asahi Kasei Corporation), and the like are used, and for example, those which disintegrate a granule by adsorbing water in contact with water, causing swelling, or making a channel between an effective ingredient constituting the nucleus and an excipient, can be used. These disintegrating agents can be used alone or in combination of two or more. The amount of the disintegrating agent used is appropriately selected depending on the kind and blending amount of a drug used, design of releasing property, and the like, and for example, from about 0.05 to about 30 w/w%, preferably from about 0.5 to about 15 w/w%, based on the total amount of the quick releasing agent.

When the immediate-release preparation is an oral solid preparation, it may further contain, in addition to the above-mentioned composition, if desired, additives conventional in solid preparations. As such an additive, there are used, for example, a binder (e.g., sucrose, gelatin, gum Arabic powder, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin and the like), a lubricant (e.g., polyethylene glycol, magnesium stearate, talc, light anhydrous silicic acid (for example, Aerosil (Nippon Aerosil)), a surfactant (e.g., anionic surfactants such as sodium alkylsulfate and the like, nonionic surfactants such as polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil derivatives and the like), a coloring agent (e.g., tar coloring matter, caramel, iron oxide red, titanium oxide, riboflavins), if necessary, an appetizing agent (e.g., sweetening agent, flavoring agent and the like), an adsorbent, preservative, wetting agent, antistatic agent, and the like. Further, as the stabilizer, an organic acid such as tartaric acid, citric acid, succinic acid, fumaric acid and the like may also be added.

As the above-mentioned binder, hydroxypropylcellulose,

polyethylene glycol and polyvinylpyrrolidone and the like are preferably used.

The immediate-release preparation can be prepared by, based on a usual technology of producing preparations, mixing the above-mentioned components, and if necessary, further kneading the mixture, and molding it. The above-mentioned mixing is conducted by generally used methods, for example, mixing, kneading and the like. Specifically, when a immediate-release preparation is formed, for example, into a particle, it can be prepared, according to the same means as in the above-mentioned method for preparing a nucleus of a sustained release preparation, by mixing the components using a vertical granulator, universal kneader (manufactured by Hata Tekkosho), fluidized bed granulator FD-5S (manufactured by Powrex Corporation), and the like, and then, granulating the mixture by a wet extrusion granulation method, fluidized bed granulation method and the like.

Thus obtained immediate-release preparation and sustained release preparation may be themselves made into products or made into products appropriately together with preparation excipients and the like, separately, by an ordinary method, then, may be administered simultaneously or may be administered in combination at any administration interval, or they may be themselves made into one oral preparation (e.g., granule, fine particle, tablet, capsule and the like) or made into one oral preparation appropriately together with preparation excipients and the like. It may also be permissible that they are made into granules or fine particles, and filled in the same capsule to be used as a preparation for oral administration.

[3] Sublingual, buccal or intraoral quick disintegrating agent and preparation thereof

Sublingual, buccal or intraoral quick disintegrating agents may be a solid preparation such as tablet and the like, or may be an oral mucosa membrane patch (film).

As the sublingual, buccal or intraoral quick

disintegrating agent, a preparation containing the compound of the present invention or the concomitant drug and an excipient is preferable. It may contain also auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer and the like. Further, for easy absorption and increased *in vivo* use efficiency, β-cyclodextrin or β-cyclodextrin derivatives (e.g., hydroxypropyl-β-cyclodextrin and the like) and the like may also be contained.

As the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like are listed. As the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica and the like are listed, and particularly, magnesium stearate and colloidal silica are preferable. As the isotonizing agent, sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerin, urea and the like are listed, and particularly, mannitol is preferable. As the hydrophilic carrier, swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinkable polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like are listed, and particularly, crystalline cellulose (e.g., microcrystalline cellulose and the like) is preferable. As the water-dispersible polymer, gums (e.g., gum tragacanth, acacia gum, cyamoposis gum), alginates (e.g., sodium alginate), cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, water-soluble starch, polyacrylic acids (e.g., Carbomer), polymethacylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbophil, ascorbic acid, palmitates and the like are listed, and hydroxypropylmethylcellulose, polyacrylic acid, alginates, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like are preferable. Particularly, hydroxypropylmethylcellulose is preferable. As the stabilizer, cysteine, thiosorbitol, tartaric

acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like are listed, and particularly, citric acid and ascorbic acid are preferable.

The sublingual, buccal or intraoral quick disintegrating agent can be produced by mixing the compound of the present invention or the concomitant drug and an excipient by a method known *per se*. Further, if desired, auxiliary agents such as a lubricant, isotonizing agent, hydrophilic carrier, water-dispersible polymer, stabilizer, coloring agent, sweetening agent, preservative and the like may be mixed. The sublingual, buccal or intraoral quick disintegrating agent is obtained by mixing the above-mentioned components simultaneously or at a time interval, then subjecting the mixture to tablet-making molding under pressure. For obtaining suitable hardness, it may also be permissible that the materials are moistened by using a solvent such as water, alcohol and the like if desired before and after the tablet making process, and after the molding, the materials are dried, to obtain a product.

In the case of molding into a mucosa membrane patch (film), the compound of the present invention or the concomitant drug and the above-mentioned water-dispersible polymer (preferably, hydroxypropylcellulose, hydroxypropylmethylcellulose), excipient and the like are dissolved in a solvent such as water and the like, and the resulted solution is cast to give a film. Further, additives such as a plasticizer, stabilizer, antioxidant, preservative, coloring agent, buffer, sweetening agent and the like may also be added. For imparting suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be contained, or for enhancing adhesion of the film to an intraoral mucosa membrane lining, a bio-adhesive polymer (e.g., polycarbophil, carbopol) may also be contained. In the casting, a solution is poured on the non-adhesive surface, spread to uniform thickness (preferably, about 10 to 1000 micron) by an application tool such as a doctor blade and the like, then, the solution is dried to form a film. It may be

advantageous that thus formed film is dried at room temperature or under heat, and cut into a desired area.

As the preferable intraoral quick disintegrating agent, there are listed solid quick scattering dose agents composed of a network body comprising the compound of the present invention or the concomitant drug, and a water-soluble or water-diffusible carrier which is inert to the compound of the present invention or concomitant drug, are listed. This network body is obtained by sublimating a solvent from the solid composition constituted of a solution prepared by dissolving the compound of the present invention or the concomitant drug in a suitable solvent.

It is preferable that the composition of an intraoral quick disintegrating agent contains a matrix forming agent and a secondary component, in addition to the compound of the present invention or the concomitant drug.

Examples of the matrix forming agent include gelatins, dextrins, animal proteins or vegetable proteins such as soybean, wheat and psyllium seed protein and the like; rubber substances such as gum Arabic, guar gum, agar, xanthane gum and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carageenans; dextrans; pectines; synthetic polymers such as polyvinylpyrrolidone and the like; substances derived from a gelatin-gum Arabic complex, and the like. Further, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicate and the like; amino acids having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like, are contained.

One or more of the matrix forming agents can be introduced in a solution or suspension before solidification. Such as matrix forming agent may be present in addition to a surfactant, or may be present while a surfactant being excluded. The matrix forming agents aid to maintain the compound of the present

invention or the concomitant drug in the solution or suspension in diffused condition, in addition to formation of the matrix.

The composition may contain secondary components such as a preservative, antioxidant, surfactant, thickening agent, coloring agent, pH controlling agent, flavoring agent, sweetening agent, food taste masking agent and the like. As the suitable coloring agent, there are listed red, black and yellow iron oxides, and FD & C dyes such as FD & C Blue 2, FD & C Red 40 and the like manufactured by Ellis and Everard. Examples of the suitable flavoring agent include mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry, grape flavor and combinations thereof. Examples of the suitable pH controlling agent include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Examples of the suitable sweetening agent include aspartame, acesulfame K and thaumatin and the like. Examples of the suitable food taste masking agent include sodium bicarbonate, ion exchange resin, cyclodextrin-inclusion compounds, adsorbent substances and microcapsulated apomorphine.

The preparation contains the compound of the present invention or the concomitant drug in an amount usually from about 0.1 to about 50% by weight, preferably from about 0.1 to about 30% by weight, and preferable are preparations (such as the above-mentioned sublingual agent, buccal and the like) which can dissolve 90% or more of the compound of the present invention or the concomitant drug (into water) within the time range of about 1 to about 60 min, preferably of about 1 to about 15 min, more preferably of about 2 to about 5 min, and intraoral quick disintegrating preparations which are disintegrated within the range of 1 to 60 sec, preferably of 1 to 30 sec, further preferably of 1 to 10 sec, after placed in an oral cavity.

The content of the above-mentioned excipient in the whole preparation is from about 10 to about 99% by weight, preferably from about 30 to about 90% by weight. The content of β-cyclodextrin or β-cyclodextrin derivative in the whole

preparation is from 0 to about 30% by weight. The content of the lubricant in the whole preparation is from about 0.01 to about 10% by weight, preferably from about 1 to about 5% by weight. The content of the isotonizing agent in the whole preparation is from about 0.1 to about 90% by weight, preferably, from about 10 to about 70% by weight. The content of the hydrophilic carrier in the whole preparation is from about 0.1 to about 50% by weight, preferably, from about 10 to about 30% by weight. The content of the water-dispersible polymer in the whole preparation is from about 0.1 to about 30% by weight, preferably, from about 10 to about 25% by weight. The content of the stabilizer in the whole preparation is from about 0.1 to about 10% by weight, preferably, from about 1 to 5% by weight. The above-mentioned preparation may further contain additives such as a coloring agent, sweetening agent, preservative and the like, if necessary.

The dosage of a combination agent of the present invention differs depending on the kind of a compound of the present invention, age, body weight, condition, drug form, administration method, administration period and the like, and for example, for one cancer patient (adult, body weight: about 60 kg), the combination agent is administered intravenously, at a dose of about 0.01 to about 1000 mg/kg/day, preferably about 0.01 to about 100 mg/kg/day, more preferably about 0.1 to about 100 mg/kg/day, particularly about 0.1 to about 50 mg/kg/day, especially about 1.5 to about 30 mg/kg/day, in terms of the compound of the present invention or the concomitant drug, respectively, once or several times in division a day. Of course, since the dose as described above varies depending on various conditions, amounts smaller than the above-mentioned dosage may sometimes be sufficient, further, amounts over that range sometimes have to be administered.

The amount of the concomitant drug can be set at any value unless side effects are problematical. The daily dosage in terms of the concomitant drug differs depending on the severity of the

symptom, age, sex, body weight, sensitivity difference of the subject, administration period, interval, and nature, pharmacy, kind of the pharmaceutical preparation, kind of effective ingredient, and the like, and not particularly restricted, and the amount of a drug is, in the case of oral administration for example, usually from about 0.001 to 2000 mg, preferably from about 0.01 to 500 mg, further preferably from about 0.1 to 100 mg, per 1 kg of a mammal and this is usually administered once to 4-times in division a day.

In administration of a combination agent of the present invention, the compound of the present invention may be administered after administration of the concomitant drug or the concomitant drug may be administered after administration of the compound of the present invention, though they may be administered simultaneously. When administered at a time interval, the interval differs depending on the effective ingredient to be administered, drug form and administration method, and for example, when the concomitant drug is administered first, a method in which the compound of the present invention is administered within time range of from 1 min to 3 days, preferably from 10 min to 1 day, more preferably from 15 min to 1 hr after administration of the concomitant drug is exemplified. When the compound of the present invention is administered first, a method in which the concomitant drug is administered within time range of from 1 min to 1 day, preferably from 10 min to 6 hrs, more preferably from 15 min to 1 hr after administration of the compound of the present invention is exemplified.

In a preferable administration method, for example, the concomitant drug which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.001 to 200 mg/kg, and about 15 min later, the compound of the present invention which has been molded into an oral administration preparation is administered orally at a daily dose of about 0.005 to 100 mg/kg.

Furthermore, the compound of the present invention or the combination agent of the present invention can be used concurrently with a non-drug therapy. To be precise, the compound of the present invention and the combination agent of the present invention can be combined with a non-drug therapy such as (1) surgery, (2) hypertensive chemotherapy using angiotensin II etc., (3) gene therapy, (4) thermotherapy, (5) cryotherapy, (6) laser cauterization, (7) radiotherapy, and the like.

For example, by using the compound of the present invention or the combination agent of the present invention before or after an surgery and the like, or before or after a combined treatment of two or three kinds thereof, effects such as prevention of emergence of resistance, prolongation of Disease-Free Survival, suppression of cancer metastasis or recurrence, prolongation of life and the like can be afforded.

In addition, it is possible to combine a treatment with the compound of the present invention or the combination agent of the present invention with a supportive therapy [(i) administration of antibiotic (e.g., β-lactam type such as pansporin and the like, macrolide type such as clarithromycin and the like etc.) for the complication with various infectious diseases, (ii) administration of total parenteral nutrition, amino acid preparation or general vitamin preparation for the improvement of malnutrition, (iii) administration of morphine for pain mitigation, (iv) administration of a pharmaceutical agent for improving side effects such as nausea, vomiting, anorexia, diarrhea, leucopenia, thrombocytopenia, decreased hemoglobin concentration, hair loss, hepatopathy, renopathy, DIC, fever and the like and (v) administration of a pharmaceutical agent for suppressing multiple drug resistance of cancer and the like].

Preferably, the compound of the present invention or the combination agent of the present invention is administered orally (including sustained-release preparations), intravenously

(including boluses, infusions and clathrates), subcutaneously and intramuscularly (including boluses, infusions and sustained-release preparations), transdermally, intratumorally or proximally before or after the above-described treatment is conducted.

As a period for administering the compound of the present invention or the combination agent of the present invention before the surgery, etc., for example, it can be administrated 1-time about 30 min to 24 hrs before the surgery, etc., or in 1 to 3 cycles about 3 months to 6 months before the surgery, etc. In this way, the surgery, etc. can be conducted easily because, for example, a cancer tissue would be reduced by administering the compound of the present invention or the combination agent of the present invention before the surgery, and the like.

As a period for administering the compound of the present invention or the combination agent of the present invention after the surgery, etc., for example, it can be administrated repeatedly per a few weeks to 3 months, about 30 min to 24 hrs after the surgery, and the like. In this way, it enhances the effect of the surgery, etc. by administering the compound of the present invention or the combination agent of the present invention after the surgery, and the like.

Examples

The present invention is specifically explained in the following by way of Reference Examples, Examples, Formulation Examples, Experimental Examples and Test Examples, which are not to be construed as limitative.

The LC/MS analysis in the Examples was performed under the following conditions.

measurement tool: Waters Corporation ZQ

column: manufactured by Shiseido Co., Ltd. CAPCELL PAK C18 UG120 S-3 3 μm, 35 X 1.5 mm

solvent: SOLUTION A; 5 mM aqueous ammonium acetate/acetonitrile=98/2

SOLUTION B; 100 mM aqueous ammonium

acetate/acetonitrile=5/95
gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=100/0), 2.00 min (SOLUTION A/SOLUTION B=0/100), 3.00 min (SOLUTION A/SOLUTION B=0/100), 3.01 min (SOLUTION A/SOLUTION B=100/0), 3.80 min (SOLUTION A/SOLUTION B=100/0)
flow rate: 0.5 mL/min, Column temperature was room temperature with no temperature control.
ionization method: Electron Spray Ionization, ESI positive and negative ion peaks were detected.
The percentage of the peak area detected at UV: 220 nm of the resultant product peak was taken as the purity of the compound.

In the Examples, preparative HPLC was performed as in the following.
Preparative HPLC tools: Gilson, Inc. High-Throughput purification system
column: YMC Combiprep Hydrosphere C18 S-5 5 μm, 12 nM. 50 X 20 mm
solvent: SOLUTION A; water
SOLUTION B; acetonitrile
gradient cycle: 0.00 min (SOLUTION A/SOLUTION B=98/2), 1.10 min (SOLUTION A/SOLUTION B=98/2), 5.00 min (SOLUTION A/SOLUTION B=0/100), 6.40 min (SOLUTION A/SOLUTION B=0/100), 6.50 min (SOLUTION A/SOLUTION B=2/98), 6.52 min (SOLUTION A/SOLUTION B=2/98)
flow rate: 25 mL/min, detection method: UV 220 nm

Unless otherwise specified, the elution by column chromatography was performed under observation by TLC (thin layer chromatography) in Reference Examples and Examples. For TLC observation, 60F254 manufactured by Merck, or NH TLC plate manufactured by Fuji Silysia Chemical Ltd. was used as a TLC plate, and the solvent used as an elution solvent in column chromatography was used as a developing solvent. For detection, moreover, a UV detector was employed. As the silica gel for column chromatography, silica gel 60 (70-230 mesh) manufactured by Merck, NH silica gel (100-200 mesh) manufactured by Fuji

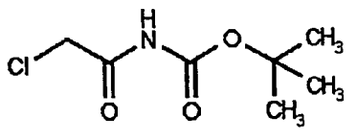
Silysia Chemical Ltd. and the like were used. The room temperature generally means from about 10°C to 35°C. For drying the extract, anhydrous sodium sulfate or anhydrous magnesium sulfate was used.

In Formulation Examples, the Japanese Pharmacopoeia 14th Edition or Japanese Pharmaceutical Excipients 2003 compatible products are used as the preparation additives (e.g., lactose, cornstarch, magnesium stearate, microcrystalline cellulose). Abbreviations in the Examples and Reference Examples mean the following.

LC: liquid chromatography
MS: mass spectrometry
ESI: electrospray ionization
FAB: fast atomic beam
M: molecular ion peak
NMR: nuclear magnetic resonance spectra
Hz: hertz
J: coupling constant
m: multiplet
q: quartet
t: triplet
d: doublet
s: singlet
br: broad
dt: double triplet
brs: broad singlet
wt%: weight percent
DMSO: dimethyl sulfoxide

Reference Example 1

Production of tert-butyl (chloroacetyl)carbamate

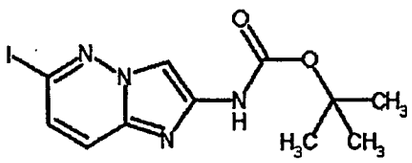


To a suspension of 2-chloroacetamide (25 g, 267 mmol) in 1,2-dichloroethane (125 mL) was added dropwise oxalyl chloride (28 mL, 321 mmol) at 0°C. After heating under reflux for 3 hr, the mixture was cooled to 0°C, tert-butyl alcohol/1,2-dichloroethane (75 mL, 1/1) was added to the mixture, and the mixture was stirred for 20 min. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with 1,2-dichloroethane. After washing with saturated aqueous sodium hydrogencarbonate solution and water, the extract was dried over anhydrous magnesium sulfate and filtrated. The solvent was evaporated under reduced pressure, and the residue was recrystallized from cyclohexane to give the title compound (25.6 g, 49%) as white crystals.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.58 (9H, s), 4.46 (2H, s), 7.59 (1H, br).

Reference Example 2

Production of tert-butyl (6-iodoimidazo[1,2-b]pyridazin-2-yl)carbamate

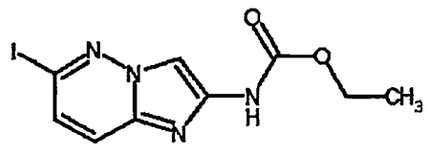


To a solution of 3-amino-6-iodopyridazine (10.0 g, 45.2 mmol) in N,N-dimethylacetamide (100 mL) were added tert-butyl (chloroacetyl)carbamate (14.0 g, 72.4 mmol) and disodium hydrogenphosphate (16.1 g, 113 mmol), and the mixture was stirred at 120°C for 3 hr. After cooling the mixture to room temperature, water (400 mL) was added to the mixture, and the precipitated crystals were filtrated, and washed with acetonitrile and petroleum ether to give the title compound (10.2 g, 63%) as a green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.49 (9H, s), 7.45 (1H, d, J = 9.5 Hz), 7.69 (1H, d, J = 9.5 Hz), 8.01 (1H, brs), 10.20 (1H, brs).

Reference Example 3

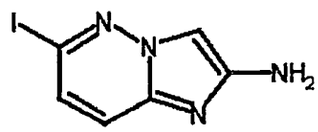
Production of ethyl (6-iodoimidazo[1,2-b]pyridazin-2-yl)carbamate



To a solution of 3-amino-6-iodopyridazine (27.0 g, 122 mmol) in N,N-dimethylacetamide (270 mL) were added ethyl (chloroacetyl)carbamate (32.4 g, 195 mmol) and disodium hydrogenphosphate (43.4 g, 305 mmol), and the mixture was stirred at 110°C for 3 hr. After cooling the mixture to room temperature, water (810 mL) was added, and the precipitated crystals were filtrated, and washed with acetonitrile and ether to give the title compound (33.0 g, 81%) as a dark brown powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.26 (3H, t, J = 7.1 Hz), 4.17 (2H, q, J = 7.1 Hz), 7.47 (1H, d, J = 9.2 Hz), 7.70 (1H, d, J = 9.2 Hz), 8.06 (1H, s), 10.51 (1H, brs).

Reference Example 4-1

Production of 6-iodoimidazo[1,2-b]pyridazin-2-amine

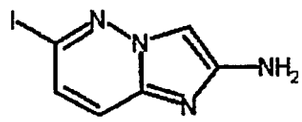


To a suspension of tert-butyl (6-iodoimidazo[1,2-b]pyridazin-2-yl)carbamate (10.2 g, 28.3 mmol) in ethyl acetate (50 mL) was added 4N hydrochloric acid/ethyl acetate (75 mL), and the mixture was stirred at room temperature for 4 hr. Diethyl ether (200 mL) was added to the reaction mixture, and the precipitate was filtrated. After washing with saturated aqueous sodium hydrogencarbonate solution, the filtrate was washed with water, acetonitrile and diethyl ether to give the title compound (4.9 g, 67%) as a green powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.61 (2H, s), 7.22 (1H, d, J = 8.7

Hz), 7.36 (1H, s), 7.39 (1H, d, J = 8.7 Hz).

Reference Example 4-2

Production of 6-iodoimidazo[1,2-b]pyridazin-2-amine

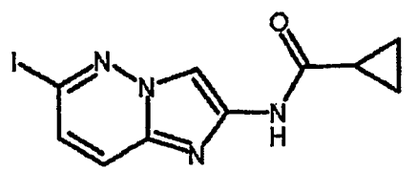


To barium hydroxide octahydrate (14.5 g, 46.1 mmol) was added water (240 mL), and the mixture was stirred at 80°C for 15 min. A solution of ethyl (6-iodoimidazo[1,2-b]pyridazin-2-yl)carbamate (10.2 g, 30.7 mmol) in N-methylpyrrolidone (80 mL) was added to the mixture, and the mixture was stirred at 120°C for 8 hr. After cooling the mixture to room temperature, water (480 mL) was added to the mixture, and the mixture was stirred for 1 hr. The mixture was extracted twice with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, diisopropyl ether was added to the residue, and the precipitated crystals were collected by filtration to give the title compound (6.1 g, 76%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.61 (2H, s), 7.22 (1H, d, J = 8.7 Hz), 7.36 (1H, s), 7.39 (1H, d, J = 8.7 Hz).

Reference Example 5

Production of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

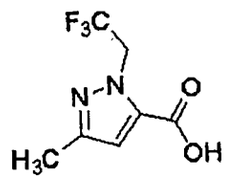


To a solution (10 mL) of 6-iodoimidazo[1,2-b]pyridazin-2-amine (1.0 g, 3.85 mmol) in N,N-dimethylacetamide was added cyclopropylcarbonyl chloride (0.38 mL, 4.23 mmol), and the

mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with hexane/ethyl acetate (4/1) to give the title compound (1.01 g, 80%) as a dark brown powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.82 - 0.86 (4H, m), 1.90 - 2.00 (1H, m), 7.49 (1H, d, J = 9.3 Hz), 7.73 (1H, d, J = 9.3 Hz), 8.23 (1H, s), 11.20 (1H, s).

Reference Example 7

Production of 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylic acid



To a suspension of sodium hydride (1.62 g, 40.4 mmol) in N,N-dimethylformamide (250 mL) was added dropwise a solution of ethyl 3-methyl-1H-pyrazole-5-carboxylate (5660 mg, 36.8 mmol) in N,N-dimethylformamide (50 mL) over 10 min under ice-cooling. After the completion of the dropwise addition, the reaction mixture was stirred at 0°C for 10 min and at room temperature for 40 min. To the mixture was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (9.87 g, 40.4 mmol), and the mixture was stirred at room temperature for 3 hr. Under ice-cooling, 1N hydrochloric acid (36 mL) was added to the mixture, and the solvent was evaporated under reduced pressure. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and

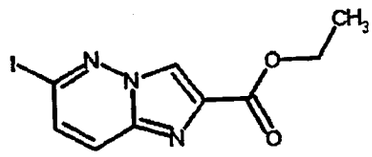
filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→60/40), and recrystallized from ethyl acetate/hexane to give ethyl 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylate (1.98 g, 23%) as white crystals.

To a solution of ethyl 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylate (1.74 g, 7.36 mmol) in tetrahydrofuran (5.0 mL) was added 8N sodium hydroxide (4.6 mL), and the mixture was stirred at room temperature for 2 hr. 6N hydrochloric acid (6.0 mL) was added to the mixture (pH=3), and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was filtrated, and washed with ethyl acetate/hexane to give the title compound (1.28 g, 84%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 5.36 (2H, q, J = 9.0 Hz), 6.76 (1H, s), 13.66 (1H, brs).

Reference Example 8

Production of ethyl 6-iodoimidazo[1,2-b]pyridazine-2-carboxylate

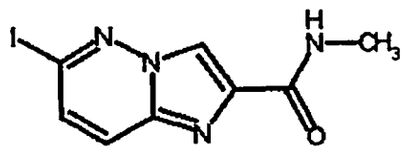


Using 3-amino-6-iodopyridazine (2.0 g, 9.05 mmol), N,N-dimethylacetamide (20 mL), ethyl 3-bromo-2-oxopropanate (1.82 mL, 14.5 mmol) and disodium hydrogenphosphate (3.21 g, 22.6 mmol), and in the same manner as in Reference Example 3, the title compound (1.2 g, 44%) was obtained as a green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.33 (3H, t, J = 7.1 Hz), 4.33 (2H, q, J = 7.1 Hz), 7.65 (1H, d, J = 9.5 Hz), 7.96 (1H, d, J = 9.5 Hz), 8.88 (1H, s).

Reference Example 9

Production of 6-iodo-N-methylimidazo[1,2-b]pyridazine-2-carboxamide

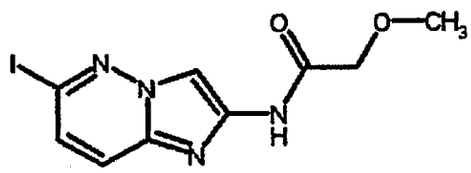


To a suspension of ethyl 6-iodoimidazo[1,2-b]pyridazine-2-carboxylate (4.5 g, 14.8 mmol) in methanol (13.5 mL) was added dropwise a solution of methylamine/tetrahydrofuran (2 mol/L, 37.1 mL, 74.2 mmol), and the mixture was stirred at room temperature for 96 hr. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate, saturated brine and water to give the title compound (3.2 g, 71%) as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.79 (3H, d, J = 4.8 Hz), 7.62 (1H, d, J = 9.6 Hz), 7.90 (1H, d, J = 9.6 Hz), 8.46 - 8.55 (1H, m), 8.65 (1H, s).

Reference Example 10

Production of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methoxyacetamide



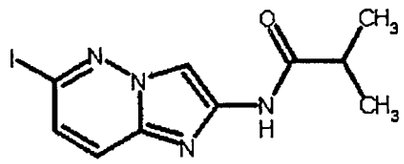
Using 6-iodoimidazo[1,2-b]pyridazin-2-amine (1.0 g, 3.85 mmol), N,N-dimethylacetamide (10 mL) and methoxyacetyl chloride (0.46 g, 4.23 mmol) as starting materials and in the same manner as in Reference Example 5, the title compound (1.01 g, 79%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.36 (3H, s), 4.09 (2H, s), 7.51 (1H, d, J = 9.6 Hz), 7.75 (1H, d, J = 9.6 Hz), 8.30 (1H, s), 10.73

(1H, s).

Reference Example 11

Production of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylpropanamide

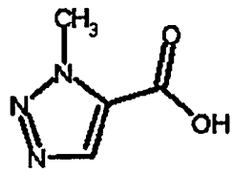


Using 6-iodoimidazo[1,2-b]pyridazin-2-amine (1.0 g, 3.85 mmol), N,N-dimethylacetamide (8.0 mL) and isobutyryl chloride (0.44 mL, 4.23 mmol) as starting materials and in the same manner as in Reference Example 5, the title compound (0.93 g, 73%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.10 (6H, d, J = 6.6 Hz), 2.67 - 2.74 (1H, m), 7.49 (1H, d, J = 9.3 Hz), 7.73 (1H, d, J = 9.3 Hz), 8.27 (1H, s), 10.87 (1H, s).

Reference Example 12

Production of 1-methyl-1H-1,2,3-triazole-5-carboxylic acid

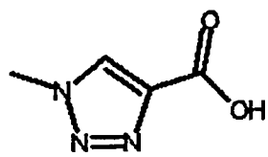


To a solution of ethyl 1-methyl-1H-1,2,3-triazole-5-carboxylate (1.15 g, 7.41 mmol) in methanol (17 mL) was added 1N sodium hydroxide (11.5 mL), and the mixture was stirred at room temperature for 1 hr. Methanol was evaporated under reduced pressure, 1N hydrochloric acid (12 mL) was added to the mixture, the precipitated crystals were collected by filtration and washed with water. The crystals were vacuum dried at 90°C to give the title compound (148 mg, 16%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.23 (3H, s), 8.20 (1H, s).

Reference Example 13

Production of 1-methyl-1H-1,2,3-triazole-4-carboxylic acid

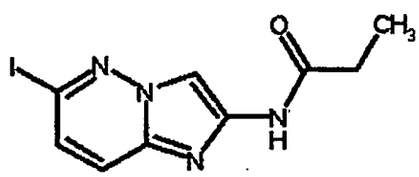


Using ethyl 1-methyl-1H-1,2,3-triazole-4-carboxylate (1.48 g, 9.54 mmol), methanol (22 mL), 1N sodium hydroxide (15 mL) and 1N hydrochloric acid (15 mL) as starting materials and in the same manner as in Reference Example 12, the title compound (605 mg, 50%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.09 (3H, s), 8.62 (1H, s), 10.06 (1H, br).

Reference Example 14

Production of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)propaneamide

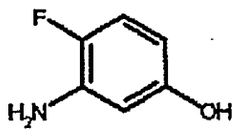


Using 6-iodoimidazo[1,2-b]pyridazin-2-amine (1.0 g, 3.85 mmol), N,N-dimethylacetamide (10 mL) and propionyl chloride (0.37 mL, 4.23 mmol) as starting materials and in the same manner as in Reference Example 5, the title compound (0.88 g, 72%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.08 (3H, d, J = 7.5 Hz), 2.39 (2H, q, J = 7.5 Hz), 7.48 (1H, d, J = 9.3 Hz), 7.73 (1H, d, J = 9.3 Hz), 8.26 (1H, s), 10.86 (1H, s).

Reference Example 15

Production of 3-amino-4-fluorophenol

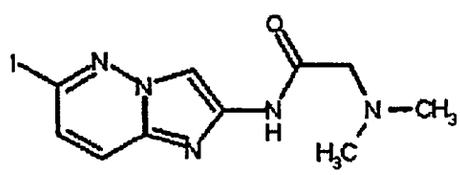


To a solution of 2-chloro-4-fluoro-5-nitrophenol (3.20 g, 16.7 mmol) in methanol (60 mL) was added 20 wt% palladium hydroxide on carbon (1.60 g) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 8 hr under hydrogen atmosphere. After nitrogen replacement, triethylamine (2.32 mL, 16.7 mmol) was added to the reaction mixture, and the mixture was filtered through a kiriyama funnel. Saturated brine was added to the filtrate, and the mixture was extracted twice with diethyl ether. The extract was dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was recrystallized from diethyl ether/hexane to give the title compound (1.40 g, 66%) as pale-brown crystals.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.70 (2H, brs), 4.50 (1H, s), 6.10 (1H, dt, J = 8.7, 3.0 Hz), 6.26 (1H, dd, J = 7.5, 3.0 Hz), 6.81 (1H, dd, J = 10.8, 8.7 Hz).

Reference Example 16

Production of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-N^2,N^2-dimethylglycinamide



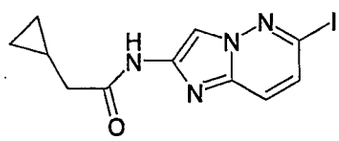
To a solution of 6-iodoimidazo[1,2-b]pyridazin-2-amine (1040 mg, 4.0 mmol) in N-methylpyrrolidone (5.0 mL) was added dimethylaminoacetyl chloride hydrochloride (948 mg, 6.0 mmol), and the mixture was stirred at room temperature for 6 hr. The

reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30), and precipitated from diisopropyl ether to give the title compound (1019 mg, 74%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.28 (6H, s), 3.16 (2H, s), 7.51 (1H, d, J = 9.2 Hz), 7.75 (1H, d, J = 9.2 Hz), 8.29 (1H, s), 10.50 (1H, s).

Reference Example 17

Production of 2-cyclopropyl-N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide

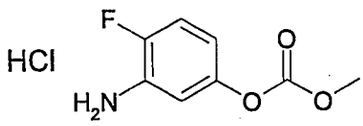


To a solution of cyclopropylacetic acid (441 mg, 4.4 mmol) in tetrahydrofuran (8.0 mL) were added N,N-dimethylformamide (1 drop) and thionyl chloride (0.32 mL, 4.4 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure, and dissolved in N,N-dimethylacetamide (2.0 mL). To a solution of 6-iodoimidazo[1,2-b]pyridazin-2-amine (1.04 g, 4.0 mmol) in N,N-dimethylacetamide (6.0 mL) was added dropwise the above-mentioned solution under ice-cooling. The mixture was stirred at room temperature for 2 hr. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by basic silica gel column chromatography (ethyl acetate/hexane=80/20→100/0), and recrystallized from ethyl acetate to give the title compound (982 mg, 72%) as pale-green crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.10 - 0.25 (2H, m), 0.45 - 0.55 (2H, m), 1.00 - 1.15 (1H, m), 2.27 (2H, d, J = 6.9 Hz), 7.48 (1H, d, J = 9.4 Hz), 7.72 (1H, d, J = 9.4 Hz), 8.28 (1H, s), 10.82 (1H, s).

Reference Example 18

Production of 3-amino-4-fluorophenyl methyl carbonate hydrochloride

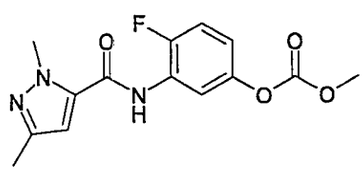


To a solution (20 mL) of 2-chloro-4-fluoro-5-nitrophenyl methyl carbonate (1.00 g, 4.0 mmol) in methanol was added 20% palladium hydroxide on carbon (0.4 g) under a nitrogen atmosphere. The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 5 days. After nitrogen replacement, the catalyst was filtered off. The solvent was evaporated from the filtrate under reduced pressure, and the residue was recrystallized from diethyl ether to give the title compound (759 mg, 86%) as a pale-green powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.89 (3H, s), 6.75-6.85 (1H, m), 7.05-7.15 (2H, m).

Reference Example 19

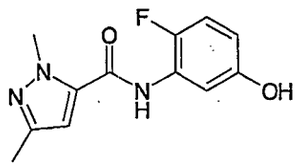
Production of 3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-fluorophenyl methyl carbonate



Using a solution of 3-amino-4-fluorophenyl methyl carbonate hydrochloride (740 mg, 3.34 mmol) and 1,3-dimethyl-1H-pyrazole-5-carbonylchloride (556 mg, 3.51 mmol) in N,N-dimethylacetamide (10 mL), and by a reaction in the same manner as in Example 148, the title compound (895 mg, 87%) was obtained

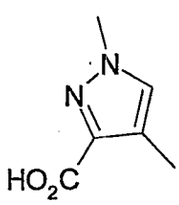
as a white powder.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.30 (3H, s), 3.91 (3H, s), 4.14 (3H, s), 6.45 (1H, s), 6.85 - 6.95 (1H, m), 7.13 (1H, dd, J = 9.0 Hz, 10.5 Hz), 7.83 (1H, br s), 8.33 (1H, dd, J = 2.7 Hz, 6.6 Hz).

Reference Example 20
Production of N-(2-fluoro-5-hydroxyphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



To a solution of 3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-fluorophenyl methyl carbonate (448 mg, 1.46 mmol) in methanol (10 mL) was added 1N aqueous sodium hydroxide solution (2 mL, 2 mmol) under ice-cooling, and the mixture was stirred at room temperature for 40 min. Under ice-cooling, 1N hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was recrystallized from diethyl ether/hexane to give the title compound (305 mg, 84%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.98 (3H, s), 6.56 (1H, m), 6.82 (1H, s), 6.97 - 7.10 (2H, m), 9.47 (1H, s), 9,85 (1H, s).

Reference Example 21
Production of 1,4-dimethyl-1H-pyrazole-3-carboxylic acid



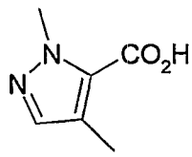
Using ethyl 1,4-dimethyl-1H-pyrazole-3-carboxylate (440 mg,

2.62 mmol), 1N aqueous sodium hydroxide solution (3 mL, 3 mmol) and ethanol (3 mL), and by a reaction in the same manner as in Reference Example 20, the title compound (152 mg, 41%) was obtained as pale-yellow crystals.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.30 (3H, s), 3.92 (3H, s), 7.21 (1H, s).

Reference Example 22

Production of 1,4-dimethyl-1H-pyrazole-5-carboxylic acid

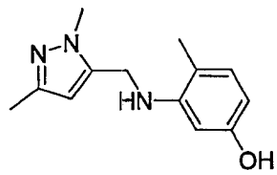


Using ethyl 1,4-dimethyl-1H-pyrazole-5-carboxylate (565 mg, 3.36 mmol), 1N aqueous sodium hydroxide solution (4 mL, 4 mmol) and ethanol (4 mL), and by a reaction in the same manner as in Reference Example 20, the title compound (261 mg, 55%) was obtained as colorless crystals.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.31 (3H, s), 4.16 (3H, s), 7.34 (1H, s).

Reference Example 23

Production of 3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}-4-methylphenol



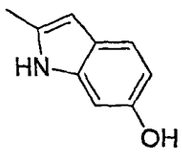
To a solution of 3-amino-4-methylphenol (930 mg, 7.5 mmol) in N,N-dimethylacetamide (10 mL) was added a solution of 1,3-dimethyl-1H-pyrazole-5-carbonylchloride (1370 mg, 8.7 mmol) in N,N-dimethylacetamide (5 mL), and the mixture was stirred at 0°C for 20 min. To the mixture were added ethyl acetate/tetrahydrofuran, saturated aqueous sodium hydrogencarbonate solution, and the aqueous layer was extracted

4 times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give N-(5-hydroxy-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (1170 mg, 63%) as a white solid. To a suspension of lithium aluminum hydride (1130 mg, 24 mmol) in tetrahydrofuran (35 mL) was slowly added dropwise a solution of N-(5-hydroxy-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (1170 mg, 4.8 mmol) in tetrahydrofuran (10 mL) under ice-cooling. After dropwise addition, the reaction mixture was heated under reflux for 5 hr. A saturated aqueous sodium sulfate solution was added to the mixture under cooling, magnesium sulfate was added and the insoluble material was filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (570 mg, 52%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.98 (3H, s), 2.06 (3H, s), 3.72 (3H, s), 4.21 (2H, d, J = 5.7 Hz), 5.23 (1H, t, J = 5.7 Hz), 5.89 (1H, s), 5.93 (1H, dd, J = 8.0, 2.3 Hz), 5.97 (1H, d, J = 2.3 Hz), 6.71 (1H, d, J = 8.3 Hz), 8.73 (1H, s).

Reference Example 24

Production of 2-methyl-1H-indole-6-ol

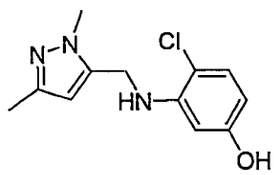


To a suspension of lithium aluminum hydride (3.7 g, 97 mmol) in 1,4-dioxane (97 mL) was slowly added dropwise a solution of methyl 6-methoxy-1H-indole-2-carboxylate (2.0 g, 9.8 mmol) in 1,4-dioxane (30 mL) under ice-cooling. After dropwise addition, the reaction mixture was heated under reflux for 24 hr. A saturated aqueous sodium sulfate solution was added to the mixture under cooling, magnesium sulfate was added and the

insoluble material was filtrated. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from hexane to give 6-methoxy-2-methyl-1H-indole (1.0 g, 6.5 mmol) as a yellow solid. To a solution of 6-methoxy-2-methyl-1H-indole (1.0 g, 6.2 mmol) in acetic acid (15 mL) was added 48% aqueous hydrogen bromide (31 mL) at room temperature, and the reaction mixture was heated under reflux for 3 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (600 mg, 65%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.29 (3H, d, J = 0.8 Hz), 5.88 - 5.95 (1H, m), 6.43 (1H, dd, J = 8.3, 2.3 Hz), 6.63 (1H, d, J = 2.3 Hz), 7.12 (1H, d, J = 8.3 Hz), 8.70 (1H, s), 10.45 (1H, br, s).

Reference Example 25

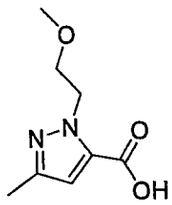
Production of 4-chloro-3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}phenol



In the same manner as in Reference Example 23 and using 3-amino-4-chlorophenol (920 mg, 6.4 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonylchloride (1170 mg, 7.4 mmol) and N, N-dimethylacetamide (13 mL) as starting materials, N-(2-chloro-5-hydroxyphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (1190 mg, 4.5 mmol) was obtained. Using lithium aluminum hydride (1060 mg, 22 mmol), N-(2-chloro-5-hydroxyphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (1190 mg, 4.5 mmol) and tetrahydrofuran (40 mL) as starting materials, the title compound (810 mg, 72%) was

obtained as a brown solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.06 (3H, s), 3.72 (3H, s), 4.29 (2H, d, J = 5.7 Hz), 5.73 (1H, t, J = 5.7 Hz), 5.87 (1H, s), 6.02 (1H, dd, J = 8.3, 2.7 Hz), 6.11 (1H, d, J = 2.7 Hz), 6.99 (1H, d, J = 8.3 Hz), 9.27 (1H, s).

Reference Example 26
Production of 1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxylic acid



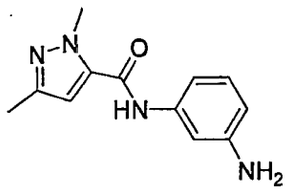
To a suspension of sodium hydride (310 mg, 7.8 mmol) in N,N-dimethylformamide (10 mL) was slowly added a solution of ethyl 3-methyl-1H-pyrazole-5-carboxylate (1000 mg, 6.5 mmol) in N,N-dimethylformamide (5 mL) under ice-cooling, and the mixture was stirred at 0°C for 10 min, then at room temperature for 20 min. To the reaction mixture was added a solution of 1-bromo-2-methoxyethane (1090 mg, 7.8 mmol) in N,N-dimethylformamide (4 mL), and the mixture was stirred at room temperature for 7 hr. The solvent was evaporated under reduced pressure, and ethyl acetate/tetrahydrofuran and water were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→70/30) to give ethyl 1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxylate (430 mg, 2.0 mmol) as a colorless liquid. To a solution of the obtained ethyl 1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxylate (430 mg, 2.0 mmol) in tetrahydrofuran (6 mL) was added 8N aqueous sodium hydroxide solution (1.3 mL), and the mixture was stirred at room

temperature for 3 hr. 1N Hydrochloric acid (13 mL) and ethyl acetate were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (310 mg, 83%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.15 (3H, s), 3.17 (3H, s), 3.61 (2H, t, J = 5.8 Hz), 4.55 (2H, t, J = 5.8 Hz), 6.56 (1H, s), 13.19 (1H, br. s).

Reference Example 27

Production of N-(3-aminophenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

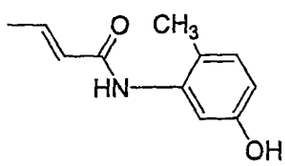


To a solution of 3-nitroaniline (1.0 g, 7.2 mmol) in N, N-dimethylacetamide (6 mL) was added a solution of 1,3-dimethyl-1H-pyrazole-5-carbonylchloride (1260 mg, 8.0 mmol) in N,N-dimethylacetamide (2 mL), and the mixture was stirred at room temperature for 30 min. Water (200 mL) was added to the mixture under ice-cooling, and the mixture was filtrated. The obtained solid was washed with water and diethyl ether to give 1,3-dimethyl-N-(3-nitrophenyl)-1H-pyrazole-5-carboxamide (1850 mg, 7.1 mmol). To a solution of the obtained 1,3-dimethyl-N-(3-nitrophenyl)-1H-pyrazole-5-carboxamide (1850 mg, 7.1 mmol) in ethanol (50 mL) was added 10% palladium/carbon (190 mg). Hydrazine monohydrate (1090 mg, 22 mmol) was slowly added to the mixture at room temperature and the mixture was stirred at 60°C for 1 hr. The reaction mixture was filtrated, and the filtrate was evaporated under reduced pressure. To the residue were added ethyl acetate and water, and the aqueous layer was extracted

with ethyl acetate (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (1650 mg, 99%) as a pale-yellow solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.98 (3H, s), 5.09 (2H, s), 6.31 (1H, d, J = 9.1 Hz), 6.76 - 6.83 (2H, m), 6.95 (1H, t, J = 8.0 Hz), 7.03 - 7.08 (1H, m), 9.81 (1H, s).

Reference Example 28

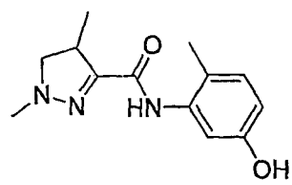
Production of (2E)-N-(5-hydroxy-2-methylphenyl)but-2-ene amide



In the same manner as in Example 259 and using (2E)-but-2-enoic acid (1680 mg, 19 mmol), tetrahydrofuran (5 mL), N, N-dimethylformamide (1 drop), oxalyl chloride (1670 μL, 19 mmol), 3-amino-4-methylphenol (2000 mg, 16 mmol) and N, N-dimethylacetamide (35 mL) as starting materials, the title compound (1830 mg, 59%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.85 (3H, dd, J = 7.0, 1.7 Hz), 2.07 (3H, s), 6.22 (1H, d, J = 15.5 Hz), 6.47 (1H, dd, J = 8.3, 2.5 Hz), 6.68 - 6.83 (1H, m), 6.95 (1H, d, J = 8.3 Hz), 7.02 (1H, s), 9.05 (1H, s), 9.16 (1H, s).

Reference Example 29

Production of N-(5-hydroxy-2-methylphenyl)-1,4-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxamide



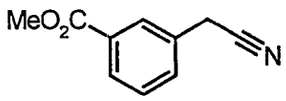
A mixture of (2E)-N-(5-hydroxy-2-methylphenyl)but-2-ene amide (1830 mg, 9.6 mmol) and 3-methyl-1,2,3-oxadiazol-3-ium-5-

olate (4 mL) was stirred at 150°C for 2 days. The reaction mixture was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→60/40) to give the title compound (351 mg, 15%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.15 (3H, d, J = 6.4 Hz), 2.07 (3H, s), 2.91 (3H, s), 3.04 - 3.11 (1H, m), 3.23 - 3.33 (2H, m), 6.47 (1H, dd, J = 8.3, 2.7 Hz), 6.97 (1H, d, J = 8.3 Hz), 7.13 (1H, d, J = 2.7 Hz), 8.94 (1H, s), 9.22 (1H, s).

Reference Example 30

Production of methyl 3-(cyanomethyl)benzoate

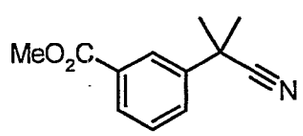


To a solution of methyl 3-(bromomethyl)benzoate (10.0 g, 44 mmol) in acetonitrile (100 mL) were added potassium cyanide (5.7 g, 87 mmol) and 18-crown-6 (1.0 g), and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtrated, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→30/70). The combined solution was concentrated under reduced pressure to give the title compound (7.0 g, 91%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.88 (3H, s), 4.17 (2H, s), 7.57 (1H, t, J = 7.6 Hz), 7.61 - 7.69 (1H, m), 7.88 - 7.95 (1H, m), 7.97 (1H, br s).

Reference Example 31

Production of methyl 3-(1-cyano-1-methylethyl)benzoate



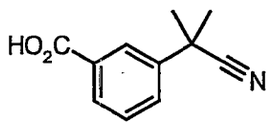
To a solution of methyl 3-(cyanomethyl)benzoate (7.0 g, 40 mmol) in dimethylsulfoxide (80 mL) was slowly added sodium hydride (60% in oil, 4.8 g, 120 mmol) under cooling at not more

than 25°C. The reaction mixture was stirred at room temperature for 20 min. To the mixture was added methyl iodide (7.5 mL, 120 mmol), and the mixture was stirred at room temperature for 16 hr. Under ice-cooling, the reaction mixture was diluted with water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→50/50). The combined solution was concentrated under reduced pressure to give the title compound (6.4 g, 79%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.72 (6 H, s), 3.89 (3 H, s), 7.61 (1 H, t, J = 7.8 Hz), 7.84 (1 H, ddd, J = 7.8, 2.1, 1.2 Hz), 7.95 (1 H, dt, J = 7.8, 1.2 Hz), 8.08 (1 H, t, J = 1.5 Hz).

Reference Example 32

Production of 3-(1-cyano-1-methylethyl)benzoic acid

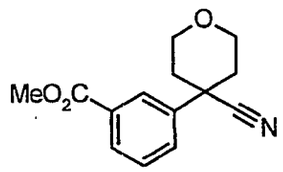


To a solution of methyl 3-(1-cyano-1-methylethyl)benzoate (2.8 g, 14 mmol) in tetrahydrofuran (30 mL) were added lithium hydroxide·monohydrate (0.98 g, 24 mmol), methanol (10 mL) and water (10 mL), and the mixture was stirred at room temperature for 18 hr. The solvent was evaporated under reduced pressure, and the residue was diluted with water (15 mL). The mixture was adjusted to pH 3 by slowly adding 1N hydrochloric acid. The precipitated white precipitate was collected by filtration, washed with water, and air-dried to give the title compound (2.5 g, 98%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.72 (6H, s), 7.57 (1H, t, J = 7.8 Hz), 7.78 (1H, dq, J = 7.8, 1.5 Hz), 7.92 (1H, dt, J = 7.8, 1.5 Hz), 8.08 (1H, t, J = 1.5 Hz) , 13.19 (1H, s).

Reference Example 33

Production of methyl 3-(4-cyanotetrahydro-2H-pyran-4-yl)benzoate

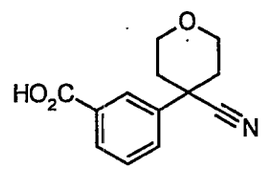


Using methyl 3-(cyanomethyl)benzoate (1.0 g, 5.7 mmol), sodium hydride (60% in oil, 0.69 g, 17 mmol), bis(2-bromoethyl)ether (1.8 g, 6.9 mmol) and dimethyl sulfoxide (12 mL) as starting materials and in the same manner as in Reference Example 31, the title compound (650 mg, 46%) was obtained as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.02 - 2.21 (4H, m), 3.61 - 3.75 (2H, m), 3.89 (3H, s), 3.98 - 4.09 (2H, m), 7.64 (1H, t, J = 7.8 Hz), 7.83 - 7.91 (1H, m), 7.93 - 8.01 (1H, m), 8.10 (1H, t, J = 1.7 Hz).

Reference Example 34

Production of 3-(4-cyanotetrahydro-2H-pyran-4-yl)benzoic acid

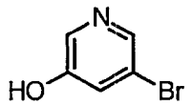


To a solution of methyl 3-(4-cyanotetrahydro-2H-pyran-4-yl)benzoate (0.62 g, 2.5 mmol) in tetrahydrofuran (6.0 mL) were added lithium hydroxide·monohydrate (0.18 g, 4.3 mmol), methanol (2.0 mL) and water (2.0 mL), and the mixture was stirred at room temperature for 12 hr. The solvent was evaporated under reduced pressure, and the residue was diluted with water (5.0 mL). The mixture was adjusted to pH 3 by slowly adding 1N hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure to give the title compound (0.48 g, 83%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.00 - 2.23 (4H, m), 3.57 - 3.77 (2H, m), 3.94 - 4.10 (2H, m), 7.61 (1H, t, J = 7.8 Hz), 7.77 - 7.87 (1H, m), 7.90 - 8.00 (1H, m), 8.05 - 8.12 (1H, m), 13.20 (1H, br s).

Reference Example 35

Production of 5-bromopyridine-3-ol

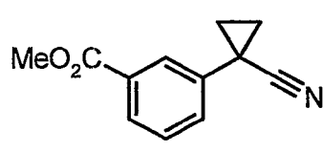


To a solution of 3-bromo-5-methoxypyridine (5.0 g, 27 mmol) in acetic acid (15 mL) was added 48% hydrobromic acid (23 mL), and the reaction mixture was heated under reflux for 16 hr. The mixture was allowed to cool to room temperature, and the solvent was evaporated under reduced pressure. The residue was adjusted to pH9 - 10 by adding 8N aqueous sodium hydroxide solution. The obtained aqueous solution was washed with diethyl ether, and the pH was adjusted to 5 - 6 by adding 6N hydrochloric acid. The obtained precipitate was collected by filtration, and washed with diisopropyl ether to give the title compound (2.8 g, 61%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.40 (1H, t, J = 2.1 Hz), 8.12 - 8.15 (2H, m), 10.47 (1H, br. s).

Reference Example 36

Production of methyl 3-(1-cyanocyclopropyl)benzoate

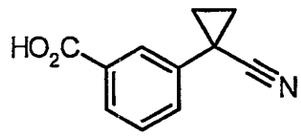


Using methyl 3-(cyanomethyl)benzoate (1.5 g, 8.6 mmol), sodium hydride (60% in oil, 1.0 g, 26 mmol), 1,2-dibromoethane (2.4 g, 13 mmol) and dimethyl sulfoxide (30 mL) as starting materials and in the same manner as in Reference Example 31, the title compound (1.3 g, 76%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.38 - 1.56 (2H, m), 1.74 - 1.82 (2H, m), 3.93 (3H, s), 7.40 - 7.49 (1H, m), 7.55 - 7.62 (1H, m), 7.88 (1H, t, J = 1.5 Hz), 7.96 (1H, dt, J = 7.8, 1.5 Hz).

Reference Example 37

Production of 3-(1-cyanocyclopropyl)benzoic acid

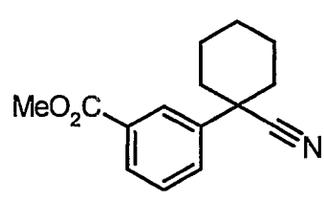


To a solution of methyl 3-(1-cyanocyclopropyl)benzoate (1.3 g, 6.4 mmol) in tetrahydrofuran (12 mL) were added lithium hydroxide·monohydrate (0.44 g, 11 mmol), methanol (4.0 mL) and water (6.0 mL), and the mixture was stirred at room temperature for 14 hr. The solvent was evaporated under reduced pressure, and the residue was diluted with water (5.0 mL). The mixture was adjusted to pH 5 by slowly adding 1N hydrochloric acid. The precipitated white precipitate was collected by filtration, washed with water, and air-dried to give the title compound (0.73 g, 61%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.50 - 1.62 (2 H, m), 1.76 - 1.86 (2 H, m), 7.41 - 7.59 (2 H, m), 7.82 - 7.97 (2 H, m), 13.19 (1 H, br. s.).

Reference Example 38

Production of methyl 3-(1-cyanocyclohexyl)benzoate

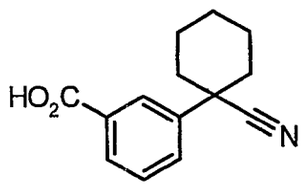


Using methyl 3-(cyanomethyl)benzoate (1.5 g, 8.6 mmol), sodium hydride (60% in oil, 1.0 g, 26 mmol), 1,5-dibromopentane (3.0 g, 13 mmol) and dimethyl sulfoxide (30 mL) as starting materials and in the same manner as in Reference Example 31, the

title compound (1.4 g, 68%) was obtained as a colorless oil.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 - 1.46 (1H, m), 1.53 - 2.17 (9H, m), 3.88 (3 H, s), 7.61 (1H, t, J = 7.8 Hz), 7.80 - 7.88 (1H, m), 7.95 (1H, dt, J = 7.8, 1.2 Hz), 8.10 (1H, t, J = 1.8 Hz).

Reference Example 39

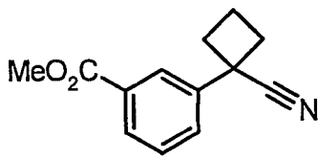
Production of 3-(1-cyanocyclohexyl)benzoic acid



Using methyl 3-(1-cyanocyclohexyl)benzoate (1.3 g, 5.3 mmol), lithium hydroxide·monohydrate (0.52 g, 13 mmol), tetrahydrofuran (18 mL), methanol (6.0 mL) and water (6.0 mL) as starting materials and in the same manner as in Reference Example 37, the title compound (1.1 g, 88%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.21 - 1.43 (1H, m), 1.52 - 2.17 (9H, m), 7.58 (1H, t, J = 7.8 Hz), 7.80 (1H, dq, J = 7.8, 1.2 Hz), 7.92 (1H, dt, J = 7.8, 1.2 Hz), 8.09 (1H, t, J = 1.8 Hz).

Reference Example 40

Production of methyl 3-(1-cyanocyclobutyl)benzoate

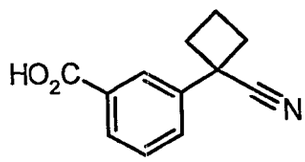


Using methyl 3-(cyanomethyl)benzoate (1.8 g, 10 mmol), sodium hydride (60% in oil, 1.2 g, 30 mmol), 1,3-dibromopropane (3.0 g, 15 mmol) and dimethyl sulfoxide (30 mL) as starting materials and in the same manner as in Reference Example 31, the title compound (0.91 g, 42%) was obtained as a colorless oil.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.92 - 2.12 (1H, m), 2.18 - 2.41 (1H, m), 2.56 - 2.91 (4H, m), 3.88 (3H, s), 7.59 - 7.66 (1H, m), 7.75

- 7.83 (1H, m), 7.91 - 8.02 (2H, m).

Reference Example 41

Production of 3-(1-cyanocyclobutyl)benzoic acid

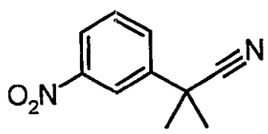


Using methyl 3-(1-cyanocyclobutyl)benzoate (0.9 g, 4.2 mmol), lithium hydroxide·monohydrate (0.26 g, 6.3 mmol), tetrahydrofuran (9.0 mL), methanol (3.0 mL) and water (4.0 mL) as starting materials and in the same manner as in Reference Example 37, the title compound (0.73 g, 86%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.93 - 2.13 (1H, m), 2.20 - 2.42 (H, m), 2.56 - 2.90 (4H, m), 7.59 (1H, t, J = 7.8 Hz), 7.68 - 7.81 (1H, m), 7.85 - 8.01 (2H, m).

Reference Example 42

Production of 2-methyl-2-(3-nitrophenyl)propanenitrile

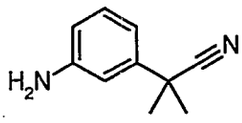


To a two-phase solution of (3-nitrophenyl)acetonitrile (5.0 g, 31 mmol) and tetraethylammoniumbromide (600 mg) in 2N aqueous sodium hydroxide (47 mL, 93 mmol) and methylene chloride (50 mL) was added methyl iodide (8.0 mL, 130 mmol), and the mixture was stirred at room temperature for 12 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=2/98→10/90) to give the title compound (0.38 g, 6.5%) as a yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.76 (6H, s), 7.76 (1H, t, J = 8.0 Hz), 8.04 (1H, dd, J = 7.8, 0.8 Hz), 8.24 (1H, d, J = 8.3 Hz), 8.32 (1H, s).

Reference Example 43

Production of 2-(3-aminophenyl)-2-methylpropanenitrile

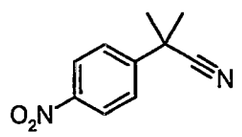


To a solution of 2-methyl-2-(3-nitrophenyl)propanenitrile (0.35 g, 1.8 mmol) in ethyl acetate (10 mL) was added 10% palladium/carbon (35 mg), and the mixture was stirred for 10 hr under hydrogen atmosphere. The residual catalyst was filtered through celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give the title compound (0.35 g, 1.8 mmol) as a pale-yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.61 (6H, s), 5.21 (2H, br. s), 6.46 - 6.55 (1H, m), 6.56 - 6.63 (1H, m), 6.71 (1H, t, J = 2.1 Hz), 7.04 (1H, t, J=7.8 Hz).

Reference Example 44

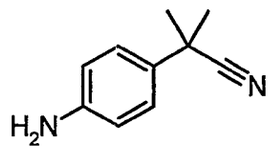
Production of 2-methyl-2-(4-nitrophenyl)propanenitrile



To a two-phase solution of (4-nitrophenyl)acetonitrile (5.0 g, 31 mmol) and tetraethylammoniumbromide (2.0 g) in 2N aqueous sodium hydroxide (75 mL, 150 mmol) and methylene chloride (50 mL) was added methyl iodide (9.6 mL, 150 mmol), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture were added 2N aqueous sodium hydroxide solution (10 mL, 20 mmol) and methyl iodide (1.5 mL, 24 mmol), and the mixture was further stirred for 2 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous

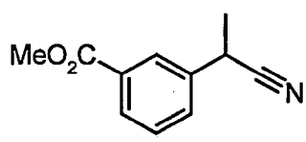
sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→10/90) to give the title compound (3.8 g, 65%) as a pale-yellow oil.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.75 (6H, s), 7.79 - 7.88 (2H, m), 8.25 - 8.34 (2H, m).

Reference Example 45
2-(4-aminophenyl)-2-methylpropanenitrile



To a solution of 2-methyl-2-(4-nitrophenyl)propanenitrile (0.95 g, 5.0 mmol) in ethyl acetate (10 mL) was added 10% palladium/carbon (100 mg), and the mixture was stirred at room temperature for 14 hr under hydrogen atmosphere. The residual catalyst was filtered through celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give the title compound (0.81 g, 99%) as a pale-yellow oil.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.59 (6H, s), 5.14 (2H, br. s), 6.57 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz).

Reference Example 46
Production of methyl 3-(1-cyanoethyl)benzoate



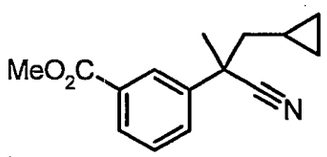
To a solution of 3-(1-cyanoethyl)benzoic acid (2.0 g, 11 mmol) in methanol (20 mL) was added conc. sulfuric acid (0.2 mL), and the mixture was stirred at 60°C for 8 hr. The reaction mixture was concentrated under reduced pressure, and neutralized with saturated aqueous sodium hydrogencarbonate solution. The mixture was diluted with water and extracted with ethyl acetate.

The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure to give the title compound (1.9 g, 89%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.57 (3H, d, J = 7.2 Hz), 3.88 (3H, s), 4.46 (1H, q, J = 7.2 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.68 - 7.76 (1H, m), 7.94 (1H, dt, J = 7.8, 1.5 Hz), 8.00 (1H, t, J = 1.8 Hz).

Reference Example 47

Production of methyl 3-(1-cyano-2-cyclopropyl-1-methylethyl)benzoate

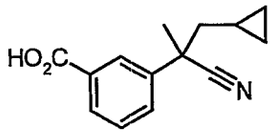


To a solution of methyl 3-(1-cyanoethyl)benzoate (1.5 g, 7.9 mmol) in acetonitrile (20 mL) were added sodium methoxide (0.95 g, 17 mmol) and (bromomethyl)cyclopropane (1.3 g, 9.5 mmol), and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added sodium hydride (60% in oil, 0.7 g, 17 mmol) under ice-cooling, and the mixture was stirred at room temperature for 16 hr. The mixture was diluted with diethyl ether, and washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine. The organic layer was dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→40/60) to give the title compound (129 mg, 6.7%) as a colorless oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ -0.10 - 0.03 (1H, m), 0.21 (1H, dt, J = 4.9, 9.1 Hz), 0.26 - 0.39 (1H, m), 0.39 - 0.50 (1H, m), 0.51 - 0.66 (1H, m), 1.70 - 1.77 (3H, m), 1.77 - 1.89 (1H, m), 1.92 - 2.03 (1H, m), 3.88 (3H, s), 7.55 - 7.67 (1H, m), 7.77 - 7.86 (1H, m), 7.95 (1H, d, J = 7.7 Hz), 8.08 - 8.13 (1H, m).

Reference Example 48

Production of 3-(1-cyano-2-cyclopropyl-1-methylethyl)benzoic acid

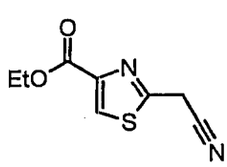


To a solution of methyl 3-(1-cyano-2-cyclopropyl-1-methylethyl)benzoate (120 mg, 0.49 mmol) in tetrahydrofuran/methanol/water (=3.0 mL/1.0 mL/1.0 mL) was added lithium hydroxide monohydrate (40 mg, 0.99 mmol), and the reaction mixture was stirred at room temperature for 4 hr. The mixture was concentrated under reduced pressure, and the obtained aqueous solution was adjusted to pH 5 by adding 1N hydrochloric acid. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give the title compound (76 mg, 66%) as a colorless oil.

^{1}H NMR (DMSO-d_6, 300 MHz) δ -0.04 - 0.09 (1 H, m), 0.18 - 0.31 (1 H, m), 0.36 - 0.49 (1H, m), 0.49 - 0.62 (1H, m), 0.64 - 0.82 (1H, m), 1.73 - 1.87 (2H, m), 1.91 - 2.03 (2H, m), 7.44 - 7.63 (1H, m), 7.79 - 7.86 (1H, m), 8.09 (1H, d, J=7.9 Hz), 8.15 - 8.22 (1H, m), 11.25 - 12.45 (1H, br. s).

Reference Example 49

Production of ethyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate



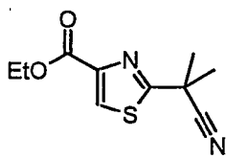
To a solution of ethyl 3-bromo-2-oxopropanate (21 g, 110 mmol) in N,N-dimethylformamide (50 mL) was added a solution of 2-cyanoethanethioamide (10 g, 100 mmol) in N,N-dimethylformamide (50 mL) under ice-cooling, and the reaction mixture was stirred

at room temperature for 12 hr. The mixture was concentrated under reduced pressure, and the obtained residue was dissolved in ethyl acetate, and washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine. The organic layer was dried over anhydrous sodium sulfate and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→60/40) to give the title compound (5.1 g, 26%) as a yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.31 (3H, t, J = 7.2 Hz), 4.31 (2H, q, J = 7.2 Hz), 4.63 (2H, s), 8.53 (1H, s).

Reference Example 50

Production of ethyl 2-(1-cyano-1-methylethyl)-1,3-thiazole-4-carboxylate

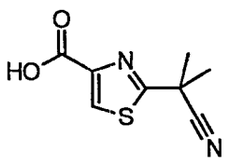


To a solution of ethyl 2-(cyanomethyl)-1,3-thiazole-4-carboxylate (2.0 g, 10 mmol) in dimethylsulfoxide (20 mL) was added sodium hydride (60% in oil, 1.6 g, 41 mmol), and the mixture was stirred at room temperature for 30 min. Under cooling, a solution of methyl iodide (2.5 mL, 41 mmol) in dimethylsulfoxide (10 mL) was added dropwise to the mixture, and the mixture was stirred at room temperature for 6 hr. Water was added to the mixture under cooling, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=5/95→50/50) to give the title compound (0.90 g, 39%) as a pale-yellow oil.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.31 (3H, t, J = 7.2 Hz), 1.83 (6H, s), 4.33 (2H, q, J=7.2 Hz), 8.59 (1H, s).

Reference Example 51

Production of 2-(1-cyano-1-methylethyl)-1,3-thiazole-4-carboxylic acid

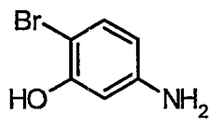


To a solution of ethyl 2-(1-cyano-1-methylethyl)-1,3-thiazole-4-carboxylate (0.9 g, 4.0 mmol) in tetrahydrofuran/methanol/water (=12 mL/4.0 mL/4.0 mL) was added lithium hydroxide monohydrate (330 mg, 8.0 mmol), and the reaction mixture was stirred at room temperature for 10 hr. The mixture was concentrated under reduced pressure, and the obtained aqueous solution was adjusted to pH 5 by adding 1N hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure to give the title compound (256 mg, 53%) as a white powder.

^{1}H NMR (DMSO-d, 300 MHz$_6$) δ 1.82 (6H, s), 8.43 (1H, s).

Reference Example 52

Production of 5-amino-2-bromophenol

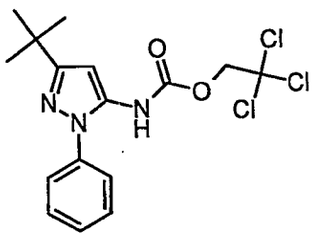


4-Bromo-3-methoxyaniline (5.0 g, 25 mmol) was added to 48% hydrobromic acid (20 mL), and the reaction mixture was stirred at 80°C for 16 hr. After completion of the reaction, the mixture was allowed to cool to room temperature, and adjusted to pH 7 - 8 by adding 8N aqueous sodium hydroxide solution. The mixture was extracted with ethyl acetate, and the obtained organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under

reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=10/90→100/0) to give the title compound (2.0 g, 43%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.10 (2H, s), 5.97 (1H, dd, J=8.4, 2.4 Hz), 6.19 (1H, d, J=2.4 Hz), 6.99 (1H, d, J=8.4 Hz), 9.64 (1H, s).

Reference Example 53

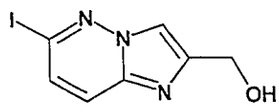
Production of 2,2,2-trichloroethyl (3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)carbamate



To a two-phase solution of 3-tert-butyl-1-phenyl-1H-pyrazol-5-amine (5.0 g, 23 mmol) in ethyl acetate (45 mL)/3N aqueous sodium hydroxide (20 mL) was added 2,2,2-trichloroethyl chlorocarbonate (4.5 mL, 33 mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The obtained organic layer was washed with 5% aqueous sodium hydrogencarbonate, water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure to give the title compound (5.0 g, 55%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (9H, s), 4.85 (2H, br. s), 6.30 (1H, s), 7.28 - 7.53 (5H, m).

Reference Example 54

Production of (6-iodoimidazo[1,2-b]pyridazin-2-yl)methanol

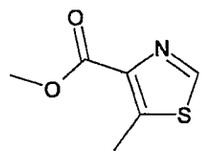


To a solution of 3-amino-6-iodopyridazine (2.0 g, 9.0 mmol) in ethanol (40 mL) was added 3-chloro-2-oxopropyl acetate

(2.73 g, 18.1 mmol), and the mixture was heated under reflux for 24 hr. After cooling the mixture to room temperature, saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was collected by filtration and washed with ethyl acetate/hexane to give the title compound (498 mg, 20%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.62 (2H, d, J = 5.6 Hz), 5.33 (1H, t, J = 5.6 Hz), 7.49 (1H, d, J = 9.3 Hz), 7.80 (1H, d, J = 9.3 Hz), 8.14 (1H, s).

Reference Example 55

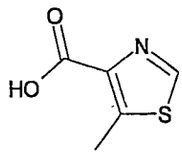
Production of methyl 5-methyl-1,3-thiazole-4-carboxylate



To a solution of methyl 2-amino-5-methyl-1,3-thiazole-4-carboxylate (2.15 g, 12.5 mmol) in tetrahydrofuran (60 mL) was slowly added tert-butyl nitrite (2.23 mL, 18.7 mmol) with stirring at 50°C, and the mixture was stirred at 60°C for 2 hr. The mixture was diluted with water (100 mL), and extracted with ethyl acetate (100 mL×2). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=80/20→0/100) to give the title compound (1.17 g, yield 60%).
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.72 (3H, s), 3.82 (3H, s), 8.90 (1H, s).

Reference Example 56

Production of 5-methyl-1,3-thiazole-4-carboxylic acid

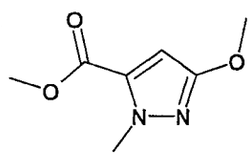


To a solution of methyl 5-methyl-1,3-thiazole-4-carboxylate (1.17 g, 7.4 mmol) in methanol (15 mL) was added 8N aqueous sodium hydroxide solution (2.00 mL), and the mixture was stirred at room temperature for 18 hr. 6N Hydrochloric acid (2.67 mL) was added to the mixture, and the mixture was concentrated under reduced pressure. Water was added to the residue, and the precipitate was collected by filtration, and washed with water. The precipitate was suspended in a mixed solvent of ethyl acetate (9 mL) and ethanol (1 mL), and the mixture was stirred at 80°C for 3 min. After allowing to cool to room temperature, the precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (531 mg, yield 50%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.71 (3H, s), 8.87 (1H, s), 12.88 (1H, br s).

Reference Example 57

Production of methyl 3-methoxy-1-methyl-1H-pyrazole-5-carboxylate



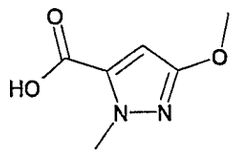
A mixture of methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (2.34 g, 15.0 mmol), iodomethane (3.19 g, 22.5 mmol), potassium carbonate (4.15 g, 30.0 mmol) and N,N-dimethylformamide (15 mL) was stirred at room temperature for 18 hr. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (50 mL×3). The organic layer was washed with water (10 mL×2), and concentrated under reduced pressure. The

residue was purified by silica gel column chromatography (hexane/ethyl acetate=100/0→50/50) to give the title compound (2.01 g, yield 79%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.78 (3H, s), 3.81 (3H, s), 3.94 (3H, s), 6.27 (1H, s).

Reference Example 58

Production of 3-methoxy-1-methyl-1H-pyrazole-5-carboxylic acid

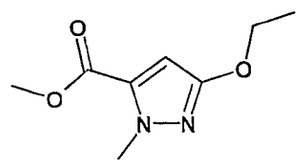


To a solution of methyl 3-methoxy-1-methyl-1H-pyrazole-5-carboxylate (2.01 g, 11.8 mmol) in methanol (15 mL) was added 8N aqueous sodium hydroxide solution (3.00 mL), and the mixture was stirred at room temperature for 18 hr. 6N Hydrochloric acid (4.00 mL) was added to the mixture, and the mixture was concentrated under reduced pressure. Water was added to the residue, and the precipitate was collected by filtration, washed with water and air-dried. The precipitate was suspended in diisopropyl ether, and the mixture was stirred at 80°C for 15 min. After allowing to cool to room temperature, the precipitate was collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to give the title compound (746 mg, yield 40%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.77 (3H, s), 3.93 (3H, s), 6.20 (1H, s), 13.37 (1H, br s).

Reference Example 59

Production of methyl 3-ethoxy-1-methyl-1H-pyrazole-5-carboxylate



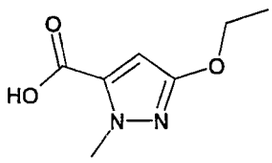
Using methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate

(2.34 g, 15.0 mmol), iodoethane (3.51 g, 22.5 mmol), potassium carbonate (4.15 g, 30.0 mmol) and N,N-dimethylformamide (15 mL), and in the same manner as in Reference Example 57, the title compound (2.59 g, yield 94%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 3.81 (3H, s), 3.93 (3H, s), 4.10 (2H, q, J = 7.0 Hz), 6.25 (1H, s).

Reference Example 60

Production of 3-ethoxy-1-methyl-1H-pyrazole-5-carboxylic acid

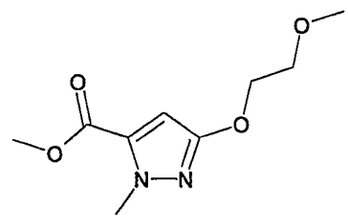


Using methyl 3-ethoxy-1-methyl-1H-pyrazole-5-carboxylate (2.59 g, 14.1 mmol), methanol (15 mL) and 8N aqueous sodium hydroxide solution (3.00 mL), and in the same manner as in Reference Example 58, the title compound (1.94 g, yield 81%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.28 (3H, t, J = 7.0 Hz), 3.92 (3H, s), 4.09 (2H, q, J = 7.0 Hz), 6.19 (1H, s), 13.37 (1H, br s).

Reference Example 61

Production of methyl 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carboxylate

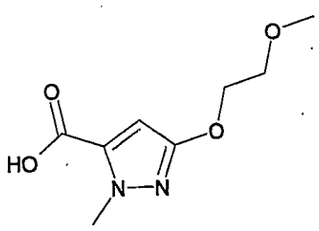


Using methyl 3-hydroxy-1-methyl-1H-pyrazole-5-carboxylate (2.34 g, 15.0 mmol), 1-bromo-2-methoxyethane (3.13 g, 22.5 mmol), potassium carbonate (4.15 g, 30.0 mmol) and N,N-dimethylformamide (15 mL), and in the same manner as in Reference Example 57, the title compound (3.03 g, yield 94%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.28 (3H, s), 3.57 - 3.64 (2H, m), 3.81 (3H, s), 3.93 (3H, s), 4.14 - 4.20 (2H, m), 6.28 (1H, s).

Reference Example 62

Production of 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carboxylic acid

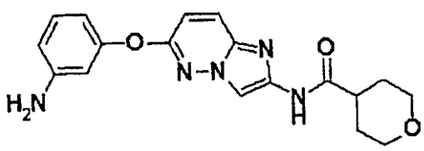


Using methyl 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carboxylate (3.03g, 14.1 mmol), methanol (15 mL) and 8N aqueous sodium hydroxide solution (3.00 mL), and in the same manner as in Reference Example 58, the title compound (2.72g, yield 96%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.28 (3H, s), 3.57 - 3.63 (2H, m), 3.92 (3H, s), 4.13 - 4.19 (2H, m), 6.21 (1H, s), 13.39 (1H, br s).

Example 1

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]tetrahydro-2H-pyran-4-carboxamide



A mixture of 6-iodoimidazo[1,2-b]pyridazin-2-amine (550 mg, 2.11 mmol), tetrahydro-2H-pyran-4-carbonyl chloride (320 mg, 2.15 mmol) and N,N-dimethylacetamide (5.0 mL) was stirred at room temperature for 3 hr. The reaction mixture was poured into water, and the precipitated solid was collected by filtration, washed with water, and air-dried to give N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)tetrahydro-2H-pyran-4-carboxamide as a white

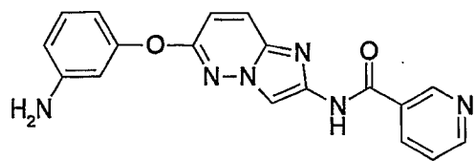
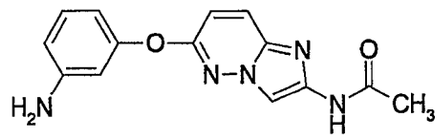
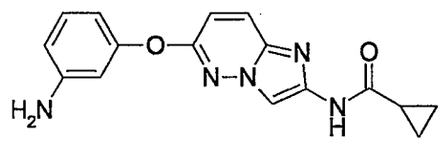
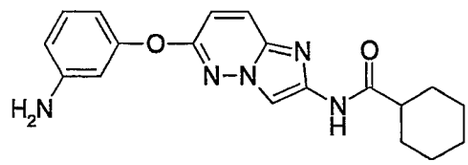
powder.

A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)tetrahydro-2H-pyran-4-carboxamide, 3-aminophenol (436 mg, 4.0 mmol), potassium carbonate (552 mg, 4.0 mmol) and N,N-dimethylformamide (5.0 mL) was stirred with heating at 180°C for 15 min using a microwave synthesizer. After cooling, the reaction mixture was filtrated, and the filtrate was purified by preparative HPLC to give the title compound (364 mg, 49%) as a dark brown powder.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.67 - 1.81 (4H, m), 2.34 - 2.44 (1H, m), 3.25 - 3.34 (2H, m), 3.78 (2H, s), 3.86 - 3.94 (2H, m), 6.33 - 6.37 (1H, m), 6.37 - 6.43 (2H, m), 6.67 (1H, d, J = 9.5 Hz), 7.02 (1H, t, J = 8.1 Hz), 7.54 (1H, d, J = 9.5 Hz), 7.89(1H, s), 8.06 (1H, s).

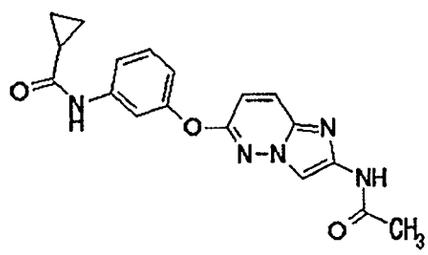
In the same manner as in Example 1, the compounds of Examples 2 to 5 were synthesized. The structures of the compounds of Examples 2 to 5 are shown in Table 1.

Table 1

Example No.	Chemical structural formula	MS (m/Z)
2		347
3		284
4		310
5		352

Example 6

Production of N-(3-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)cyclopropanecarboxamide



A mixture of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (17 mg, 0.06 mmol), cyclopropanecarbonyl chloride (9.5 mg, 0.09 mmol) and N,N-dimethylacetamide (0.5 mL) was stirred at room temperature for 14 hr. The reaction mixture was purified by preparative HPLC to give the title compound (10.8 mg, 51%).

LC-MS 352(M+H).

In the same manner as in Example 6, the compounds of Examples 7 to 51 were synthesized. The structures of the compounds of Examples 7 to 51 are shown in Tables 2 to 7.

Table 2

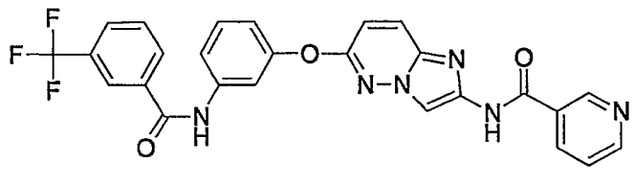
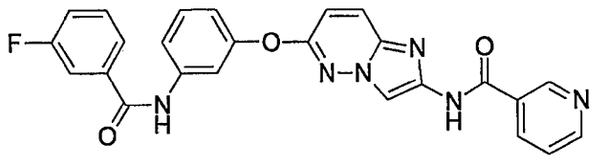
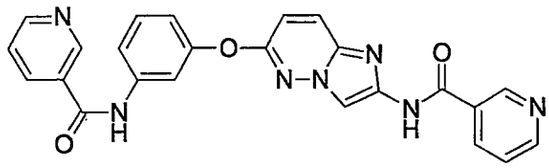
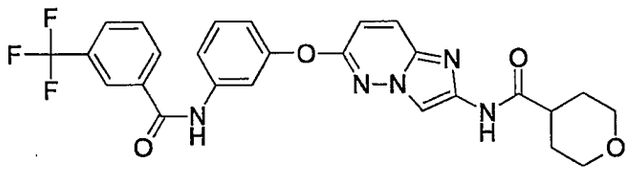
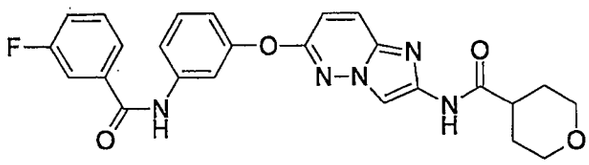
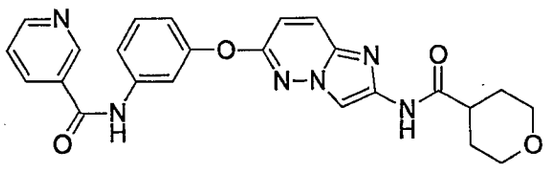
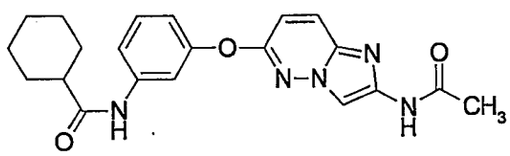
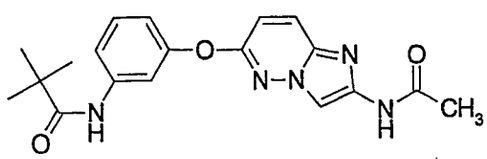
Example No.	Chemical structural formula	MS (m/Z)
7		519
8		469
9		452
10		526
11		476
12		459
13		394
14		368

Table 3

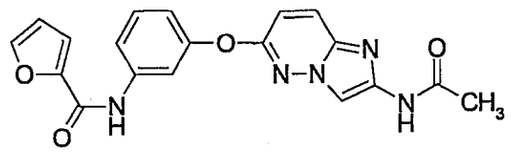
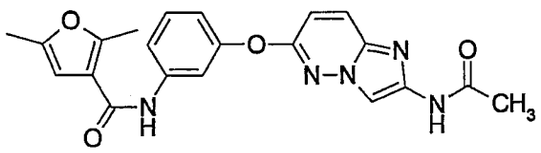
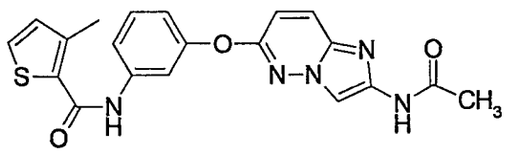
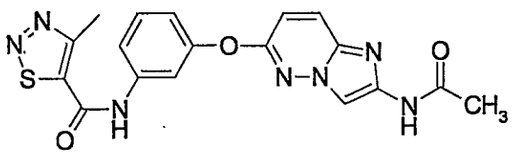
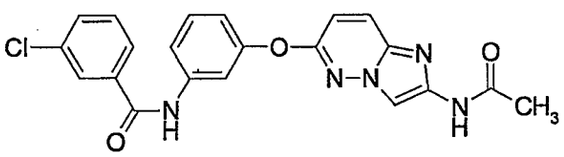
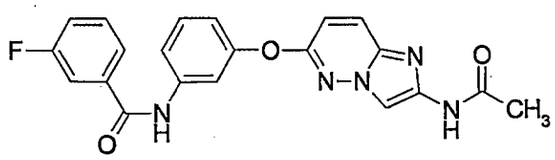
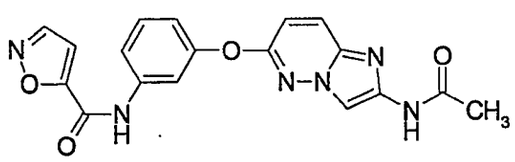
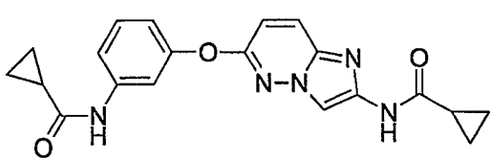
Example No.	Chemical structural formula	MS (m/Z)
15		378
16		406
17		408
18		410
19		422
20		406
21		379
22		378

Table 4

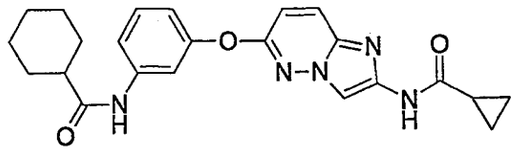
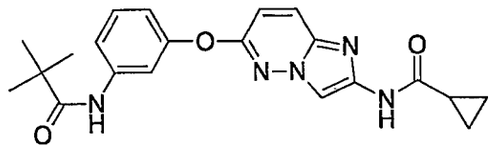
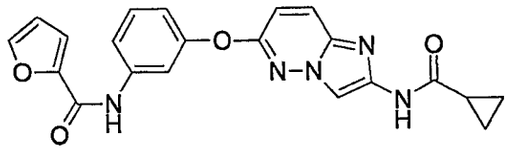
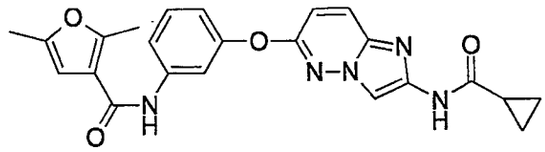
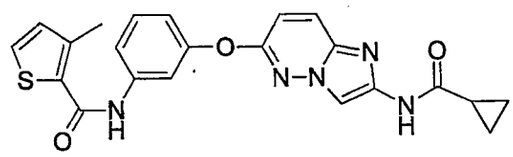
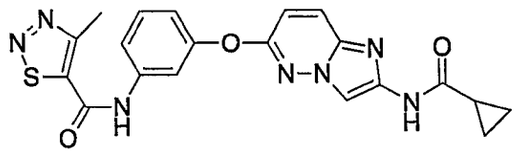
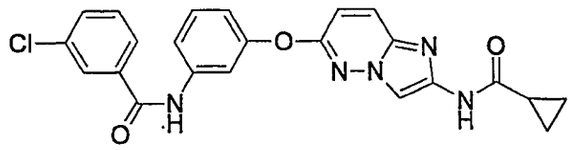
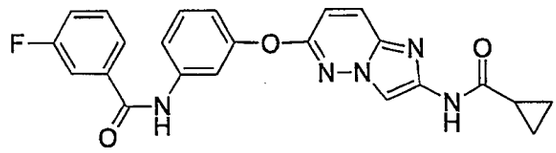
Example No.	Chemical structural formula	MS (m/Z)
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24		394
25		404
26		432
27		434
28		436
29		448
30		432

Table 5

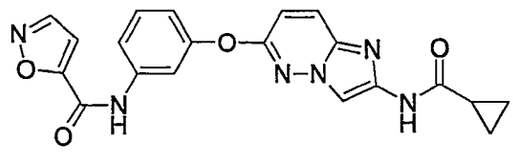
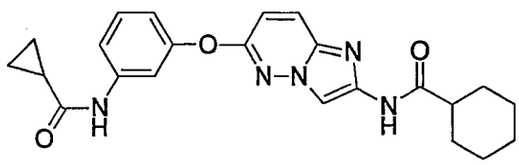
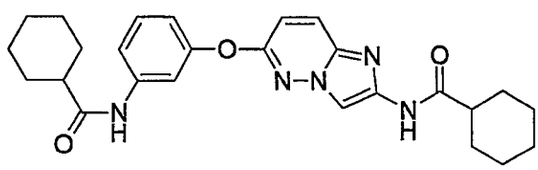
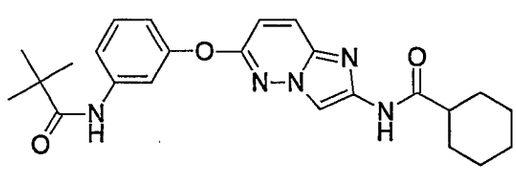
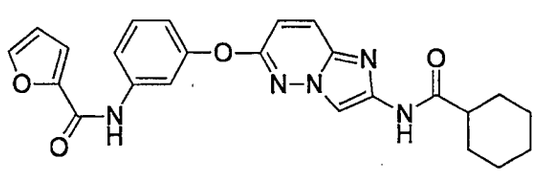
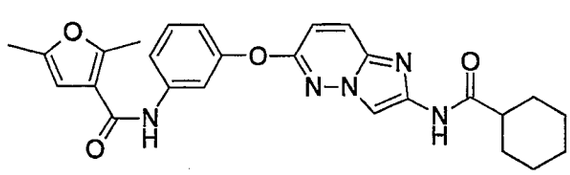
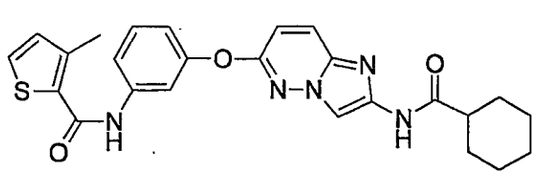
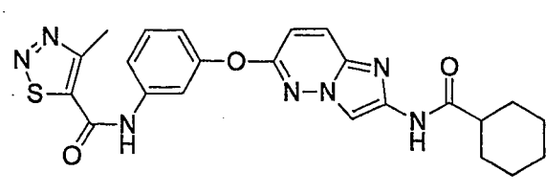
Example No.	Chemical structural formula	MS (m/Z)
31		405
32		420
33		462
34		436
35		446
36		474
37		476
38		478

Table 6

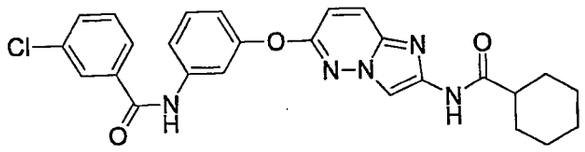
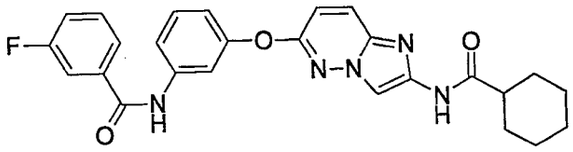
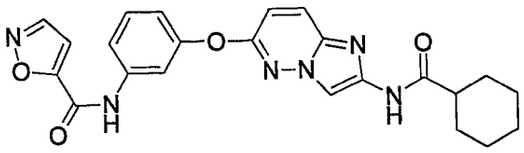
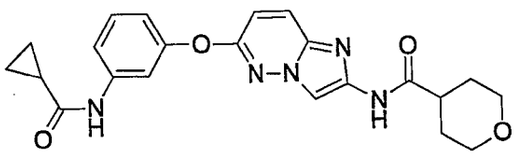
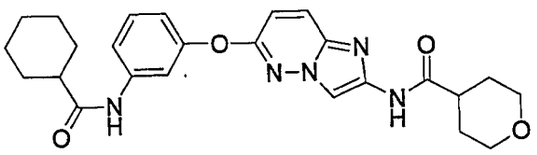
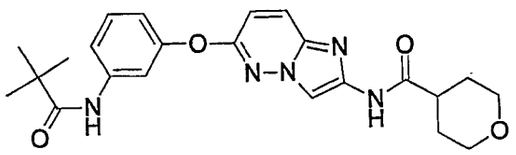
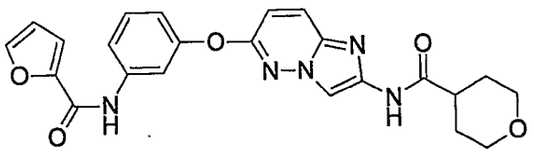
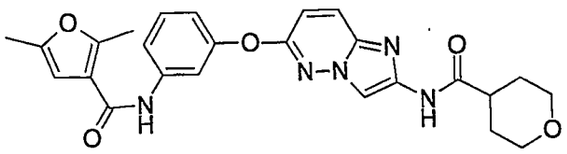
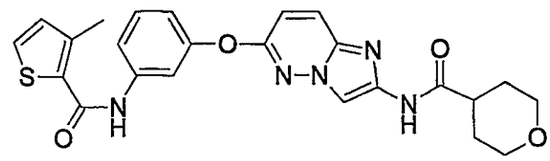
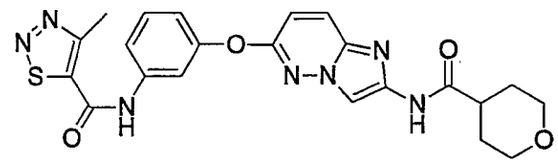
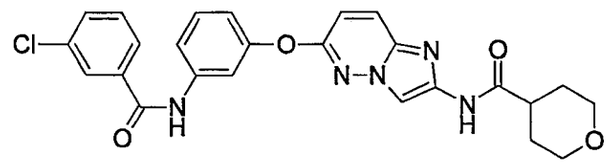
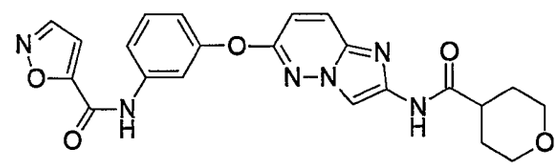
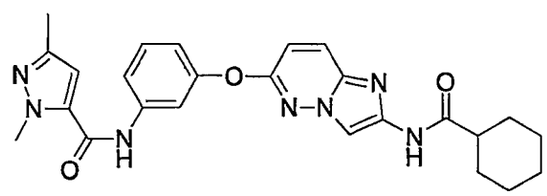
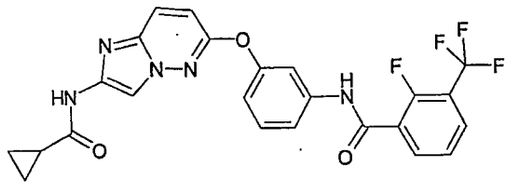
Example No.	Chemical structural formula	MS (m/Z)
39		490
40		474
41		447
42		422
43		464
44		438
45		448
46		476

Table 7

Example No.	Chemical structural formula	MS (m/Z)
47		478
48		480
49		492
50		449
51		474

Example 52

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-fluoro-3-(trifluoromethyl)benzamide

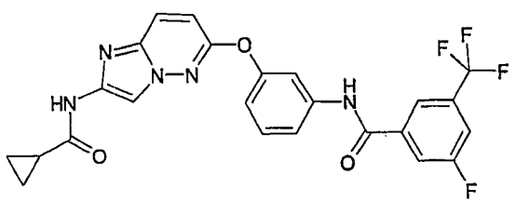


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (309 mg, 1.00 mmol), 2-fluoro-3-(trifluoromethyl)benzoic acid (312 mg, 1.50 mmol), 1-hydroxybenzotriazole (203 mg, 1.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg, 1.50 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (380 mg, 76%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.88 - 1.95 (1H, m), 7.03 - 7.09 (2H, m), 7.45 (1H, t, J = 8.1 Hz), 7.52 - 7.57 (2H, m), 7.66 - 7.67 (1H, m), 7.94 - 8.07 (4H, m), 10.79 (1H, s), 11.09 (1H, s).

Example 53

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-fluoro-5-(trifluoromethyl)benzamide



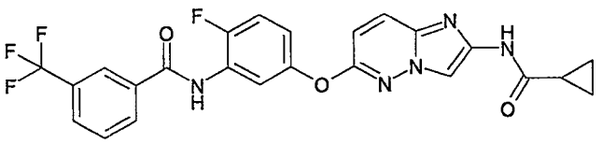
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (309 mg, 1.00 mmol), 3-fluoro-5-(trifluoromethyl)benzoic acid (312 mg, 1.50 mmol), 1-hydroxybenzotriazole (203 mg, 1.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg, 1.50

mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (437 mg, 88%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.88 - 1.97 (1H, m), 7.04 - 7.10 (2H, m), 7.47 (1H, t, J = 8.4 Hz), 7.64 - 7.72 (2H, m), 7.96 - 8.15 (5H, m), 10.63 (1H, s), 11.10 (1H, s).

Example 54

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(trifluoromethyl)benzamide

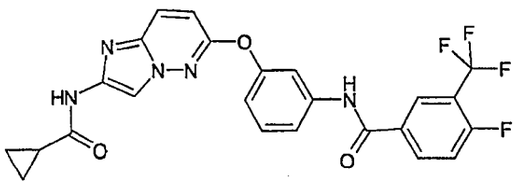


Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (163 mg, 0.50 mmol), 3-(trifluoromethyl)benzoic acid (950 mg, 5.00 mmol), 1-hydroxybenzotriazole (676 mg, 5.00 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (959 mg, 5.00 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (160 mg, 64%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.81 (4H, m), 1.88 - 1.95 (1H, m), 7.08 - 7.25 (2H, m), 7.42 (1H, t, J = 9.6 Hz), 7.60 - 7.79 (2H, m), 7.95 - 8.07 (3H, m), 8.25 - 8.30 (2H, m), 10.51 (1H, s), 11.08 (1H, s).

Example 55

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-4-fluoro-3-(trifluoromethyl)benzamide

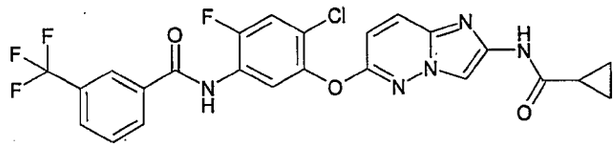


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (309 mg, 1.00 mmol), 4-fluoro-3-(trifluoromethyl)benzoic acid (312 mg, 1.50 mmol), 1-hydroxybenzotriazole (203 mg, 1.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg, 1.50 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (380 mg, 76%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.80 - 0.82 (4H, m), 1.88 - 1.96 (1H, m), 7.02 - 7.10 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.63 - 7.74 (3H, m), 7.98 (1H, s), 8.06 - 8.36 (3H, m), 10.59 (1H, s), 11.10 (1H, s).

Example 56

Production of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(trifluoromethyl)benzamide



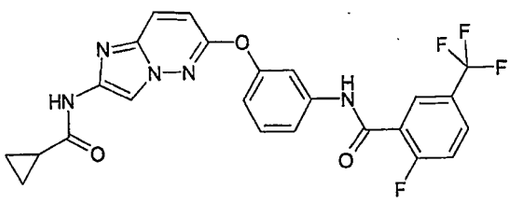
Using N-[6-(3-amino-6-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (181 mg, 0.50 mmol), 3-(trifluoromethyl)benzoic acid (114 mg, 0.60 mmol), 1-hydroxybenzotriazole (81 mg, 0.60 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (115 mg, 0.60 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (54 mg, 20%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.88 - 1.94 (1H, m), 7.17 (1H, d, J = 9.6 Hz), 7.76 - 7.85 (3H, m), 7.92 (1H, s), 7.98 - 8.08 (2H, m), 8.24 - 8.30 (2H, m), 10.60 (1H, s), 11.08 (1H, s).

Example 57

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

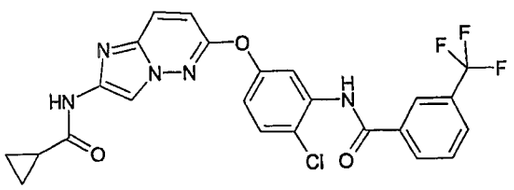
b]pyridazin-6-yl}oxy)phenyl]-2-fluoro-5-(trifluoromethyl)benzamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (309 mg, 1.00 mmol), 2-fluoro-5-(trifluoromethyl)benzoic acid (312 mg, 1.50 mmol), 1-hydroxybenzotriazole (203 mg, 1.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (288 mg, 1.50 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (198 mg, 40%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.88 - 1.94 (1H, m), 7.02 - 7.09 (2H, m), 7.43 - 7.68 (4H, m), 7.98 - 8.09 (4H, m), 10.76 (1H, s), 11.09 (1H, s).

Example 58

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

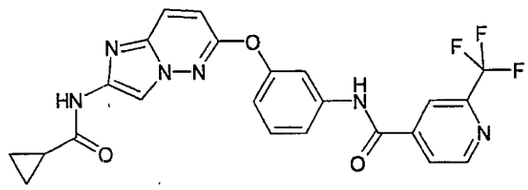


A mixture of N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (103 mg, 0.30 mmol), 3-(trifluoromethyl)benzoyl chloride (75 mg, 0.36 mmol) and N-methylpyrrolidone (3.0 mL) was heated to 50°C, and the mixture was stirred for 10 min. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate solution, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate. The solvent was evaporated under

reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/19→ethyl acetate) to give the title compound (131 mg, 85%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.90 - 1.94 (1H, m), 7.10 (1H, d, J = 9.9 Hz), 7.27 (1H, dd, J = 2.7 Hz, 8.7 Hz), 7.57 (1H, d, J = 3.0 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.80 (1H, d, J = 7.8 Hz), 7.97 - 8.01 (2H, m), 8.06 (1H, d, J = 9.6 Hz), 8.26 - 8.31 (2H, m), 10.43 (1H, brs), 11.08 (1H, brs).

Example 59

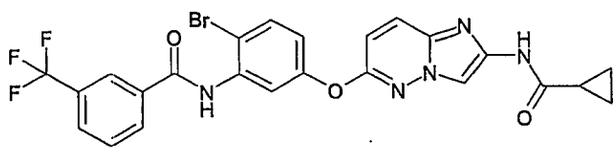
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-(trifluoromethyl)isonicotinamide



Using N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (103 mg, 0.30 mmol), 2-(trifluoromethyl)isonicotinic acid (86 mg, 0.45 mmol), 1-hydroxybenzotriazole (61 mg, 0.45 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (86 mg, 0.45 mmol) and N,N-dimethylformamide (3.0 mL) as starting materials and in the same manner as in Example 106, the title compound (102 mg, 71%) was obtained as a light blue powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.81 (4H, m), 1.89 - 1.94 (1H, m), 7.05 - 7.10 (2H, m), 7.48 (1H, t, J = 8.1 Hz), 7.64 - 7.72 (2H, m), 7.98 (1H, s), 8.07 - 8.35 (3H, m), 8.99 (1H, d, J = 5.1 Hz), 10.80 (1H, s), 11.09 (1H, s).

Example 60

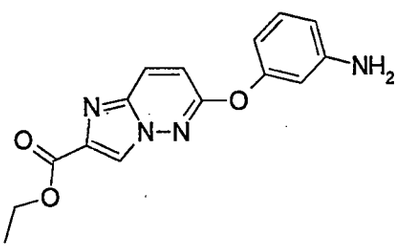
Production of N-[2-bromo-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



Using N-[6-(3-amino-4-bromophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (178 mg, 0.46 mmol), 3-(trifluoromethyl)benzoyl chloride (92 mg, 0.44 mmol), triethylamine (0.14 mL, 1.00 mmol) and tetrahydrofuran (5.0 mL) as starting materials and in the same manner as in Example 96, the title compound (67 mg, 24%) was obtained as a white powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.90 - 1.95 (1H, m), 7.11 - 7.22 (2H, m), 7.54 (1H, d, J = 2.7 Hz), 7.77 - 7.82 (2H, m), 7.97 - 8.08 (3H, m), 8.26 - 8.31 (2H, m), 10.43 (1H, s), 11.09 (1H, s).

Example 61

Production of ethyl 6-(3-aminophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate



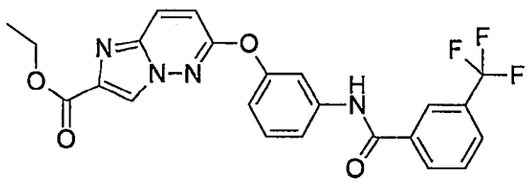
A mixture of ethyl 6-iodoimidazo[1,2-b]pyridazine-2-carboxylate (951 mg, 3.00 mmol), 3-aminophenol (655 mg, 6.00 mmol), potassium carbonate (622 mg, 4.50 mmol) and N,N-dimethylformamide (9.0 mL) was stirred at 150°C for 6 hr. After allowing the reaction mixture to cool to room temperature, ethyl acetate and water were added to the mixture and the insoluble material was filtered through celite. The organic layer was collected from the filtrate, washed with saturated aqueous sodium hydrogencarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/19→ethyl acetate alone)

to give the title compound (350 mg, 39%).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.30 (3H, t, J=7.2 Hz), 4.29 (2H, q, J=7.2 Hz), 5.34 (2H, brs), 6.35 - 6.48 (3H, m), 7.07 (1H, t, J=8.1 Hz), 7.17 (1H, d, J=9.9 Hz), 8.20 (1H, d, J=9.6 Hz), 8.61 (1H, s).

Example 62

Production of ethyl 6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylate

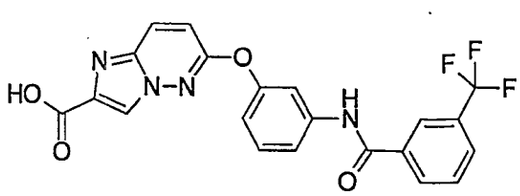


Using ethyl 6-(3-aminophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate (350 mg, 1.17 mmol), 3-(trifluoromethyl)benzoic acid (342 mg, 1.80 mmol), 1-hydroxybenzotriazole (243 mg, 1.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (345 mg, 1.80 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (496 mg, 90%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ1.29 (3H, t, J = 7.1 Hz), 4.29 (2H, q, J = 7.1 Hz), 7.10 (1H, dd, J = 1.5 Hz, 7.5 Hz), 7.29 (1H, d, J = 9.9 Hz), 7.49 (1H, t, J = 8.4 Hz), 7.68 - 7.82 (3H, m), 7.97 - 8.00 (1H, m), 8.25 - 8.28 (3H, m), 8.62 (1H, s), 10.63 (1H, s).

Example 63

Production of 6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylic acid



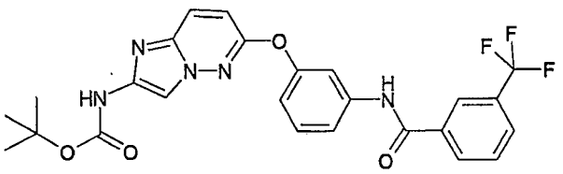
A mixture of ethyl 6-(3-{[3-

(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylate (470 mg, 1.00 mmol), 8N aqueous sodium hydroxide solution (2.0 mL) and methanol (6.0 mL) was stirred at room temperature for 4 hr. 6N Hydrochloric acid (2.7 mL) and water (25 mL) were added to the mixture, and the mixture was extracted with ethyl acetate (50 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give the title compound (425 mg, 96%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.10 (1H, dd, J = 2.1 Hz, 7.8 Hz), 7.27 (1H, d, J = 9.9 Hz), 7.48 (1H, t, J = 7.8 Hz), 7.69-7.82 (3H, m), 7.98 (1H, d, J = 7.5 Hz), 8.23 - 8.29 (3H, m), 8.52 (1H, s), 10.62 (1H, s), 12.85 (1H, brs).

Example 64

Production of tert-butyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate



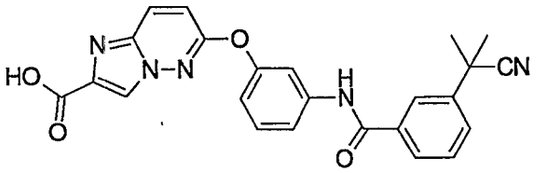
A suspension of 6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylic acid (111 mg, 0.25 mmol), diphenylphosphoryl azide (103 mg, 0.375 mmol), triethylamine (51 mg, 0.5 mmol) and tert-butanol (5.0 mL) was stirred at room temperature for 5 min, heated to 100°C and stirred overnight. After allowing the reaction mixture to cool to room temperature, ethyl acetate was added to the mixture, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/19→ethyl acetate alone) to give the title compound (79 mg, 39%) as a

white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.47 (9H, s), 7.00 - 7.05 (2H, m), 7.45 (1H, t, J = 8.1 Hz), 7.65 - 7.81 (4H, m), 7.96 - 8.03 (2H, m), 8.24 - 8.28 (2H, m), 10.04 (1H, brs), 10.58 (1H, brs).

Example 65

Production of 6-(3-{[3-(1-cyano-1-methylethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylic acid

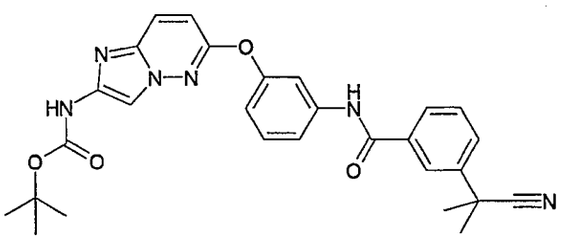


To a mixture of 3-(1-cyano-1-methylethyl)benzoic acid (454 mg, 2.40 mmol), tetrahydrofuran (10 mL) and N,N-dimethylformamide (0.01 mL) was added oxalyl chloride (366 mg, 2.88 mmol), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, tetrahydrofuran was added to the residue, and the mixture was azeotroped twice. The residue was dissolved in N-methylpyrrolidone (4 mL), added to a solution of ethyl 6-(3-aminophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate (350 mg, 1.17 mmol) in N-methylpyrrolidone (6 mL), and the mixture was stirred at room temperature for 2 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. To the residue were added 8N aqueous sodium hydroxide solution (4.0 mL) and methanol (10.0 mL), and the mixture was stirred at room temperature for 10 min. 6N Hydrochloric acid (5.0 mL) and water (60 mL) were added to the mixture, and the mixture was extracted with ethyl acetate (150 mL). The extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was washed with hexane to give the title compound (828 mg, 94%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ1.75 (6H, s), 7.08 (1H, dd, J = 1.5 Hz, 8.4 Hz), 7.27 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 7.8 Hz), 7.60 - 7.77 (4H, m), 7.92 - 8.03 (2H, m), 8.24 (1H, d, J = 10.2 Hz), 8.52 (1H, s), 10.46 (1H, s), 12.81 (1H, brs).

Example 66

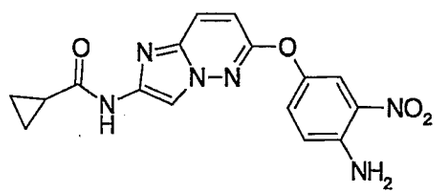
Production of tert-butyl [6-(3-{[3-(1-cyano-1-methylethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate



Using 6-(3-{[3-(1-cyano-1-methylethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazine-2-carboxylic acid (826 mg, 1.87 mmol), diphenylphosphoryl azide (771 mg, 2.81 mmol), triethylamine (381 mg, 3.74 mmol) and tert-butanol (30.0 mL), and in the same manner as in Example 64, the title compound (682 mg, 71%) was obtained as a white powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.47 (9H, s), 1.74 (6H, s), 6.99 - 7.05 (2H, m), 7.44 (1H, t, J = 8.4 Hz), 7.57 - 7.77 (5H, m), 7.91 - 7.94 (1H, m), 8.00 - 8.03 (2H, m), 10.04 (1H, brs), 10.43 (1H, s).

Example 67

Production of N-[6-(4-amino-3-nitrophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



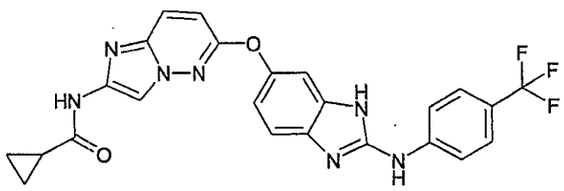
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (656 mg, 2.00 mmol), 4-amino-3-nitrophenol (616 mg, 4.00 mmol), potassium carbonate (411 mg,

3.00 mmol) and N,N-dimethylformamide (6.0 mL) was stirred at 150°C for 3 hr. After allowing the reaction mixture to cool to room temperature, ethyl acetate (100 mL), tetrahydrofuran (40 mL) and water (40 mL) were added to the mixture, and the insoluble material was filtered through celite. The organic layer was collected from the filtrate, washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. Dichloromethane (20 mL) was added to the residue, and the precipitate was collected by filtration to give the title compound (367 mg, 52%). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/19→ethyl acetate alone) to give the title compound (125 mg, 18%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ0.78 - 0.81 (4H, m), 1.84 - 1.91 (1H, m), 7.04 (1H, d, J = 9.3 Hz), 7.11 (1H, d, J = 9.3 Hz), 7.44 (1H, dd, J = 3.0 Hz, 9.3 Hz), 7.51 (2H, m), 7.83 (1H, d, J = 2.4 Hz), 7.91 (1H, s), 8.01 (1H, d, J = 9.3 Hz), 11.04 (1H, s).

Example 68

Production of N-{6-[(2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



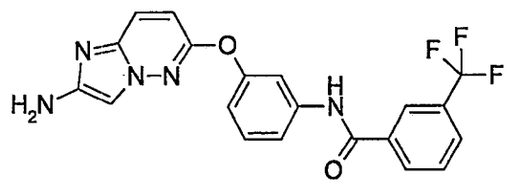
A suspension of N-[6-(4-amino-3-nitrophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (499 mg, 1.38 mmol), 10% palladium carbon (100 mg) and methanol (20.0 mL) was stirred under a hydrogen atmosphere (up to 1 atm) at room temperature overnight. The insoluble material was filtered through celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in methanol (10 mL), 4-(trifluoromethyl)phenylisothiocyanate (120 mg, 0.59 mmol) was

added to the mixture, and the mixture was stirred at room temperature for 1 hr. Iron (III) chloride (177 mg, 1.1 mmol) was added to the reaction mixture, and the mixture was further stirred at room temperature for 1.5 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. Dichloromethane (20 mL) was added to the residue, and the precipitate was collected by filtration to give the title compound (367 mg, 52%). The filtrate was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone→ethyl acetate/methanol = 9 : 1). Ethyl acetate was added to the obtained oily substance, and the precipitate was collected by filtration to give the title compound (116 mg, 32%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78-0.81 (4H, m), 1.88-1.94 (1H, m), 6.90-7.02 (2H, m), 7.22-7.39 (2H, m), 7.65-8.01 (6H, m), 9.98 (1H, d, J = 8.1 Hz), 11.03 (1H, s), 11.20 (1H, d, J = 16.2 Hz).

Example 69

Production of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide



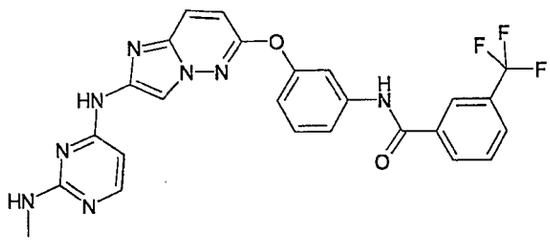
A mixture of tert-butyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate (2.37 g, 4.62 mmol), 4N hydrochloric acid-ethyl acetate solution (50 mL) and methanol (50 mL) was stirred at room temperature for 6 hr. The solvent was evaporated under reduced pressure, saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure, and the

residue was purified by silica gel column chromatography (ethyl acetate alone→ethyl acetate/methanol = 4 : 1) to give the title compound (1.57 g, 82%) as a green solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ5.33 (2H, brs), 6.80 (1H, d, J = 9.0 Hz), 6.94 (1H, m), 7.15 (1H, s), 7.42 (1H, t, J=7.8 Hz), 7.63 - 7.80 (4H, m), 7.97 (1H, d, J=7.5 Hz), 8.23 - 8.27 (2H, m), 10.54 (1H, s).

Example 70

Production of N-{3-[(2-{[2-(methylamino)pyrimidin-4-yl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide

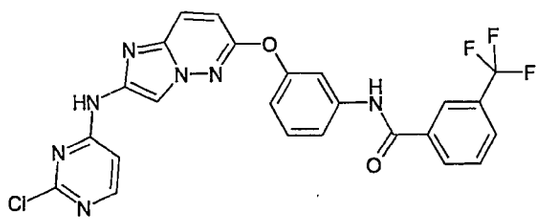


A mixture of N-[3-({2-[(2-chloropyrimidin-4-yl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (122 mg, 0.23 mmol), 2M methylamine-tetrahydrofuran solution (3.0 mL) and ethanol (6.0 mL) was heated to 70°C, and the mixture was stirred overnight. Ethyl acetate was added to the reaction mixture, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated, and the residue was purified by silica gel column chromatography (ethyl acetate alone→ethyl acetate/methanol = 4 : 1). The obtained residue was washed with ethyl acetate-hexane to give the title compound (60 mg, 50%) as a yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.76 (3H, m), 6.15 (1H, d, J = 5.1 Hz), 6.85 (1H, m), 7.04 - 7.07 (2H, m), 7.47 (1H, t, J = 8.1 Hz), 7.68 - 8.02 (6H, m), 8.24 - 8.28 (2H, m), 8.44 (1H, m), 9.96 (1H, brs), 10.59 (1H, s).

Example 71

Production of N-[3-({2-[(2-chloropyrimidin-4-yl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

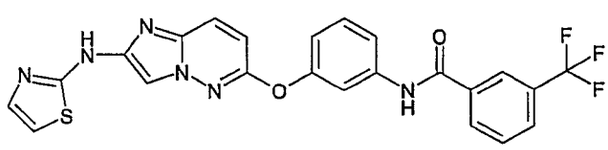


To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (103 mg, 0.25 mmol) in tetrahydrofuran (15 mL) was added sodium hydride (60% in oil, 80 mg, 2.0 mmol), and the mixture was stirred at room temperature for 10 min. 2,4-Dichloropyrimidine (149 mg, 1.00 mmol) was added to the reaction mixture, and the mixture was heated to 60°C. After 1 hr, the reaction mixture was cooled to room temperature and ethyl acetate was added thereto. The mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/19→ethyl acetate alone) and the obtained solid was washed with ethyl acetate/hexane (=1/2) to give the title compound (27 mg, 21%) as a light blue solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.97 - 7.17 (3H, m), 7.48 (1H, t, J = 8.1 Hz), 7.68 - 8.00 (4H, m), 8.08 - 8.29 (5H, m), 10.61 (1H, brs), 10.93 (1H, brs).

Example 72

Production of N-(3-{[2-(1,3-thiazol-2-ylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(trifluoromethyl)benzamide



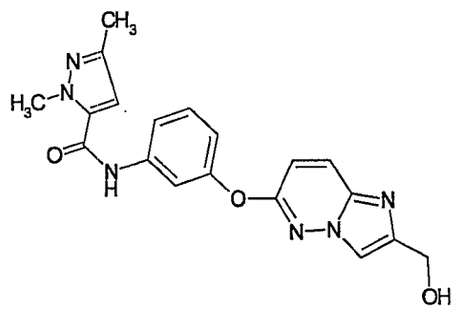
A mixture of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-

yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (165 mg, 0.4 mmol), tris(dibenzylideneacetone)dipalladium (0) (37 mg, 0.04 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (46 mg, 0.03 mmol), sodium t-butoxide (77 mg, 0.8 mmol), 2-bromothiazole (98 mg, 0.6 mmol) and N,N-dimethylacetamide (2 mL) was heated to 70°C under nitrogen atmosphere, and the mixture was stirred for 2 hr. After allowing the reaction mixture to cool to room temperature, ethyl acetate was added to the mixture, and the mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate, and filtrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1/19→ethyl acetate alone) to give the title compound (10 mg, 5%) as a light blue solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.92 - 7.27 (4H, m), 7.46 (1H, t, J = 7.8 Hz), 7.67 - 8.06 (6H, m), 8.24 - 8.28 (2H, m), 10.58 (1H, brs), 10.90 (1H, brs).

Example 73

Production of N-(3-{[2-(hydroxymethyl)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



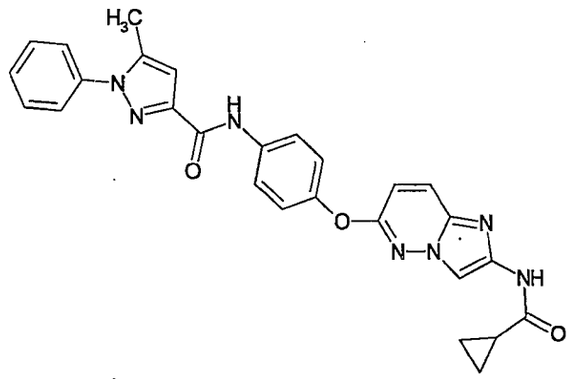
To a solution of (6-iodoimidazo[1,2-b]pyridazin-2-yl)methanol(400 mg, 1.45 mmol) in N,N-dimethylformamide (4.0 mL) were added N-(3-hydroxyphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (504 mg, 2.18 mmol) and potassium carbonate (402 mg, 2.91 mmol), and the mixture was stirred at 150°C for 16 hr. After cooling the mixture to room temperature, water was added to the reaction mixture, and the mixture was extracted with

ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/ethanol=100/0→10/1) to give the title compound (70 mg, 13%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.98 (3H, s), 4.55 (1H, d, J = 5.4 Hz), 5.19 (1H, d, J = 5.4 Hz), 6.82 (1H, s), 6.98 - 7.03 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.39 - 7.46 (1H, m), 7.59 - 7.63 (1H, m), 7.66 - 7.68 (1H, m), 7.88 (1H, s), 8.10 (1H, d, J = 9.6 Hz), 10.23 (1H, s).

Example 74

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide



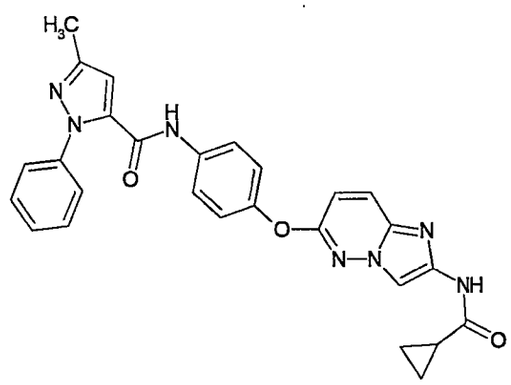
Using 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (196 mg, 0.97 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide(30 μL, 0.39 mmol), oxalyl chloride (85 μL, 0.97 mmol), N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 255, the title compound (223 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.86 -1.96 (1H, m), 2.31 (3H, s), 6.85 (1H, s), 7.02 (1H, d, J = 9.6 Hz), 7.23 (2H, d, J = 9.3 Hz), 7.36 - 7.46 (5H, m), 7.71 (2H, J = 9.3 Hz),

7.92 (1H, s), 8.01 (1H, d, J = 9.6 Hz), 10.62 (1H, s), 11.05 (1H, s).

Example 75

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide

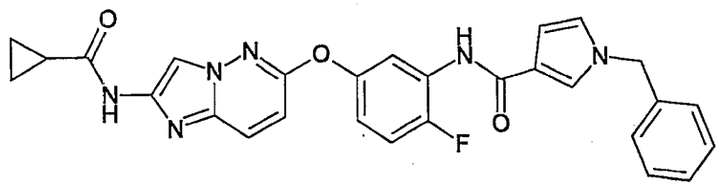


Using 3-methyl-1-phenyl-1H-pyrazole-5-carboxylic acid (196 mg, 0.97 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (85 μL, 0.97 mmol), N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 255, the title compound (209 mg, 65%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.86 -1.96 (1H, m), 2.36 (3H, s), 6.80 (1H, s), 7.03 (1H, d, J = 9.5 Hz), 7.21 - 7.25 (2H, m), 7.48 - 7.67 (5H, m), 7.86 - 7.91 (2H, m), 7.92 (1H, s), 8.01 (1H, d, J = 9.5 Hz), 10.18 (1H, s), 11.05 (1H, s).

Example 76

Production of 1-benzyl-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1H-pyrrole-3-carboxamide

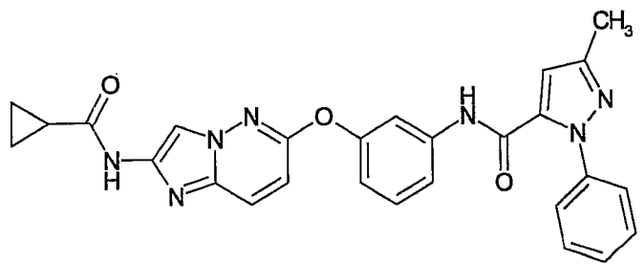


Using 1-benzyl-1H-pyrrole-3-carboxylic acid (276 mg, 1.37 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (120 μL, 1.37 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide (300 mg, 0.92 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (114 mg, 24%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.85 -1.96 (1H, m), 5.15 (2H, s), 6.62 - 6.64 (1H, m), 6.88 - 6.92 (1H, m), 7.05 (1H, d, J = 9.6 Hz), 7.07 - 7.12 (1H, m), 7.23 - 7.62 (6H, m), 7.56 - 7.62 (2H, m), 7.93 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.43 (1H, s), 11.07 (1H, s).

Example 77

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide



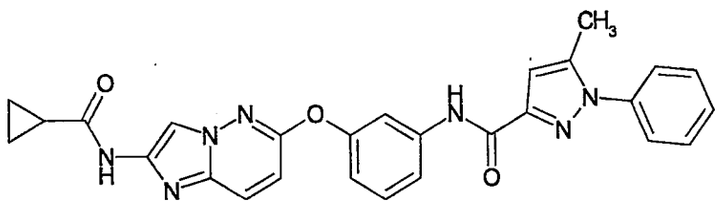
Using 3-methyl-1-phenyl-1H-pyrazole-5-carboxylic acid (294 mg, 1.45 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (127 μL, 1.45 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.97 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 255, the title compound (342 mg, 71%) was obtained as a white

powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.85 -1.95 (1H, m), 2.34 (3H, s), 6.78 (1H, s), 6.92 - 6.98 (1H, m), 7.05 (1H, d, J = 9.9 Hz), 7.33 - 7.43 (1H, m), 7.46 - 7.66 (5H, m), 7.69 - 7.78 (2H, m), 7.97 (1H, s), 8.04 (1H, d, J = 9.9 Hz), 10.21 (1H, s), 11.08 (1H, s).

Example 78

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide

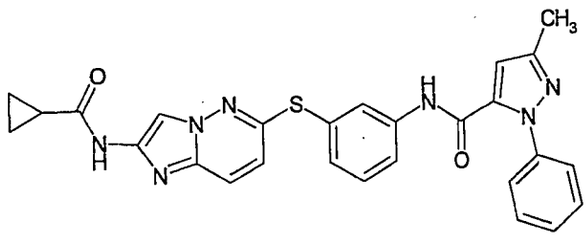


Using 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (294 mg, 1.45 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (127 μL, 1.45 mmol), N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.97 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 255, the title compound (317 mg, 66%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.84 -1.96 (1H, m), 2.29 (3H, s), 6.85 (1H, s), 6.96 - 7.01 (1H, m), 7.04 (1H, d, J = 9.6 Hz), 7.30 - 7.58 (8H, m), 7.95 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 10.64 (1H, s), 11.08 (1H, s).

Example 79

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-methyl-1-phenyl-1H-pyrazole-5-carboxamide

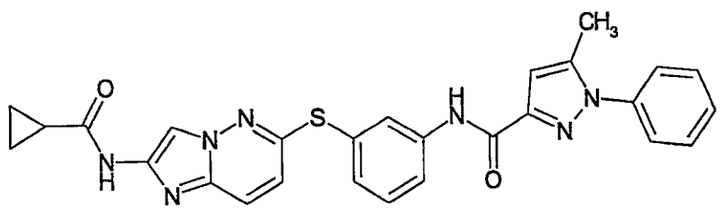


Using 3-methyl-1-phenyl-1H-pyrazole-5-carboxylic acid (186 mg, 0.92 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (80 μL, 0.92 mmol), N-{6-[(3-aminophenyl)thio]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 255, the title compound (203 mg, 65%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.84 (4H, m), 1.86 -1.96 (1H, m), 2.35 (3H, s), 6.78 (1H, s), 6.89 - 6.94 (1H, m), 7.27 - 7.31 (1H, m), 7.40 - 7.65 (7H, m), 7.86 - 7.95 (2H, m), 8.09 - 8.24 (1H, m), 10.25 (1H, s), 11.17 (1H, s).

Example 80

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide

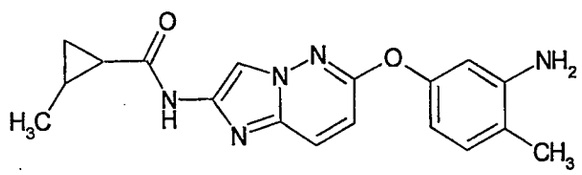


Using 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (196 mg, 0.97 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (80 μL, 0.92 mmol), N-{6-[(3-aminophenyl)thio]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide(200 mg, 0.61 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 255, the title compound (155 mg, 49%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.86 (4H, m), 1.85 -1.96 (1H, m), 2.29 (3H, s), 6.86 (1H, s), 6.94 (1H, d, J = 9.3 Hz), 7.29 - 7.46 (7H, m), 7.71 - 7.76 (1H, m), 7.87 (1H, s), 7.88 (1H, d, J = 9.3 Hz), 8.12 (1H, s), 10.63 (1H, s), 11.16 (1H, s).

Example 81

Production of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide

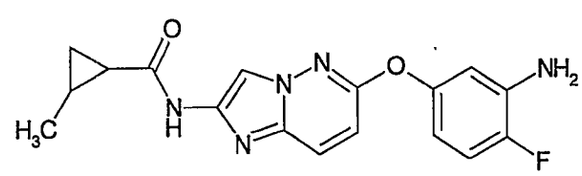


Using 3-amino-4-methylphenol (1.08 g, 8.77 mmol), N,N-dimethylformamide(30.0 mL), potassium tert-butoxide (1.02 g, 9.13 mmol), N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylcyclopropanecarboxamide (2.5 g, 7.31 mmol) and potassium carbonate (0.51 g, 3.65 mmol), and in the same manner as in Example 216, the title compound (1.38 g, 56%) was obtained as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.69 (1H, m), 0.96 -1.05 (1H, m), 1.06 - 1.09 (3H, m), 1.19 - 1.27 (1H, m), 1.63 - 1.72 (1H, m), 2.04 (3H, s), 5.05 (2H, s), 6.27 (1H, dd, J = 8.0, 2.4 Hz), 6.41 (1H, d, J = 2.4 Hz), 6.92 (1H, d, J = 9.5 Hz), 6.94 (1H, d, J = 8.0 Hz), 7.94 (1H, s), 7.96 (1H, d, J = 9.5 Hz), 10.96 (1H, s).

Example 82

Production of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide



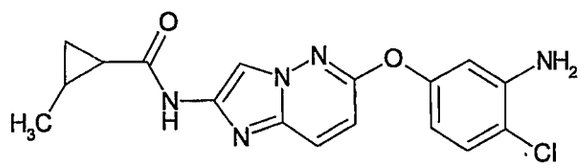
To a solution of 3-amino-4-fluorophenol (0.42 g, 3.29 mmol) in N,N-dimethylformamide (9.0 mL) were added N-(6-

iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylcyclopropanecarboxamide (0.75 g, 2.19 mmol) and potassium carbonate (0.61 g, 4.38 mmol), and the mixture was stirred at 140°C for 16 hr. Saturated brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone), and the obtained residue was washed with hexane/ethyl acetate and filtrated to give the title compound (0.63 g, 88%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.62 - 0.74 (1H, m), 0.96 -1.04 (1H, m), 1.07 - 1.09 (3H, m), 1.17 - 1.28 (1H, m), 1.62 - 1.72 (1H, m), 5.36 (2H, s), 6.30 - 6.36 (1H, m), 6.57 (1H, dd, J = 7.8, 2.7 Hz), 6.96 (1H, d, J = 9.6 Hz), 7.02 (1H, dd, J = 11.4, 8.7 Hz), 7.94 (1H, s), 7.96 - 8.00 (1H, m), 10.97 (1H, s).

Example 83

Production of N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide



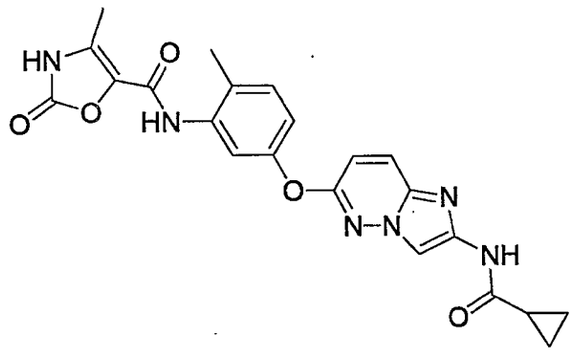
Using 3-amino-4-chlorophenol (1.57 g, 11.0 mmol), N,N-dimethylformamide (25.0 mL), N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylcyclopropanecarboxamide (2.50 g, 7.31 mmol) and potassium carbonate (2.02 g, 14.6 mmol), and in the same manner as in Example 82, the title compound (1.92 g, 73%) was obtained as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) d 0.61 - 0.72 (1H, m), 0.97 -1.04 (1H, m), 1.07 - 1.12 (3H, m), 1.17 - 1.28 (1H, m), 1.63 - 1.73 (1H, m), 5.54 (2H, s), 6.39 (1H, dd, J = 8.6, 2.9 Hz), 6.60 (1H, d, J = 2.9 Hz), 6.99 (1H, d, J = 9.5 Hz), 7.22 (1H, dd, J = 8.6 Hz),

7.96 (1H, s), 8.00 (1H, d, J = 8.6 Hz), 10.98 (1H, s).

Example 84

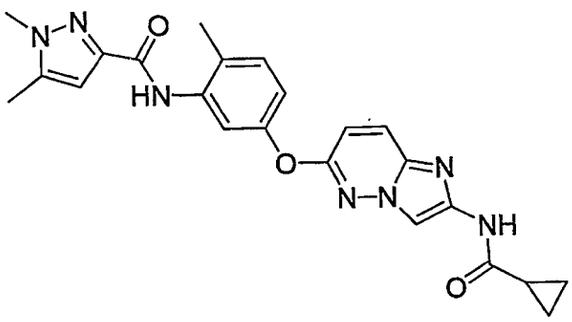
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-2-oxo-2,3-dihydro-1,3-oxazole-5-carboxamide



In the same manner as in Example 259 and using 4-methyl-2-oxo-2,3-dihydro-1,3-oxazole-5-carboxylic acid (159 mg, 1.1 mmol), tetrahydrofuran (5 mL), N, N-dimethylformamide (1 drop), oxalyl chloride (382 μL, 4.44 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.93 mmol) and N, N-dimethylacetamide (7 mL) as starting materials, the title compound (145 mg, 35%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 2.22 (3H, s), 2.27 (3H, s), 6.98 - 7.09 (2H, m), 7.24 - 7.33 (2H, m), 7.94 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.41 (1H, s), 11.07 (1H, s), 11.46 (1H, brs).

Example 85

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,5-dimethyl-1H-pyrazole-3-carboxamide

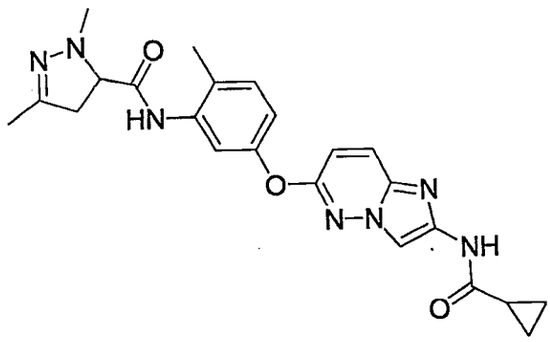


In the same manner as in Example 259 and using 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (145 mg, 1.0 mmol), tetrahydrofuran (5 mL), N, N-dimethylformamide (1 drop), oxalyl chloride (320 μL, 4.44 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (250 mg, 0.77 mmol) and N, N-dimethylacetamide (7 mL) as starting materials, the title compound (57 mg, 17%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.87 - 1.97 (1H, m), 2.27 (3H, s), 2.30 (3H, s), 3.83 (3H, s), 6.53 (1H, s), 6.97 - 7.06 (2H, m), 7.25 - 7.34 (1H, m), 7.61 (1H, d, J = 2.3 Hz), 7.92 - 7.97 (1H, m), 8.02 (1H, d, J = 9.5 Hz), 9.35 (1H, s), 11.07 (1H, s).

Example 86

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-4,5-dihydro-1H-pyrazole-5-carboxamide

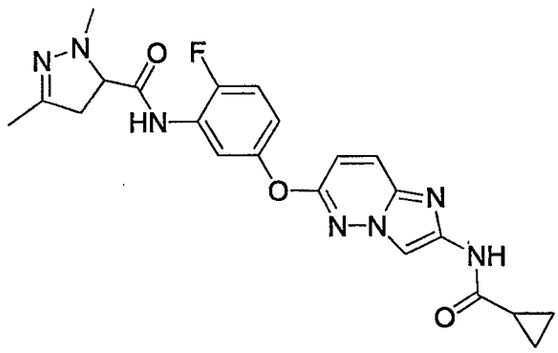


In the same manner as in Example 278 and using 1,3-dimethyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid (120 mg, 0.87 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (330 mg, 0.87 mmol), N, N-diisopropylethylamine (240 mg, 1.8 mmol) and N, N-dimethylformamide (7 mL) as starting materials, the title compound (199 mg, 72%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.87 (3H, s), 1.89 - 1.97 (1H, m), 2.23 (3H, s), 2.74 (3H, s), 2.77 - 2.87 (1H, m), 2.98 - 3.13 (1H, m), 3.57 (1H, m), 6.95 - 7.07 (2H, m), 7.30 (1H, d, J = 8.3 Hz), 7.51 (1H, d, J = 2.3 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 9.43 (1H, s), 11.07 (1H, s).

Example 87

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-4,5-dihydro-1H-pyrazole-5-carboxamide

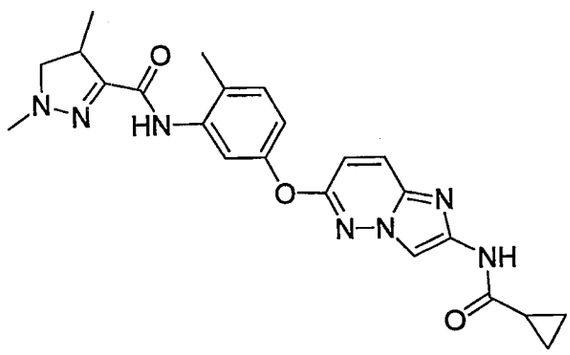


In the same manner as in Example 278 and using 1,3-dimethyl-4,5-dihydro-1H-pyrazole-5-carboxylic acid (170 mg, 1.2 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (280 mg, 0.84 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (450 mg, 1.2 mmol), N, N-diisopropylethylamine (330 mg, 2.5 mmol) and N, N-dimethylformamide (7 mL) as starting materials, the title compound (240 mg, 63%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.86 (3H, s), 1.89 - 1.96 (1H, m), 2.71 (3H, s), 2.81 (1H, dd, J = 17.4, 12.9 Hz), 2.98 - 3.11 (1H, m), 3.59 - 3.71 (1H, m), 7.06 (1H, d, J =

9.5 Hz), 7.09 - 7.14 (1H, m), 7.38 (1H, dd, J = 10.4, 8.9 Hz), 7.87 (1H, dd, J = 6.4, 3.0 Hz), 7.93 (1H, s), 8.04 (1H, d, J = 9.5 Hz), 9.75 (1H, s), 11.08 (1H, s).

Example 88

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,4-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxamide

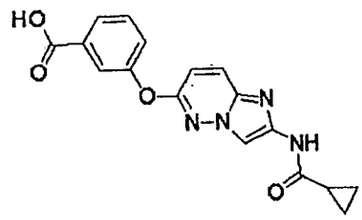


A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (300 mg, 0.91 mmol), N-(5-hydroxy-2-methylphenyl)-1,4-dimethyl-4,5-dihydro-1H-pyrazole-3-carboxamide (290 mg, 1.2 mmol), cesium carbonate (600 mg, 1.8 mmol) and dimethyl sulfoxide (2 mL) was stirred at 100°C for 6 hr. Ethyl acetate/tetrahydrofuran and water were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→100/0) to give the title compound (300 mg, 73%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.14 (3H, d, J = 6.4 Hz), 1.86 - 1.97 (1H, m), 2.23 (3H, s), 2.92 (3H, s), 3.05 - 3.12 (1H, m), 3.22 - 3.32 (2H, m), 6.98 (1H, dd, J = 8.3, 2.7 Hz), 7.03 (1H, d, J = 9.8 Hz), 7.28 (1H, d, J = 8.3 Hz), 7.53 (1H, d, J = 2.7 Hz), 7.94 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 9.18 (1H, s), 11.08 (1H, s).

Example 89

Production of 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid



A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (518 mg, 1.58 mmol), methyl 3-hydroxybenzoate (360 mg, 2.37 mmol), potassium carbonate (654 mg, 4.73 mmol) and N,N-dimethylformamide (4.0 mL) was stirred at 110°C for 2 days. The solvent was evaporated under reduced pressure, ethyl acetate, tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→85/15) to give methyl 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoate (225 mg, 41%) as a white powder.

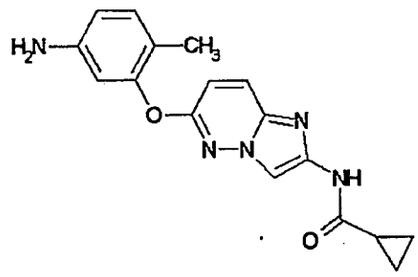
To a solution of methyl 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoate (225 mg, 0.64 mmol) in tetrahydrofuran (5.0 mL) was added 1N sodium hydroxide (2.5 mL), and the mixture was stirred at room temperature for 24 hr. 1N Hydrochloric acid was added to the mixture (pH=3), and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was filtrated, and washed with

ethyl acetate/hexane to give the title compound (150 mg, 69%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.89 (4H, m), 1.84 - 2.01 (1H, m), 7.09 (1H, d, J = 9.5 Hz), 7.48 - 7.68 (2H, m), 7.73 (1H, s), 7.84 (1H, d, J = 7.2 Hz), 7.94 (1H, s), 8.06 (1H, d, J = 9.5 Hz), 11.08 (1H, s), 13.20 (1H, brs).

Example 90

Production of N-[6-(5-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



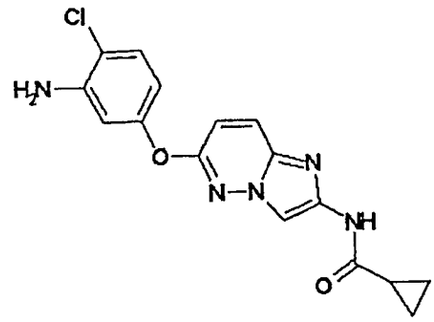
To a suspension of sodium hydride (56 mg, 1.40 mmol) in N,N-dimethylformamide (2.0 mL) was added a solution of 5-amino-2-methylphenol (173 mg, 1.40 mmol) in N,N-dimethylformamide (1.0 mL), and the mixture was stirred at 0°C for 30 min. To the reaction mixture was added a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (306 mg, 0.933 mmol) in N,N-dimethylformamide (1.5 mL), and the mixture was stirred at 110°C for 24 hr. The solvent was evaporated under reduced pressure, and ethyl acetate and water were added to the residue. The aqueous layer was extracted three times with ethyl acetate. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=17/83→90/10) to give the title compound (94 mg, 31%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.89 (4H, m), 1.84 - 2.01 (1H, m), 1.97 (3H, s), 5.08 (2H, s), 6.30 (1H, d, J = 2.3 Hz), 6.40 (1H, dd, J = 8.0, 2.3 Hz), 6.94 (1H, d, J = 8.0 Hz), 6.95 (1H, d, J = 9.5 Hz), 7.93 (1H, s), 7.99 (1H, d, J = 9.5 Hz), 11.06 (1H,

s).

Example 91

Production of N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

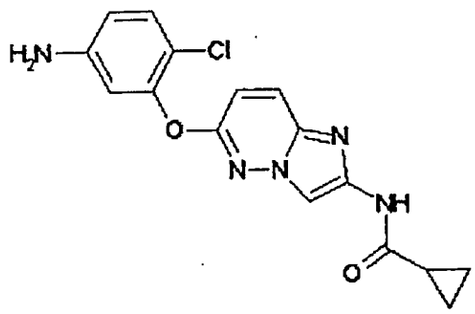


A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (800 mg, 2.44 mmol), 3-amino-4-chlorophenol (422 mg, 2.93 mmol), potassium carbonate (843 mg, 6.10 mmol) and N,N-dimethylformamide (6.0 mL) was stirred using a microwave synthesizer at 180°C for 30 min. The solvent was evaporated under reduced pressure, ethyl acetate, tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=17/83→75/25) to give the title compound (610 mg, 73%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.87 (4H, m), 1.84 - 1.98 (1H, m), 5.56 (2H, s), 6.40 (1H, dd, J = 8.5, 2.8 Hz), 6.61 (1H, d, J = 2.8 Hz), 7.00 (1H, d, J = 9.8 Hz), 7.23 (1H, d, J = 8.5 Hz), 7.98 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 11.09(1H, s).

Example 92

Production of N-[6-(5-amino-2-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

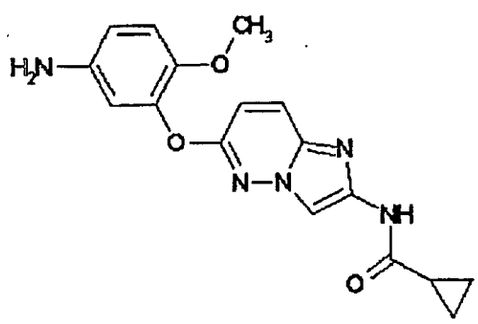


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (800 mg, 2.44 mmol), 5-amino-2-chlorophenol (422 mg, 2.93 mmol), potassium carbonate (843 mg, 6.1 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 91, the title compound (226 mg, 27%) was obtained as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 5.47 (2H, s), 6.47 - 6.51 (1H, m), 6.51 (1H, s), 7.04 (1H, d, J = 9.5 Hz), 7.17 (1H, d, J= 9.0 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 11.06 (1H, s).

Example 93

Production of N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

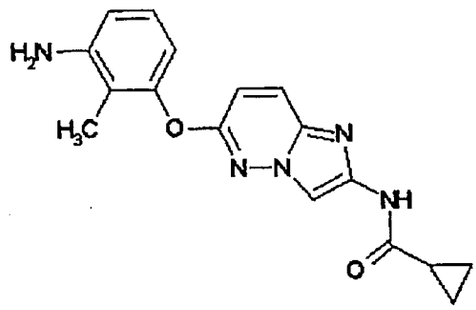


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (800 mg, 2.44 mmol), 5-amino-2-methoxyphenol (408 mg, 2.93 mmol), potassium carbonate (843 mg, 6.10 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 91, the title

compound (299 mg, 36%) was obtained as a brown powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.91 (1H, m), 3.56 (3H, s), 4.87 (2H, s), 6.41 - 6.49 (2H, m), 6.85 - 6.91 (1H, m), 6.95 (1H, d, J = 9.5 Hz), 7.90 (1H, s), 7.96 (1H, d, J = 9.5 Hz), 11.05 (1H, s).

Example 94

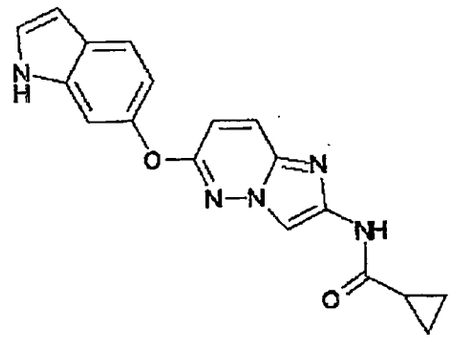
Production of N-[6-(3-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (800 mg, 2.44 mmol), 3-amino-2-methylphenol (380 mg, 2.93 mmol), potassium carbonate (843 mg, 6.10 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 91, the title compound (454 mg, 58%) was obtained as a blackish brown powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.87 (4H, m), 1.83 - 1.98 (1H, m), 1.89 (3H,s), 5.13 (2H, s), 6.32 (1H, d, J = 8.0 Hz), 6.55 (1H, d, J = 6.8 Hz), 6.93 (1H, dd, J = 8.0, 6.8 Hz), 6.94 (1H, d, J = 9.5 Hz), 7.91 (1H, s), 7.98 (1H, d, J = 9.5 Hz), 11.05 (1H, s).

Example 95

Production of N-[6-(1H-indol-6-yloxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

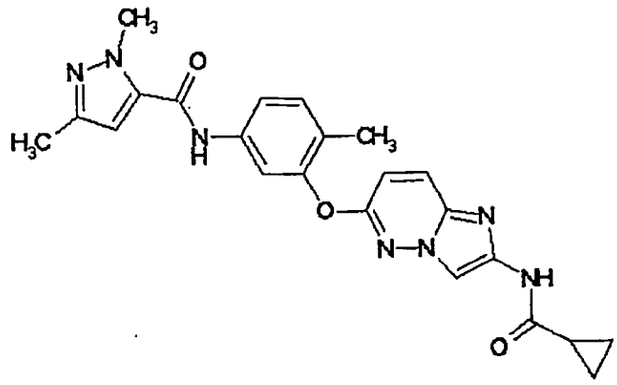


A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (473 mg, 1.44 mmol), 1H-indole-6-ol (250 mg, 1.87 mmol), potassium carbonate (597 mg, 4.32 mmol) and N,N-dimethylformamide (4.0 mL) was stirred at 110°C for 2 days. The solvent was evaporated under reduced pressure, ethyl acetate, tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→85/15), and precipitated from ethyl acetate/hexane to give the title compound (48 mg, 10%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.89 (4H, m), 1.83 - 1.97 (1H, m), 6.47 (1H, s), 6.89 (1H, dd, J = 8.3, 2.3 Hz), 7.00 (1H, d, J = 9.5 Hz), 7.26 (1H, d, J = 2.3 Hz), 7.33 - 7.42 (1H, m), 7.58 (1H, d, J = 8.3 Hz), 7.91 (1H, s), 7.99 (1H, d, J = 9.5 Hz), 11.06 (1H, s), 11.17 (1H, s).

Example 96

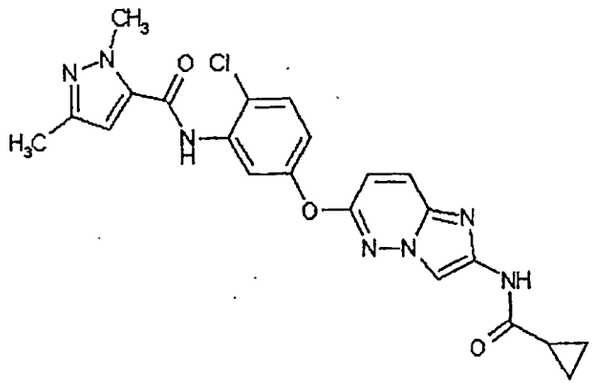
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



To a solution of N-[6-(5-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (72.6 mg, 0.224 mmol) in tetrahydrofuran (4.0 mL) were added a solution of 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (46.3 mg, 0.29 mmol) in tetrahydrofuran (0.5 mL) and triethylamine (68 mg, 0.672 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution, and extracted three times with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was filtrated, washed with ethyl acetate/hexane to give the title compound (64 mg, 64%) as a brown powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.85 - 1.97 (1H, m), 2.14 (3H, s), 2.18 (3H, s), 3.97 (3H, s), 6.81 (1H, s), 7.08 (1H, d, J = 9.5 Hz), 7.32 (1H, d, J = 8.3 Hz), 7.55 (1H, dd, J = 8.3, 1.9 Hz), 7.60 (1H, d, J = 1.9 Hz), 7.92 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 10.18 (1H, s), 11.08 (1H, s).

Example 97

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

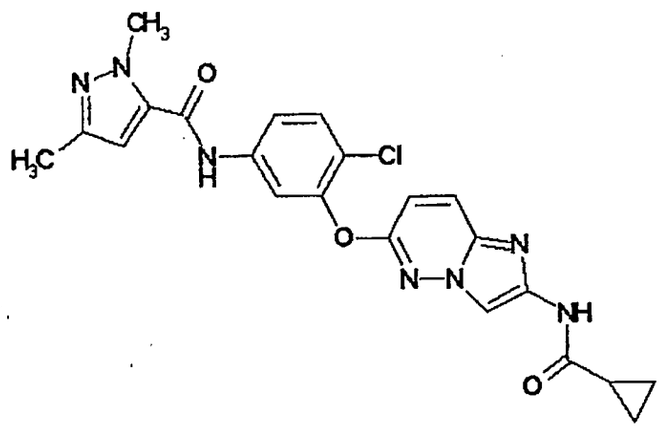


Using N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (128 mg, 0.373 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (77.2 mg, 0.485 mmol), triethylamine (113 mg, 1.12 mmol) and tetrahydrofuran (5.0 mL) as starting materials and in the same manner as in Example 96, the title compound (77 mg, 44%) was obtained as a white powder. melting point 255°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 2.20 (3H, s), 3.98 (3H, s), 6.84 (1H, s), 7.10 (1H, d, J = 9.6 Hz), 7.26 (1H, dd, J = 8.9, 2.8 Hz), 7.54 (1H, d, J = 2.8 Hz), 7.64 (1H, d, J = 8.9 Hz), 7.96 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 9.99 (1H, s), 11.09 (1H, s).

Example 98

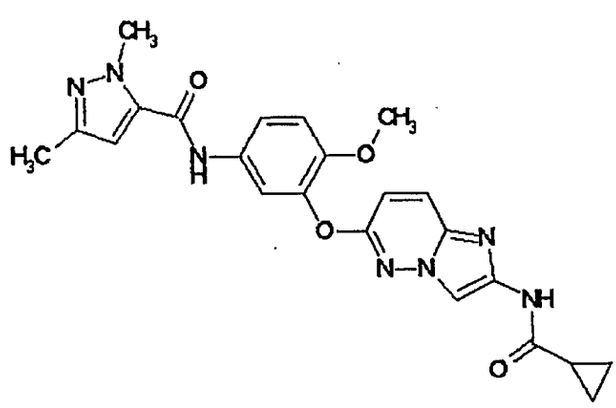
Production of N-[4-chloro-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



Using N-[6-(5-amino-2-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (131 mg, 0.382 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (91 mg, 0.573 mmol), triethylamine (116 mg, 1.15 mmol) and tetrahydrofuran (5.0 mL) as starting materials and in the same manner as in Example 96, the title compound (163 mg, 92%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.82 (4H, m), 1.81 - 1.94 (1H, m), 2.16 (3H, s), 3.96 (3H, s), 6.80 (1H, s), 7.14 (1H, dd, J = 9.6, 1.6 Hz), 7.59 (1H, m), 7.66 (1H, m), 7.83 (1H, d, J = 1.6 Hz), 7.91 (1H, s), 8.07 (1H, d, J = 9.6 Hz), 10.34 (1H, s), 11.08 (1H, s).

Example 99

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

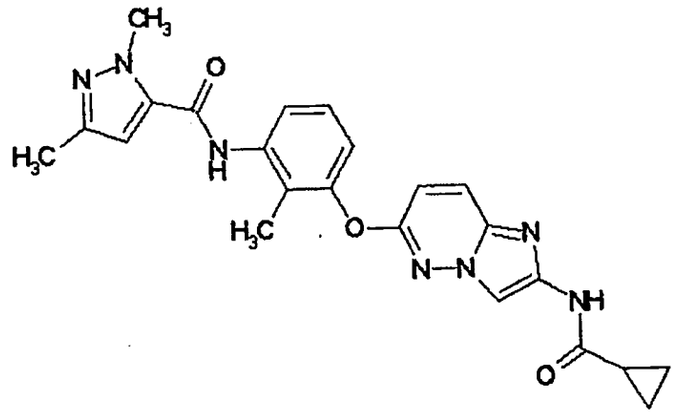


Using N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (129 mg, 0.379 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (78.3 mg, 0.493 mmol), triethylamine (115 mg, 1.14 mmol) and tetrahydrofuran (5.0 mL) as starting materials and in the same manner as in Example 96, the title compound (124 mg, 71%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 2.19 (3H, s), 3.71 (3H, s), 3.97 (3H, s), 6.80 (1H, s), 7.06 (1H, d, J = 9.5 Hz), 7.20 (1H, d, J = 8.9 Hz), 7.59 (1H, dd, J = 8.9, 2.5 Hz), 7.68 (1H, d, J = 2.5 Hz), 7.89 (1H, s), 8.01 (1H, d, J = 9.5 Hz), 10.15 (1H, s), 11.07 (1H, s).

Example 100

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



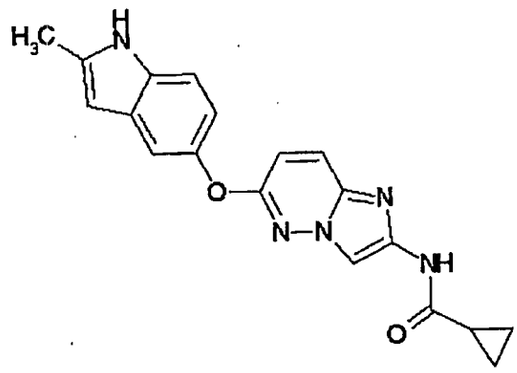
Using N-[6-(3-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (130 mg, 0.402 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (83 mg, 0.523 mmol), triethylamine (122 mg, 1.21 mmol) and tetrahydrofuran (5.0 mL) as starting materials and in the same manner as in Example 96, the title compound (146 mg, 82%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 2.06 (3H, s), 2.20 (3H, s), 4.01 (3H, s), 6.84 (1H, s), 7.09 (1H, d, J = 9.5 Hz), 7.15 (1H, dd, J = 6.8, 2.3 Hz), 7.25 - 7.36

(2H, m), 7.88 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 9.95 (1H, s), 11.07 (1H, s).

Example 101

Production of N-{6-[(2-methyl-1H-indol-5-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

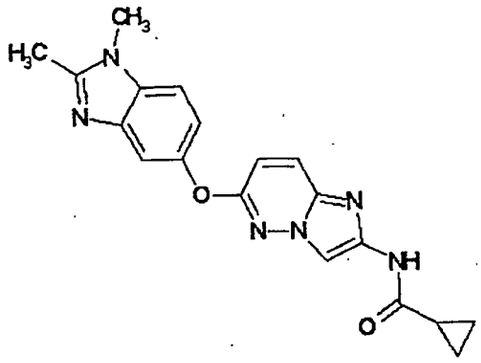


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (272 mg, 0.830 mmol), 2-methyl-1H-indole-5-ol (244 mg, 1.66 mmol), potassium carbonate (344 mg, 2.49 mmol) and N,N-dimethylformamide (3.0 mL) as starting materials and in the same manner as in Example 95, the title compound (56 mg, 19%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.82 - 1.97 (1H, m), 2.39 (3H, s), 6.13 (1H, s), 6.86 (1H, dd, J = 8.7, 2.3 Hz), 6.95 (1H, d, J = 9.5 Hz), 7.23 (1H, d, J = 2.3 Hz), 7.30 (1H, d, J = 8.7 Hz), 7.88 (1H, s), 7.96 (1H, d, J = 9.5 Hz), 11.05 (2H, s).

Example 102

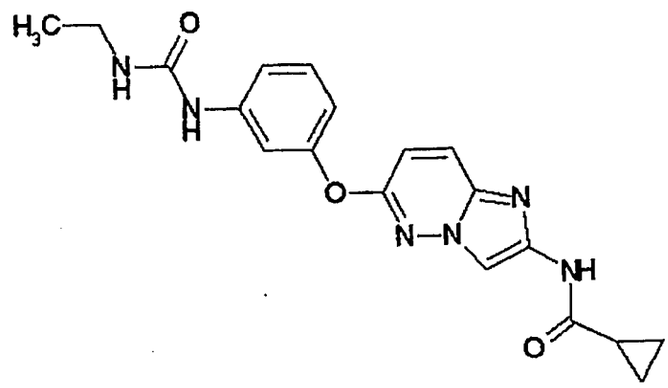
Production of N-{6-[(1,2-dimethyl-1H-benzimidazol-5-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (254 mg, 0.774 mmol), 1,2-dimethyl-1H-benzimidazole-5-ol (163 mg, 1.06 mmol), potassium carbonate (267 mg, 1.94 mmol) and N,N-dimethylformamide (3.0 mL) as starting materials and in the same manner as in Example 95, the title compound (79 mg, 28%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.84 (4H, m), 1.84 - 1.96 (1H, m), 2.54 (3H, s), 3.77 (3H, s), 7.00 (1H, d, J = 9.8 Hz), 7.09 (1H, dd, J = 8.7, 2.3 Hz), 7.39 (1H, d, J = 2.3 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.86 (1H, s), 7.99 (1H, d, J = 9.8 Hz), 11.05 (1H, s).

Example 103

Production of N-[6-(3-{[(ethylamino)carbonyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



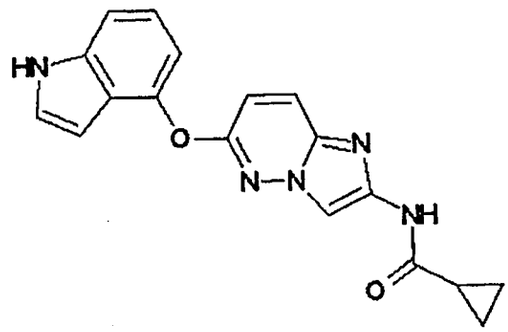
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-

b]pyridazin-2-yl]cyclopropanecarboxamide (160 mg, 0.517 mmol) in pyridine (4.0 mL) was added ethyl isocyanate (409 μL, 5.17 mmol), and the mixture was stirred at room temperature for 24 hr. The solvent was evaporated under reduced pressure, ethyl acetate and saturated aqueous sodium hydrogencarbonate solution were added to the residue, and the aqueous layer was extracted three times with ethyl acetate. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was filtrated, and washed with ethyl acetate/hexane to give the title compound (136 mg, 69%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.00 (3H, t, J = 7.1 Hz), 1.83 - 1.95 (1H, m), 2.97 - 3.12 (2H, m), 6.13 (1H, t, J = 5.5 Hz), 6.72 (1H, dd, J = 8.0, 2.5 Hz), 6.99 (1H, d, J = 9.6 Hz), 7.09 (1H, dd, J = 8.2, 1.1 Hz), 7.25 (1H, t, J = 8.2 Hz), 7.42 (1H, t, J = 1.9 Hz), 7.94 (1H, s), 8.00 (1H, d, J = 9.6 Hz), 8.61 (1H, s), 11.08 (1H, s).

Example 104

Production of N-[6-(1H-indol-4-yloxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

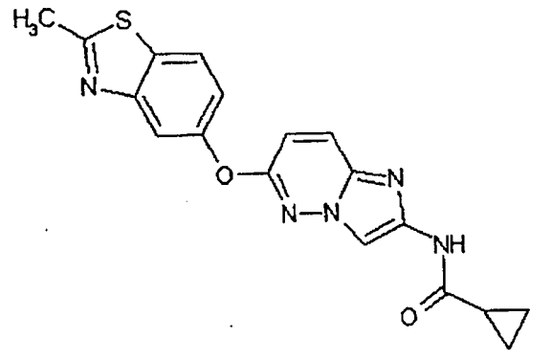


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (353 mg, 1.08 mmol), 1H-indole-4-ol (241 mg, 1.82 mmol), potassium carbonate (446 mg, 3.23 mmol) and N,N-dimethylformamide (4.0 mL) as starting materials and in the same manner as in Example 95, the title compound (66 mg, 18%)

was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.86 (4H, m), 1.83 - 1.96 (1H, m), 6.16 - 6.23 (1H, m), 6.85 (1H, dd, J = 7.8, 0.8 Hz), 7.01 (1H, d, J = 9.6 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.26 - 7.37 (2H, m), 7.89 (1H, s), 8.00 (1H, d, J = 9.6 Hz), 11.06 (1H, s), 11.37 (1H, s).

Example 105

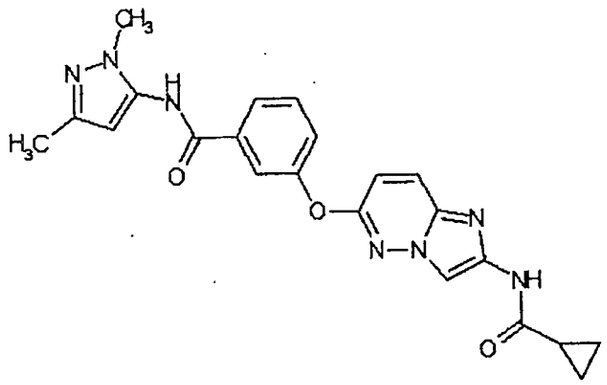
Production of N-{6-[(2-methyl-1,3-benzothiazol-5-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (355 mg, 1.08 mmol), 2-methyl-1,3-benzothiazole-5-ol (286 mg, 1.73 mmol), potassium carbonate (448 mg, 3.24 mmol) and N,N-dimethylformamide (4.0 mL) as starting materials and in the same manner as in Example 95, the title compound (275 mg, 70%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.83 - 1.97 (1H, m), 2.82 (3H, s), 7.09 (1H, d, J = 9.6 Hz), 7.35 (1H, dd, J = 8.7, 2.3 Hz), 7.82 (1H, d, J = 2.3 Hz), 7.92 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 8.10 (1H, d, J = 8.7 Hz), 11.07 (1H, s).

Example 106

Production of 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-N-(1,3-dimethyl-1H-pyrazol-5-yl)benzamide



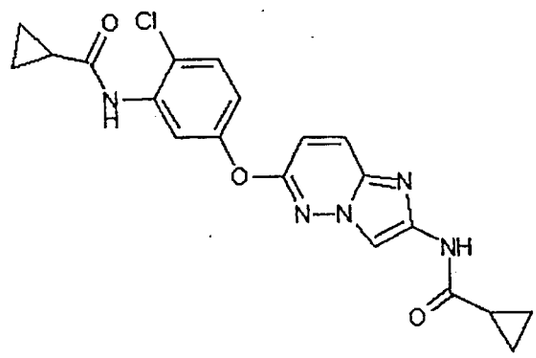
To a solution of 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid (121 mg, 0.358 mmol) in N,N-dimethylformamide (5.0 mL) were added 1,3-dimethyl-1H-pyrazol-5-amine (47.8 mg, 0.43 mmol), 1-hydroxybenzotriazole (58 mg, 0.43 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (82.4 mg, 0.43 mmol) and triethylamine (45 mg, 0.43 mmol), and the mixture was stirred at room temperature for 24 hr. The solvent was evaporated under reduced pressure, ethyl acetate, tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→90/10, then methanol/ethyl acetate=0/100→15/85), and precipitated from ethyl acetate/hexane to give the title compound (116 mg, 75%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.12 (3H, s), 3.56 (3H, s), 6.02 (1H, s), 7.11 (1H, d, J = 9.6 Hz), 7.50 - 7.57 (1H, m), 7.63 (1H, t, J = 7.9 Hz), 7.79 - 7.92 (2H, m), 7.95 (1H, s), 8.07 (1H, d, J = 9.6 Hz), 10.31 (1H, s), 11.09 (1H, s).

Example 107

Production of N-[2-chloro-5-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]cyclopropanecarboxamide

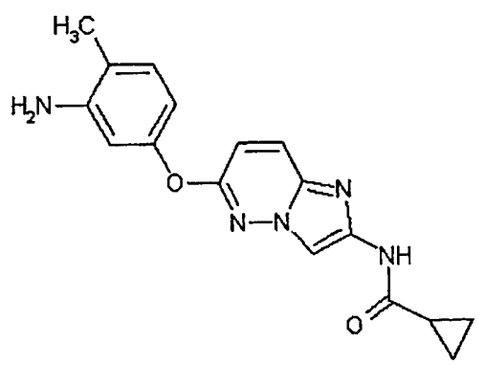


Using N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.435 mmol), cyclopropanecarbonyl chloride (71.8 mg, 0.652 mmol), triethylamine (132 mg, 1.30 mmol) and tetrahydrofuran (17 mL) as starting materials and in the same manner as in Example 96, the title compound (156 mg, 87%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.89 (8H, m), 1.84 - 1.98 (1H, m), 2.00 - 2.11 (1H, m), 7.06 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.7, 2.8 Hz), 7.56 (1H, d, J = 8.7 Hz), 7.73 (1H, d, J = 2.8 Hz), 7.95 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 9.83 (1H, s), 11.09 (1H, s).

Example 108

Production of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



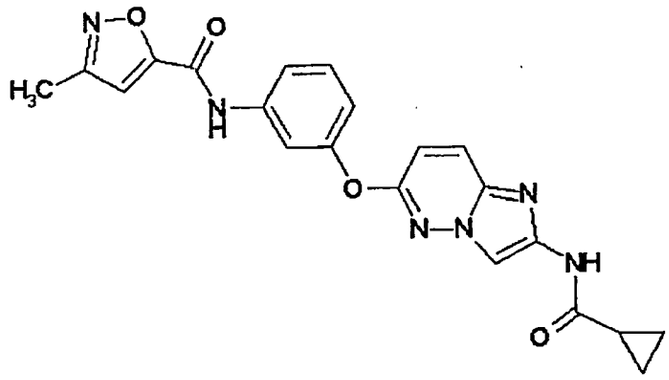
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-

yl)cyclopropanecarboxamide (743 mg, 2.26 mmol), 3-amino-4-methylphenol (446 mg, 3.62 mmol), potassium carbonate (782 mg, 5.66 mmol) and N,N-dimethylformamide (5.0 mL) was stirred using a microwave synthesizer at 180°C for 30 min . The solvent was evaporated under reduced pressure, ethyl acetate, tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=17/83→75/25) to give the title compound (424 mg, 58%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.84 - 1.97 (1H, m), 2.04 (3H, s), 5.06 (2H, s), 6.28 (1H, dd, J = 8.1, 2.4 Hz), 6.42 (1H, d, J = 2.4 Hz), 6.93 (1H, d, J = 9.3 Hz), 6.95 (1H, d, J = 8.1 Hz), 7.96 (1H, s), 7.98 (1H, d, J = 9.3 Hz), 11.07 (1H, s).

Example 109

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylisoxazole-5-carboxamide



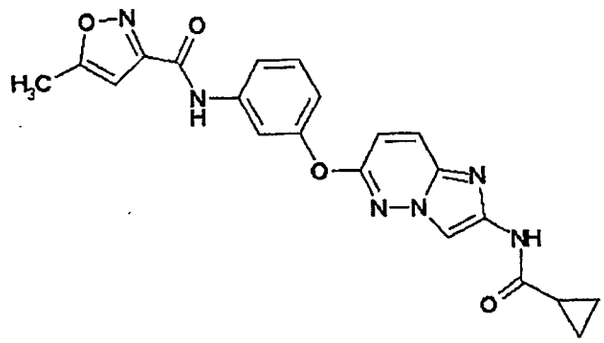
To a solution of 3-methylisoxazole-5-carboxylic acid (87 mg, 0.679 mmol) in tetrahydrofuran (2.0 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (75.8 μL, 0.88 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, and the

residue was dissolved in tetrahydrofuran (1 mL), and added to a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (140 mg, 0.453 mmol) in tetrahydrofuran (12 mL). Then, triethylamine (138 mg, 1.36 mmol) was added to the mixture, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution, and extracted three times with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→80/20) and precipitated from ethyl acetate/hexane to give the title compound (42 mg, 22%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 2.32 (3H, s), 7.01 - 7.14 (3H, m), 7.45 (1H, t, J = 8.2 Hz), 7.62 - 7.74 (2H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.8 Hz), 10.82 (1H, s), 11.10 (1H, s).

Example 110

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-methylisoxazole-3-carboxamide

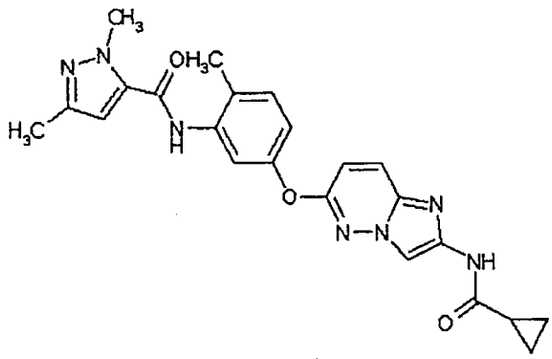


Using 5-methylisoxazole-3-carboxylic acid (87 mg, 0.679 mmol), N,N-dimethylformamide (1 drop), oxalyl chloride (75.8 μL, 0.88 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (140 mg, 0.453 mmol), triethylamine (138 mg, 1.36 mmol) and tetrahydrofuran (15 mL) as starting materials and in the same manner as in Example 109, the title

compound (109 mg, 58%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.85 - 1.96 (1H, m), 2.50 (3H, s), 6.66 (1H, d, J = 0.9 Hz), 6.97 - 7.10 (2H, m), 7.43 (1H, t, J = 8.2 Hz), 7.63 - 7.77 (2H, m), 7.98 (1H, s), 8.05 (1H, d, J = 9.4 Hz), 10.78 (1H, s), 11.09 (1H, s).

Example 111

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

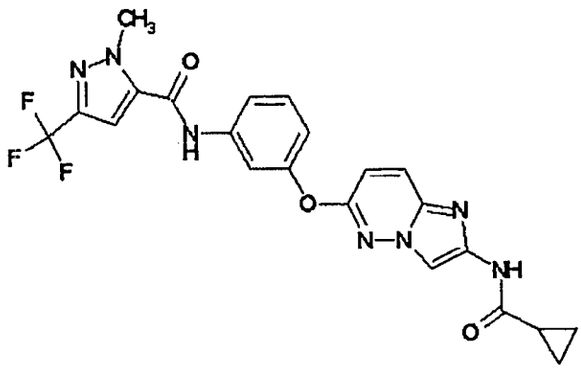


To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (213 mg, 0.659 mmol) in tetrahydrofuran (10 mL) were added a solution of 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (136 mg, 0.856 mmol) in tetrahydrofuran (0.5 mL) and triethylamine (200 mg, 1.98 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution, and extracted three times with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was filtrated and washed with ethyl acetate/hexane to give the title compound (222 mg, 77%) as a white powder. melting point 223°C.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.89 (4H, m), 1.86 - 1.97 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.04

(1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.7, 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.93 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.81 (1H, s), 11.08 (1H, s).

Example 112

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

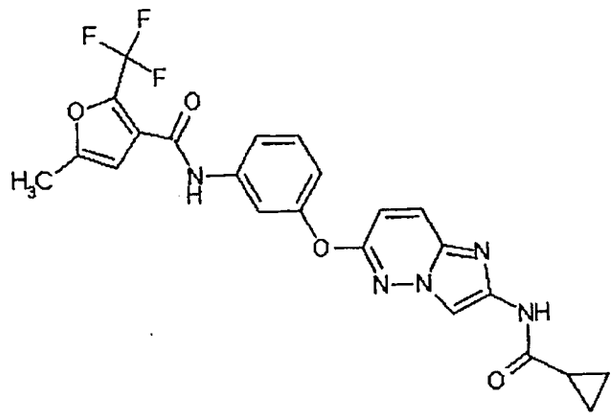


Using 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (100 mg, 0.515 mmol), N,N-dimethylformamide (1 drop), oxalyl chloride (60 μL, 0.7 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (122.5 mg, 0.396 mmol), triethylamine (120 mg, 1.19 mmol) and tetrahydrofuran (15 mL) as starting materials and in the same manner as in Example 109, the title compound (149 mg, 78%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.84 - 1.97 (1H, m), 4.15 (3H, s), 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.46 (1H, t, J = 8.2 Hz), 7.50 (1H, s), 7.59 - 7.64 (1H, m), 7.66 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.53 (1H, s), 11.10 (1H, s).

Example 113

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-methyl-2-(trifluoromethyl)-3-furancarboxamide

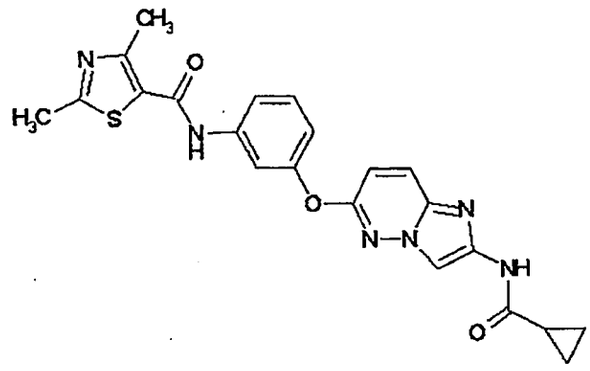


Using 5-methyl-2-(trifluoromethyl)-3-furancarboxylic acid (133.6 mg, 0.668 mmol), N,N-dimethylformamide (1 drop), oxalyl chloride (75 μL, 0.868 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (159 mg, 0.514 mmol), triethylamine (156 mg, 1.54 mmol) and tetrahydrofuran (15 mL) as starting materials and in the same manner as in Example 109, the title compound (145 mg, 58%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.85 - 1.97 (1H, m), 2.40 (3H, s), 6.80 (1H, s), 7.02 (1H, m), 7.06 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.2 Hz), 7.56 (1H, d, J = 8.3 Hz), 7.63 (1H, t, J = 2.0 Hz), 7.97 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.50 (1H, s), 11.09 (1H, s).

Example 114

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide

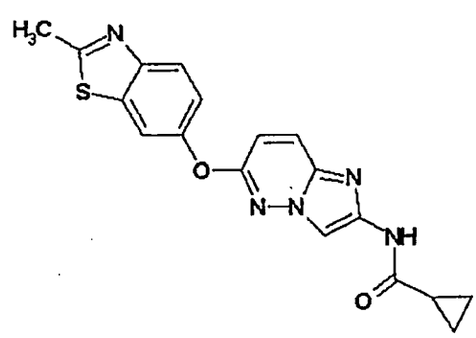


Using 2,4-dimethyl-1,3-thiazole-5-carboxylic acid (78.8 mg, 0.50 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (129 mg, 0.417 mmol), 1-hydroxybenzotriazole (68 mg, 0.50 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (96 mg, 0.50 mmol), triethylamine (50 mg, 0.50 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 106, the title compound (133 mg, 71%) was obtained as a white powder. melting point 249°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.85 - 1.98 (1H, m), 2.53 (3H, s), 2.65 (3H, s), 7.00 (1H, dd, J = 7.6, 1.9 Hz), 7.06 (1H, d, J = 9.5 Hz), 7.41 (1H, t, J = 8.1 Hz), 7.54 (1H, d, J = 8.3 Hz), 7.62 (1H, t, J = 2.1 Hz), 7.97 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 10.22 (1H, s), 11.09 (1H, s).

Example 115

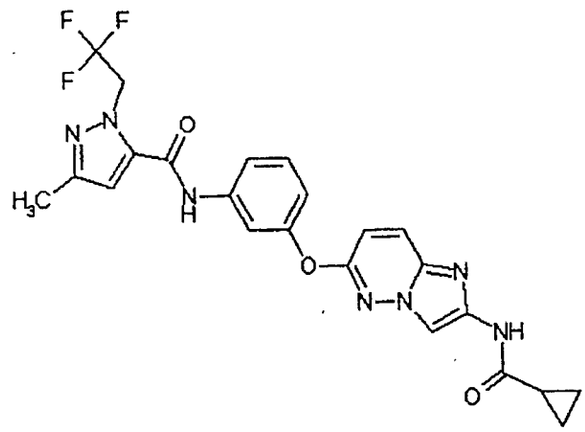
Production of N-{6-[(2-methyl-1,3-benzothiazol-6-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (309 mg, 0.942 mmol), 2-methyl-1,3-benzothiazole-6-ol (250 mg, 1.51 mmol), potassium carbonate (390 mg, 2.83 mmol) and N,N-dimethylformamide (4.0 mL) as starting materials and in the same manner as in Example 95, the title compound (151 mg, 44%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.83 (4H, m), 1.83 - 1.94 (1H, m), 2.79 (3H, s), 7.07 (1H, d, J = 9.6 Hz), 7.37 (1H, dd, J = 8.8, 2.5 Hz), 7.90 - 7.99 (3H, m), 8.02 (1H, d, J = 9.6 Hz), 11.06 (1H, s).

Example 116

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxamide

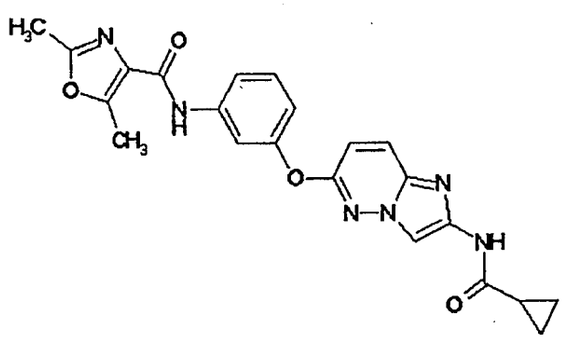


Using 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxylic acid (175 mg, 0.84 mmol), N,N-dimethylformamide (1 drop), oxalyl chloride (91 μL, 1.01 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.646 mmol), triethylamine (196 mg, 1.94 mmol) and tetrahydrofuran (15 mL) as starting materials and in the same manner as in Example 109, the title compound (281 mg, 87%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.87 - 1.98 (1H, m), 2.25 (3H, s), 5.40 (2H, q, J = 8.9 Hz), 7.00 (1H, s), 7.04 (1H, m), 7.07 (1H, d, J = 9.4 Hz), 7.45 (1H, t, J = 8.2 Hz),

7.58 - 7.69 (2H, m), 7.97 (1H, s), 8.06 (1H, d, J = 9.4 Hz), 10.45 (1H, s), 11.10 (1H, s).

Example 117

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide

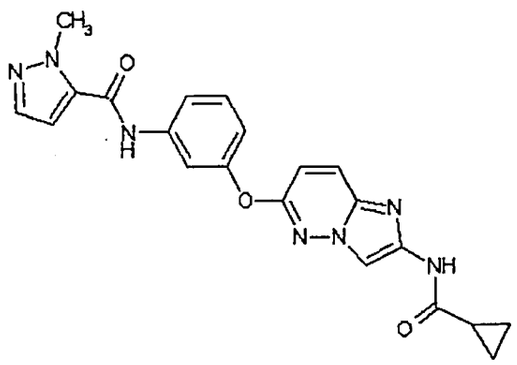


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (202 mg, 0.652 mmol) in N,N-dimethylacetamide (4.0 mL) was added a solution of 2,5-dimethyl-1,3-oxazole-4-carbonyl chloride (135 mg, 0.847 mmol) in N,N-dimethylacetamide (1.0 mL), and the mixture was stirred at 0°C for 1 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the mixture, and the aqueous layer was extracted three times with ethyl acetate/tetrahydrofuran. Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→90/10), and precipitated from ethyl acetate/hexane to give the title compound (213 mg, 76%) as a white powder. melting point 224°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.87 - 1.97 (1H, m), 2.44 (3H, s), 2.56 (3H, s), 6.96 (1H, dd, J = 8.3, 2.1 Hz), 7.05 (1H, d, J = 9.5 Hz), 7.38 (1H, t, J = 8.1 Hz), 7.72 (1H, d, J = 8.3 Hz), 7.80 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.04 (1H, d, J = 9.5 Hz), 10.12 (1H, s), 11.09 (1H, s).

Example 118

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-1H-pyrazole-5-carboxamide



To a solution of 1-methyl-1H-pyrazole-5-carboxylic acid (106 mg, 0.840 mmol) in tetrahydrofuran (2.0 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (91 μL, 1.01 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, and the residue was dissolved in N,N-dimethylacetamide (1 mL) and added to a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.646 mmol) in N,N-dimethylacetamide (5.0 mL). The mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with saturated aqueous sodium hydrogencarbonate solution, and extracted three times with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→95/5) and precipitated from ethyl acetate/hexane to give the title compound (241 mg, 89%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 4.07 (3H, s), 7.00 - 7.05 (1H, m), 7.04 - 7.10 (2H, m), 7.44 (1H, t, J = 8.2 Hz), 7.53 (1H, d, J = 2.1 Hz), 7.59 - 7.69 (2H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.33 (1H, s), 11.10 (1H, s).

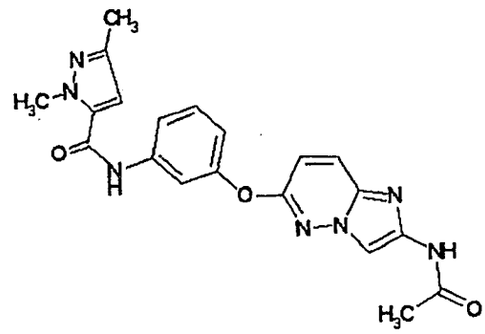
Organizacion y
Digitalizacion CSA Ltda

Patente de invención 01-0229-0

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Example 119

Production of N-(3-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



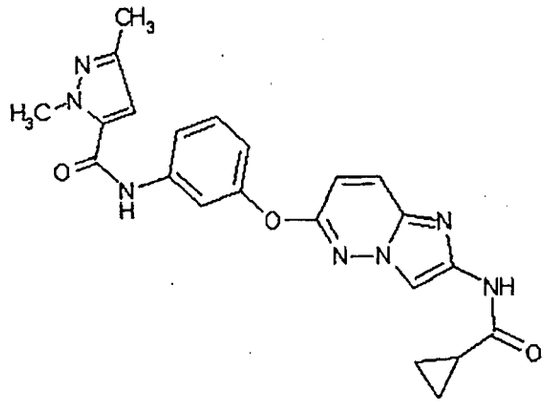
To a solution (4.0 mL) of 1,3-dimethyl-1H-pyrazole-5-carboxylic acid (109 mg, 0.85 mmol) in tetrahydrofuran were added N,N-dimethylformamide (30 μL, 0.39 mmol) and oxalyl chloride (135 μL, 1.55 mmol), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and a solution of the residue in N,N-dimethylacetamide (2.0 mL) was added dropwise to a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (200 mg, 0.71 mmol) in N,N-dimethylacetamide (2.0 mL). After the reaction mixture was stirred at room temperature for 1 hr, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate to give the title compound (182 mg, 67%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 2.19 (3H, s), 3.97 (3H, s), 6.82 (1H, s), 6.98 - 7.03 (1H, m), 7.06 (1H, d, J = 9.6 Hz), 7.42 (1H, t, J = 8.1 Hz), 7.59 - 7.63 (1H, m), 7.66 - 7.68 (1H, m), 7.98 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.24 (1H, s), 10.80 (1H, s).

Example 120

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-

carboxamide

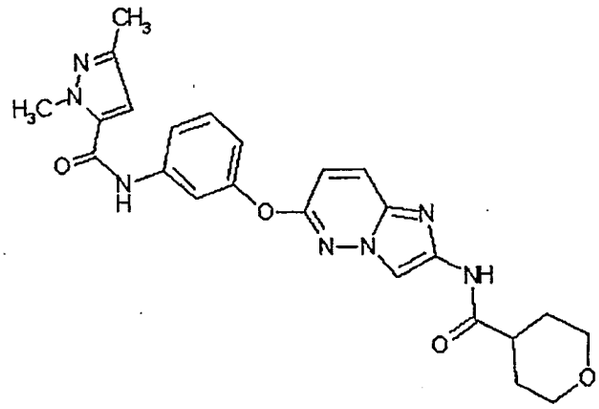


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.65 mmol) in N,N-dimethylacetamide (2.0 mL) was added 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (185 mg, 1.16 mmol). After stirring at room temperature for 1 hr, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/2→ethyl acetate) and precipitated from hexane/ethyl acetate to give the title compound (70 mg, 25%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.83 (4H, m), 1.87 -1.97 (1H, m), 2.19 (3H, s), 3.98 (3H, s), 6.82 (1H, s), 6.99 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.60 - 7.64 (1H, m), 7.65 - 7.68 (1H, m), 7.97 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.24 (1H, s), 11.10 (1H, s).

Example 121

Production of 1,3-dimethyl-N-[3-({2-[(tetrahydro-2H-pyran-4-ylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-pyrazole-5-carboxamide

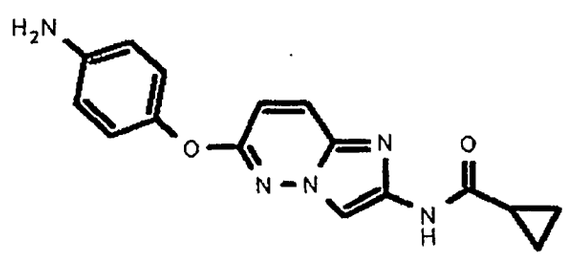


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]tetrahydro-2H-pyran-4-carboxamide (200 mg, 0.57 mmol), triethylamine (237 μL, 1.70 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (180 mg, 1.13 mmol) and tetrahydrofuran (6.0 mL) as starting materials and in the same manner as in Example 96, the title compound (73 mg, 27%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.72 (4H, m), 2.20 (3H, s), 2.63 - 2.78 (1H, m), 3.27 - 3.37 (2H, m), 3.86 - 3.92 (2H, s), 3.98 (3H, s), 6.83 (1H, s), 6.98 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.59 - 7.63 (1H, m), 7.67 - 7.70 (1H, m), 8.03 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.26 (1H, s), 10.82 (1H, s).

Example 122

Production of N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

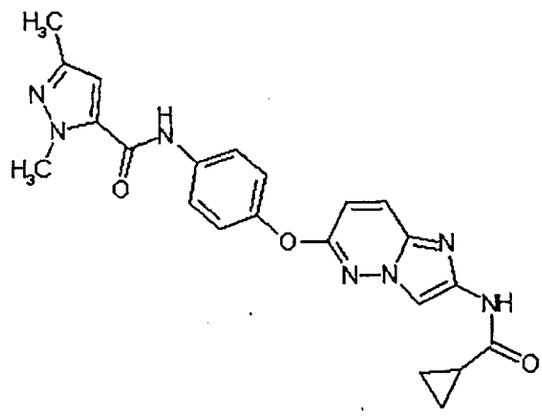


To a solution of 4-aminophenol (0.33 g, 3.05 mmol) in N,N-dimethylformamide (10 mL) was added potassium tert-butoxide (0.36 g, 3.17 mmol), and the mixture was stirred at room temperature for 2 hr. N-(6-Iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (0.80 g, 2.44 mmol) and potassium carbonate (0.17 g, 1.22 mmol) were added to the reaction mixture, and the mixture was stirred using a microwave synthesizer with heating at 150°C for 30 min. After cooling the reaction mixture, saturated brine was added to the mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/2→ethyl acetate) to give the title compound (376 mg, 50%) as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.81 (4H, m), 1.88 - 1.95 (1H, m), 5.09 (2H, s), 6.57 - 6.61 (2H, s), 6.88 - 6.94 (3H, m), 7.89 - 7.97 (2H, m), 11.05 (1H, s).

Example 123

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



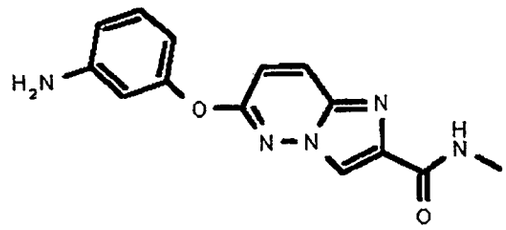
Using N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (220 mg, 0.71 mmol), triethylamine (0.30 mL, 2.13 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (230 mg, 1.42 mmol) and tetrahydrofuran (6.6 mL) as starting materials and in the same manner as in Example 96, the title compound (84 mg, 27%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.87 - 1.96 (1H, m), 2.21 (3H, s), 4.00 (3H, s), 6.82 (1H, s), 7.03 (1H, d, J = 9.6 Hz), 7.25 (2H, d, J = 9.0 Hz), 7.78 (2H, d, J = 9.0 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 10.22 (1H, s), 11.07 (1H, s).

Example 124

Production of 6-(3-aminophenoxy)-N-methylimidazo[1,2-b]pyridazine-2-carboxamide



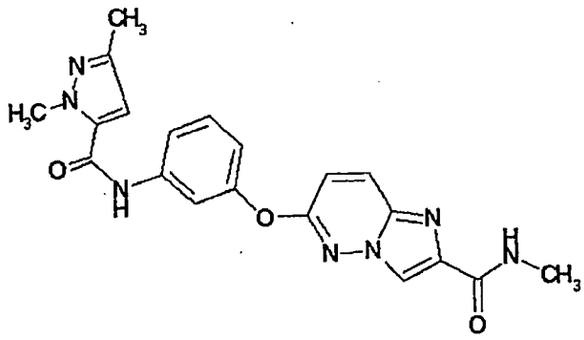
Using 6-iodo-N-methylimidazo[1,2-b]pyridazine-2-carboxamide (0.30 g, 0.99 mmol), N,N-dimethylformamide (3.0 mL), potassium carbonate (275 mg, 1.99 mmol) and 3-aminophenol (163 mg, 1.49 mmol) as starting materials and in the same manner as in Example 91, the title compound (0.10 g, 36%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.77 (3H, d, J = 5.1 Hz), 5.34 (2H, s), 6.32 - 6.40 (2H, m), 6.43 - 6.47 (1H, m), 7.06 (1H, t, J = 8.1 Hz), 7.13 (1H, d, J = 9.6 Hz), 8.15 (1H, d, J = 9.6 Hz), 8.34 (1H, s), 8.37 (1H, q, J = 5.1 Hz).

Example 125

Production of 6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}phenoxy)-N-methylimidazo[1,2-b]pyridazine-2-

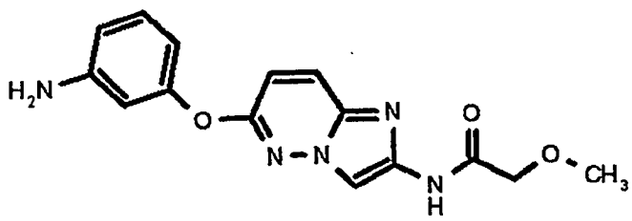
carboxamide



To a solution of 6-(3-aminophenoxy)-N-methylimidazo[1,2-b]pyridazine-2-carboxamide (250 mg, 0.88 mmol) in N,N-dimethylacetamide (2.5 mL) was added 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (253 mg, 1.59 mmol). After stirring at room temperature for 1 hr, water was added to the reaction mixture, and the precipitate was collected by filtration. The obtained residue was washed with water, acetonitrile and diethyl ether to give the title compound (262 mg, 73%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.20 (3H, s), 2.77 (3H, d, J = 5.1 Hz), 3.99 (3H, s), 6.82 (1H, s), 7.04 - 7.09 (1H, m), 7.24 (1H, d, J = 9.9 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.57 - 7.64 (1H, m), 7.71 - 7.74 (1H, m), 8.20 (1H, d, J = 9.6 Hz), 8.34 (1H, s), 8.35 - 8.41 (1H, m), 10.28 (1H, s).

Example 126

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methoxyacetamide

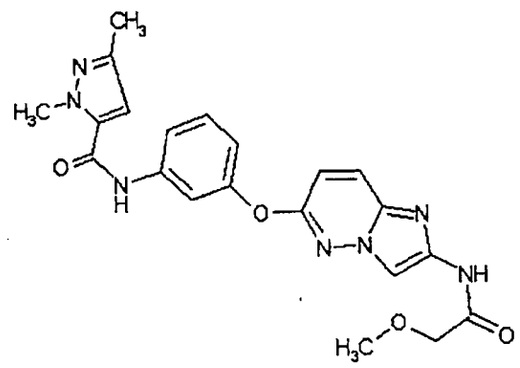


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methoxyacetamide (0.60 g, 1.81 mmol), N,N-dimethylformamide (6.0 mL), potassium carbonate (499 mg, 3.61 mmol) and 3-aminophenol (296 mg, 2.71 mmol) as starting materials and in the same manner as in Example 91, the title compound (0.29 g, 51%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.35 (3H, s), 4.06 (2H, s), 5.32 (2H, s), 6.28 - 6.37 (2H, s), 6.41 - 6.45 (1H, m), 6.98 (1H, d, J = 9.6 Hz), 7.05 (1H, t, J = 8.1 Hz), 8.01 (1H, d, J = 9.6 Hz), 8.04 (1H, s), 10.57 (1H, s).

Example 127

Production of N-[3-({2-[(methoxyacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

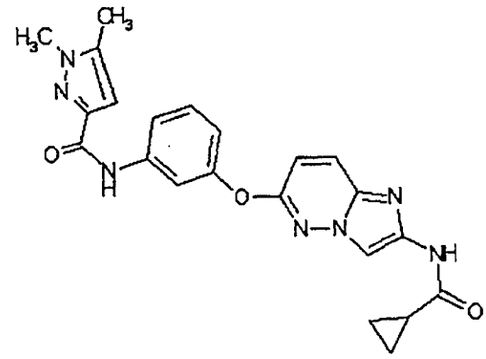


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methoxyacetamide (200 mg, 0.64 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (162 mg, 1.02 mmol) and N,N-dimethylacetamide (4.0 mL) as starting materials and in the same manner as in Example 120, the title compound (176 mg, 64%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.33 (3H, s), 3.98 (3H, s), 4.06 (2H, s), 6.82 (1H, s), 6.97 - 7.04 (1H, m), 7.09 (1H, d, J = 9.3 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.58 - 7.64 (1H, m), 7.66 - 7.69 (1H, m), 8.03 (1H, s), 8.04 (1H, d, J = 9.3 Hz), 10.24 (1H, s), 10.59 (1H, s).

Example 128

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,5-dimethyl-1H-pyrazole-3-carboxamide

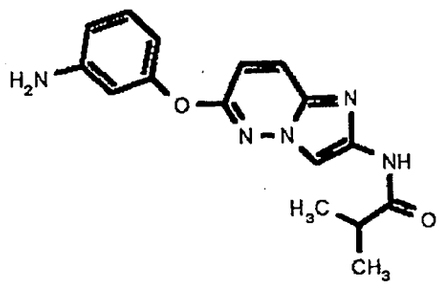


To a solution of 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (109 mg, 0.78 mmol) in tetrahydrofuran (4.0 mL) were added N,N-dimethylformamide (30 μL, 0.39 mmol) and oxalyl chloride (135 μL, 1.55 mmol), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and a solution of the residue in tetrahydrofuran (2.0 mL) was added dropwise to a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (200 mg, 0.65 mmol) and triethylamine (360 μL, 2.59 mmol) in tetrahydrofuran (4.0 mL). After stirring at room temperature for 2 hr, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/4→ethyl acetate) and precipitated from hexane/ethyl acetate to give the title compound (118 mg, 42%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.88 - 1.96 (1H, m), 2.30 (3H, s), 3.82 (3H, s), 6.54 (1H, s), 6.91 - 6.96 (1H, m), 7.05 (1H, d, J = 9.6 Hz), 7.37 (1H, t, J = 8.1 Hz), 7.69 - 7.73 (1H, m), 7.76 - 7.78 (1H, m), 7.97 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 11.09 (1H, s).

Example 129

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylpropanamide

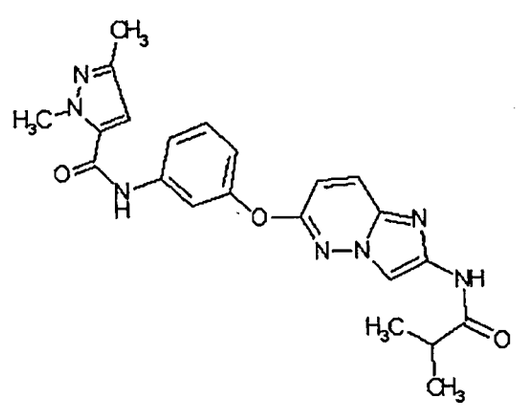


Using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylpropanamide (0.60 g, 1.82 mmol), N,N-dimethylformamide (6.0 mL), potassium carbonate (502 mg, 3.63 mmol) and 3-aminophenol (278 mg, 2.54 mmol) as starting materials and in the same manner as in Example 91, the title compound (0.26 g, 47%) was obtained as a dark brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.09 (6H, d, J = 6.9 Hz), 2.66 - 2.74 (1H, m), 5.32 (2H, s), 6.27 - 6.36 (2H, m), 6.40 - 6.44 (1H, m), 6.95 (1H, d, J = 9.6 Hz), 7.05 (1H, t, J = 8.1 Hz), 7.94 - 8.02 (2H, m), 10.74 (1H, s).

Example 130

Production of N-(3-{[2-(isobutyrylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

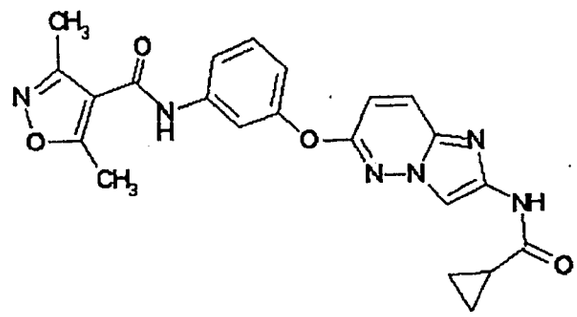


Using 1,3-dimethyl-1H-pyrazole-5-carboxylic acid (108 mg, 0.77 mmol), tetrahydrofuran (3.2 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (134 μL, 1.54 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylpropanamide (200 mg, 0.64 mmol) and N,N-dimethylacetamide (4.0 mL) as starting materials and in the same manner as in Example 119, the title compound (201 mg, 72%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.08 (6H, d, J = 6.9 Hz), 2.19 (3H, s), 2.65 - 2.74 (1H, m), 3.98 (3H, s), 6.82 (1H, s), 6.98 - 7.02 (1H, m), 7.06 (1H, d, J = 9.6 Hz), 7.42 (1H, t, J = 8.1 Hz), 7.59 - 7.63 (1H, m), 7.66 - 7.68 (1H, m), 8.01 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.24 (1H, s), 10.75 (1H, s).

Example 131

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3,5-dimethylisoxazole-4-carboxamide



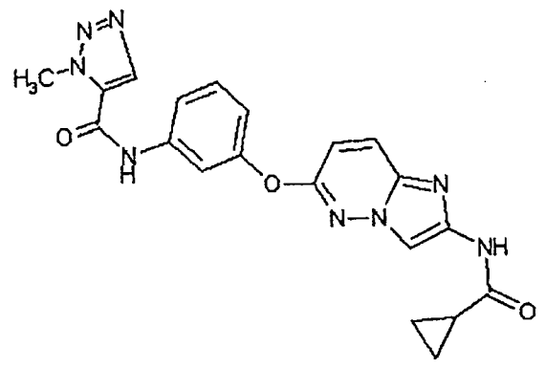
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (160 mg, 0.52 mmol), N,N-dimethylacetamide (3.2 mL) and 3,5-dimethylisoxazole-4-carbonyl chloride (99 mg, 0.62 mmol) and in the same manner as in Example 120, the title compound (163 mg, 73%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.88 - 1.95 (1H, m), 2.32 (3H, s), 2.54 (3H, s), 6.98 - 7.02 (1H, m), 7.06 (1H, d, J = 9.6 Hz), 7.42 (1H, t, J = 8.1 Hz), 7.48 - 7.51 (1H, m), 7.61

- 7.64 (1H, m), 7.96 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.19 (1H, s), 11.09 (1H, s).

Example 132

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-1H-1,2,3-triazole-5-carboxamide

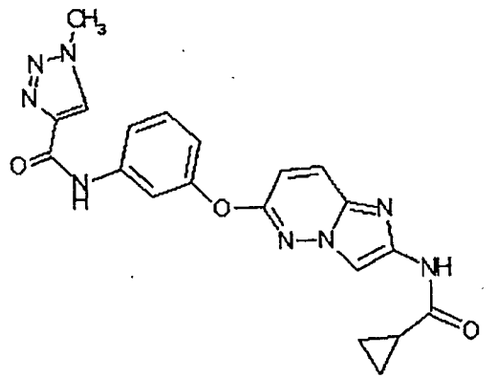


Using 1-methyl-1H-1,2,3-triazole-5-carboxylic acid (99 mg, 0.78 mmol), tetrahydrofuran (4.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (135 μL, 1.55 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL) as starting materials and in the same manner as in Example 119, the title compound (182 mg, 67%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.87 - 1.96 (1H, m), 4.23 (3H, s), 7.02 - 7.09 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.56 - 7.65 (2H, m), 7.96 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 8.37 (1H, s), 10.61 (1H, s), 11.09 (1H, s).

Example 133

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-1H-1,2,3-triazole-4-carboxamide

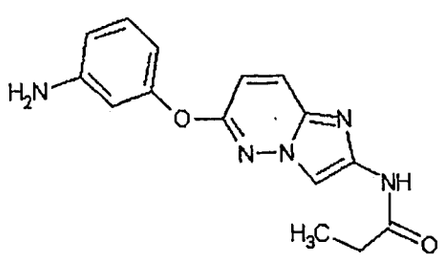


Using 1-methyl-1H-1,2,3-triazole-4-carboxylic acid (99 mg, 0.78 mmol), tetrahydrofuran (4.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (135 μL, 1.55 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL) as starting materials and in the same manner as in Example 119, the title compound (189 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.82 (4H, m), 1.87 - 1.96 (1H, m), 4.12 (3H, s), 6.98 (1H, dd, J = 11.3, 2.3 Hz), 7.06 (1H, d, J = 9.3 Hz), 7.40 (1H, t, J = 8.1 Hz), 7.72 - 7.76 (1H, m), 7.78 - 7.81 (1H, m), 7.97 (1H, s), 8.04 (1H, d, J = 9.3 Hz), 8.66 (1H, s), 10.60 (1H, s), 11.09 (1H, s).

Example 134

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]propaneamide



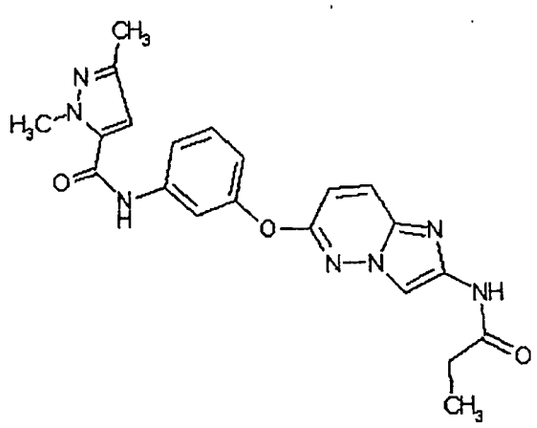
To a solution of 3-aminophenol (331 mg, 3.0 mol) in N,N-

dimethylformamide (8.0 mL) was added potassium tert-butoxide (355 mg, 3.16 mmol), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture were added N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)propaneamide (0.80 g, 2.53 mmol) and potassium carbonate (175 mg, 1.27 mmol), and the mixture was stirred at 140°C for 16 hr. Saturated brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/2) and precipitated from hexane/ethyl acetate to give the title compound (420 mg, 56%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.07 (3H, t, J = 7.5 Hz), 2.37 (2H, q, J = 7.5 Hz), 5.31 (2H, s), 6.27 - 6.35 (2H, m), 6.40 - 6.44 (1H, m), 6.95 (1H, d, J = 9.3 Hz), 7.04 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 9.3 Hz), 8.00 (1H, d, J = 1.5 Hz), 10.73 (1H, s).

Example 135

Production of 1,3-dimethyl-N-(3-{[2-(propionylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1H-pyrazole-5-carboxamide

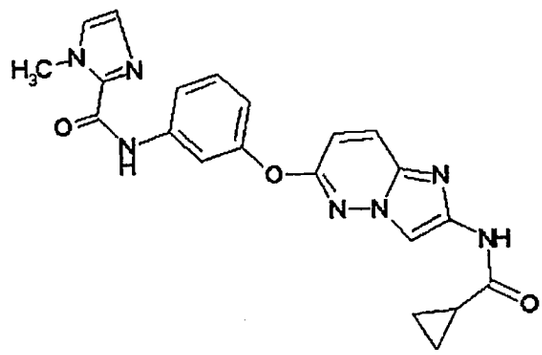


Using 1,3-dimethyl-1H-pyrazole-5-carboxylic acid (113 mg, 0.81 mol), tetrahydrofuran (4.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (141 μL, 1.61 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]propionyl carboxamide (200 mg, 0.67 mmol) and N,N-dimethylacetamide (4.0 mL) as

starting materials and in the same manner as in Example 119, the title compound (190 mg, 67%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.07 (3H, t, J = 7.5 Hz), 2.19 (3H, s), 2.37 (2H, q, J = 7.5 Hz), 3.98 (3H, s), 6.83 (1H, s), 6.99 - 7.04 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.60 - 7.64 (1H, m), 7.67 - 7.69 (1H, m), 8.02 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.25 (1H, s), 10.77 (1H, s).

Example 136

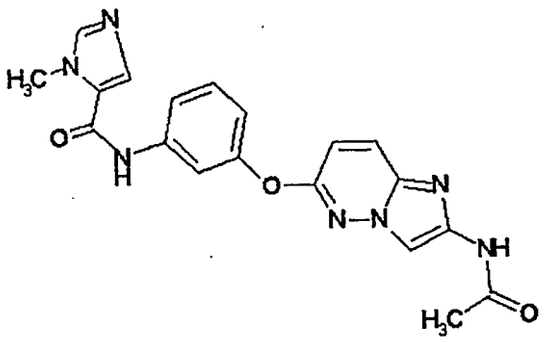
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-1H-imidazole-2-carboxamide



Using 1-methyl-1H-imidazole-2-carboxylic acid (36.7 mg, 0.29 mol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (51 μL, 0.58 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (75 mg, 0.24 mmol) and N,N-dimethylacetamide (1.5 mL) as starting materials and in the same manner as in Example 119, the title compound (48 mg, 47%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.91 - 1.97 (1H, m), 3.97 (3H,s), 6.97 (1H, dd, J = 8.1, 1.5 Hz), 7.05 (1H, d, J = 9.6 Hz), 7.07 (1H, s), 7.39 (1H, t, J = 8.1 Hz), 7.44 - 7.45 (1H, m), 7.72 (1H, d, J = 8.4 Hz), 7.78 -7.80 (1H, m), 7.97 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.43 (1H, s), 11.08 (1H, s).

Example 137

Production of N-(3-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1-methyl-1H-imidazole-5-carboxamide

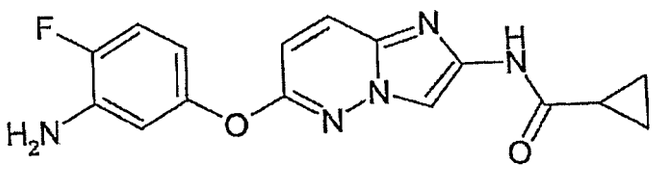


Using 1-methyl-1H-imidazole-5-carboxylic acid (80 mg, 0.64 mol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (111 μL, 1.27 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (150 mg, 0.53 mmol) and N,N-dimethylacetamide (3.0 mL) as starting materials and in the same manner as in Example 119, the title compound (98 mg, 47%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 3.84 (3H, s), 6.96 - 7.00 (1H, m), 7.06 (1H, d, J = 9.3 Hz), 7.42 (1H, t, J = 8.1 Hz), 7.57 - 7.61 (1H, m), 7.64 - 7.67 (1H, m), 7.79 (1H, s), 7.84 (1H, s), 7.99 (1H, s), 8.05 (1H, d, J = 9.3 Hz), 10.16 (1H, s), 10.81 (1H, s).

Example 138

Production of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

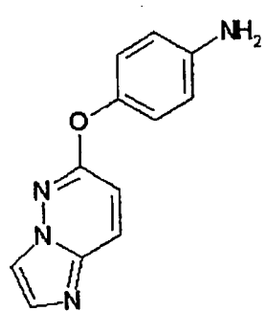


A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (2.62 g, 8.0 mmol), 3-amino-4-fluorophenol (2.03 g, 16.0 mmol), potassium carbonate(1.66 g, 12.0 mmol) and N,N-dimethylformamide (20 mL) was stirred at 150°C for 15 hr. Tetrahydrofuran/ethyl acetate and saturated brine

were added to the reaction mixture, and insoluble material was filtered off. The filtrate was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=20/80→0/100) and recrystallized from ethyl acetate to give the title compound (1.91 g, 73%) as pale-yellow crystals.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.90 (4H, m), 1.85 - 2.00 (1H, m), 5.36 (2H, s), 6.30-6.40 (1H, m), 6.50-6.60 (1H, m), 6.96 (1H, d, J = 9.8 Hz), 7.00-7.10 (1H, m), 7.95 (1H, s), 7.99 (1H, d, J = 9.8 Hz), 11.06 (1H, s).

Example 139

Production of 4-(imidazo[1,2-b]pyridazin-6-yloxy)aniline

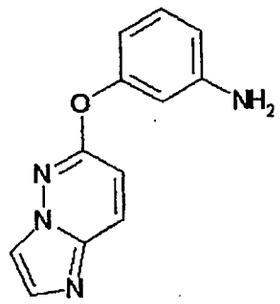


A mixture of 6-chloroimidazo[1,2-b]pyridazine (768 mg, 5.0 mmol), 4-aminophenol (818 mg, 7.5 mmol), potassium carbonate (2073 mg, 15.0 mmol) and N-methylpyrrolidone (5.0 mL) was stirred at 120°C for 18 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution and saturated brine, and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (hexane/ethyl acetate=70/30→0/100) and precipitated from diisopropyl ether to give the title compound (759 mg, 67%) as a gray powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.07 (2H, s), 6.60 (2H, d, J = 8.9 Hz), 6.92 (2H, d, J = 8.9 Hz), 7.00 (1H, d, J = 9.8 Hz), 7.61

(1H, s), 8.01 (1H, s), 8.09 (1H, d, J = 9.8 Hz).

Example 140

3-(imidazo[1,2-b]pyridazin-6-yloxy)aniline

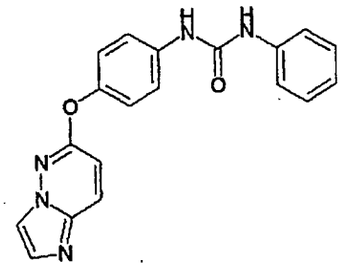


A mixture of 6-chloroimidazo[1,2-b]pyridazine (1536 mg, 10.0 mmol), 3-aminophenol (1419 mg, 13.0 mmol), potassium carbonate (4146 mg, 30.0 mmol) and N-methylpyrrolidone (10 mL) was stirred at 120°C for 48 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution and saturated brine, and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (hexane/ethyl acetate=70/30→0/100), and precipitated from diisopropyl ether to give the title compound (932 mg, 41%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.29 (2H, s), 6.31 - 6.35 (1H, m), 6.37 (1H, t, J =2.2 Hz), 6.42 - 6.47 (1H, m), 7.02 (1H, d, J = 9.8 Hz), 7.06 (1H, t, J = 7.9 Hz), 7.65 (1H, d, J = 1.2 Hz), 8.08 (1H, s), 8.13 (1H, d, J = 9.8 Hz).

Example 141

Production of N-[4-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-N'-phenylurea

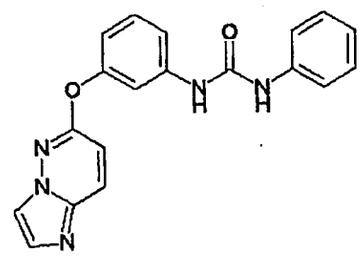


To a solution of 4-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (181 mg, 0.80 mmol) and triethylamine (0.011 mL, 0.08 mmol) in tetrahydrofuran (10 mL) was added phenyl isocyanate (0.104 mL, 0.96 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/methanol=100/0→90/10) and precipitated from ethyl acetate to give the title compound (223 mg, 81%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.97 (1H, t, J = 7.6 Hz), 7.09 (1H, d, J = 9.8 Hz), 7.22 (2H, d, J = 8.7 Hz), 7.28 (2H, t, J = 7.6 Hz), 7.46 (2H, d, J = 7.6 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.64 (1H, s), 8.05 (1H, s), 8.15 (1H, d, J = 9.8 Hz), 8.70 (1H, s), 8.76 (1H, s).

Example 142

Production of N-[3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-N'-phenylurea



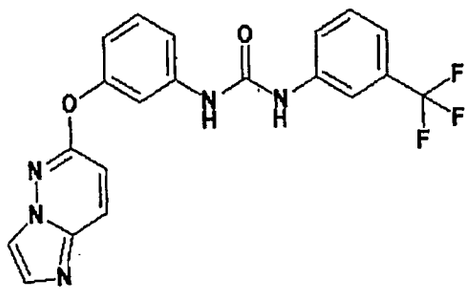
To a solution of 3-(imidazo[1,2-b]pyridazin-6-

yloxy)aniline (181 mg, 0.80 mmol) and triethylamine (0.011 mL, 0.08 mmol) in tetrahydrofuran (10 mL) was added phenyl isocyanate (0.104 mL, 0.96 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/methanol=100/0→90/10) and precipitated from ethyl acetate to give the title compound (196 mg, 71%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.85 - 6.90 (1H, m), 6.97 (1H, t, J = 7.5 Hz), 7.11 (1H, d, J = 9.6 Hz), 7.22 - 7.31 (3H, m), 7.36 (1H, t, J = 7.9 Hz), 7.43 (2H, d, J = 7.5 Hz), 7.51 (1H, t, J = 2.1 Hz), 7.66 (1H, d, J = 0.9 Hz), 8.08 (1H, s), 8.18 (1H, d, J = 9.6 Hz), 8.72 (1H, s), 8.87 (1H, s).

Example 143

Production of N-[3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-N'-[3-(trifluoromethyl)phenyl]urea



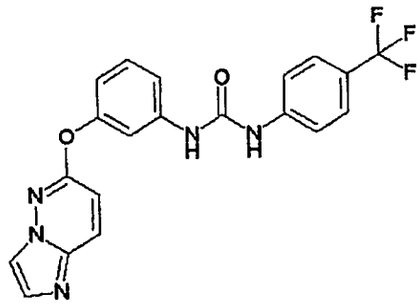
To a solution of 3-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (181 mg, 0.80 mmol) and triethylamine (0.040 mL, 0.29 mmol) in tetrahydrofuran (10 mL) was added 3-(trifluoromethyl)phenyl isocyanate (0.154 mL, 1.12 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→90/10) and precipitated from methanol to give the title compound (205 mg, 62%) as a white

powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.89 - 6.94 (1H, m), 7.12 (1H, d, J = 9.8 Hz), 7.26 - 7.34 (2H, m), 7.38 (1H, t, J = 8.1 Hz), 7.47 - 7.60 (3H, m), 7.66 (1H, d, J = 0.9 Hz), 7.99 (1H, s), 8.08 (1H, s), 8.18 (1H, d, J = 9.8 Hz), 9.01 (1H, s), 9.11 (1H, s).

Example 144

Production of N-[3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea

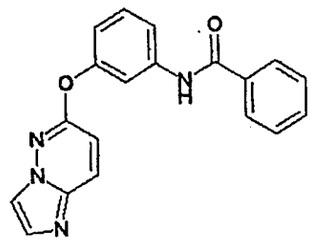


To a solution of 3-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (113 mg, 0.50 mmol) and triethylamine (0.040 mL, 0.29 mmol) in tetrahydrofuran (10 mL) was added 4-(trifluoromethyl)phenyl isocyanate (0.100 mL, 0.70 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was precipitated from methanol to give the title compound (103 mg, 50%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.86 - 6.94 (1H, m), 7.11 (1H, d, J = 9.8 Hz), 7.24 - 7.31 (1H, m), 7.38 (1H, t, J = 8.2 Hz), 7.51 (1H, t, J = 1.8 Hz), 7.58 - 7.68 (5H, m), 8.08 (1H, s), 8.18 (1H, d, J = 9.8 Hz), 9.00 (1H, s), 9.16 (1H, s).

Example 145

Production of N-[3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]benzamide

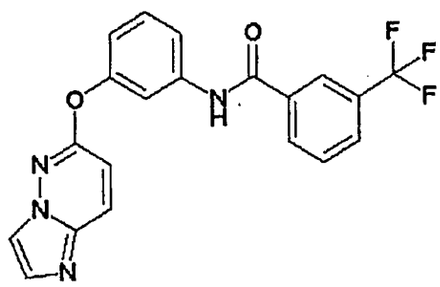


To a solution of 3-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (113 mg, 0.50 mmol) in N-methylpyrrolidone (1.0 mL) was added benzoyl chloride (0.116 mL, 1.00 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution and saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→75/25) and precipitated from ethyl acetate to give the title compound (122 mg, 74%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.01 - 7.06 (1H, m), 7.14 (1H, d, J = 9.8 Hz), 7.45 (1H, t, J = 8.2 Hz), 7.50 - 7.64 (3H, m), 7.66 - 7.71 (2H, m), 7.77 (1H, t, J = 2.1 Hz), 7.92 - 7.97 (2H, m), 8.09 (1H, s), 8.19 (1H, d, J = 9.8 Hz), 10.39 (1H, s).

Example 146

Production of N-[3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-3-(trifluoromethyl)benzamide

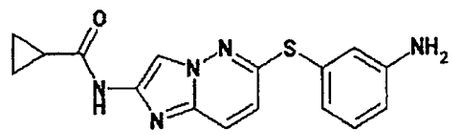


To a solution of 3-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (113 mg, 0.50 mmol) in N-methylpyrrolidone (1.0 mL) was added 3-(trifluoromethyl)benzoyl chloride (0.151 mL, 1.00 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide solution and saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→75/25), and precipitated from diisopropyl ether to give the title compound (195 mg, 98%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.05 - 7.10 (1H, m), 7.15 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 7.9 Hz), 7.67 - 7.71 (1H, m), 7.67 (1H, d, J = 1.2 Hz), 7.75 (1H, t, J = 2.1 Hz), 7.79 (1H, t, J = 7.8 Hz), 7.98 (1H, d, J = 7.8 Hz), 8.09 (1H, s), 8.20 (1H, d, J = 9.6 Hz), 8.26 (1H, d, J = 8.4 Hz), 8.29 (1H, s), 10.61 (1H, s).

Example 147

Production of N-{6-[(3-aminophenyl)sulfanyl]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



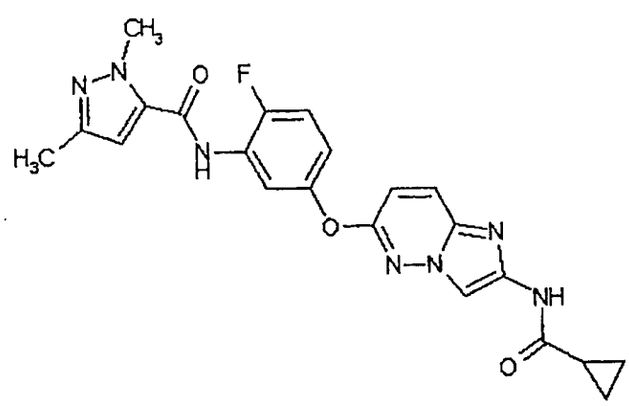
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (500 mg, 1.52 mmol), 3-aminobenzenethiol (381 mg, 3.04 mmol), potassium carbonate (630 mg, 4.56 mmol) and N,N-dimethylformamide (5.0 mL) was stirred at 80°C for 3 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→80/20)

and precipitated from ethyl acetate to give the title compound (396 mg, 80%).

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.86 (4H, m), 1.89 - 1.99 (1H, m), 5.38 (2H, s), 6.61 - 6.66 (1H, m), 6.66 - 6.70 (1H, m), 6.74 (1H, t, J = 1.9 Hz), 6.83 (1H, d, J = 9.6 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.86 (1H, d, J = 9.6 Hz), 8.14 (1H, s), 11.16 (1H, s).

Example 148

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



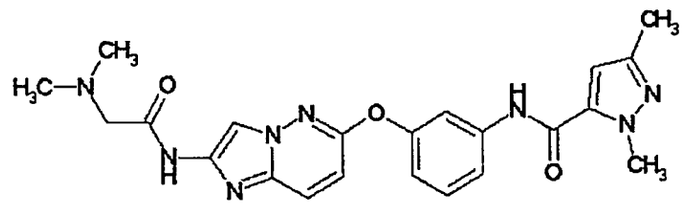
To a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.306 mmol) in N,N-dimethylacetamide (4.0 mL) was added a solution of 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (51 mg, 0.321 mmol) in N,N-dimethylacetamide (1.0 mL) under ice-cooling, and the mixture was stirred at room temperature for 30 min. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (methanol/ethyl acetate=0/100→5/95) and recrystallized from methanol/ethyl acetate to give the title

compound (88.8 mg, 65%) as pale-yellow crystals. melting point 237°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.90 (4H, m), 1.85 -2.00 (1H, m), 2.19 (3H, s), 3.97 (3H, s), 6.84 (1H, s), 7.07 (1H, d, J = 9.3 Hz), 7.15 -7.25 (1H, m), 7.40 (1H, t, J = 9.6 Hz), 7.50-7.60 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 11.07 (1H, s).

Example 149

Production of N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



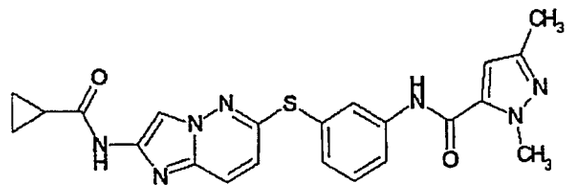
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-N^2,N^2-dimethylglycinamide (196 mg, 0.6 mmol) in N-methylpyrrolidone (5.0 mL) was added 1,3-dimethylpyrazole-5-carbonyl chloride (270 mg, 1.7 mmol), and the mixture was stirred at room temperature for 5 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution, and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→60/40) and precipitated from ethyl acetate to give the title compound (131 mg, 49%) as a white powder. melting point 210°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 2.27 (6H, s), 3.13 (2H, s), 3.98 (3H, s), 6.83 (1H, s), 6.99 - 7.04 (1H, m), 7.09 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.59 - 7.64 (1H, m), 7.68 (1H, t, J = 2.1 Hz), 8.04 (1H, s), 8.07 (1H, d, J = 9.6 Hz),

10.25 (1H, s), 10.37 (1H, s).

Example 150

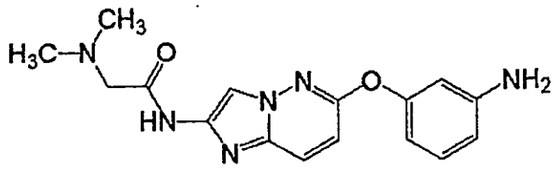
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



To a solution of N-{6-[(3-aminophenyl)sulfanyl]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (195 mg, 0.6 mmol) in N-methylpyrrolidone (3.0 mL) was added 1,3-dimethylpyrazole-5-carbonyl chloride (159 mg, 1.0 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30) and precipitated from methanol to give the title compound (245 mg, 91%) as a white powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.87 (4H, m), 1.89 - 1.99 (1H, m), 2.19 (3H, s), 3.98 (3H, s), 6.82 (1H, s), 6.94 (1H, d, J = 9.4 Hz), 7.31 - 7.36 (1H, m), 7.47 (1H, t, J = 7.8 Hz), 7.81 - 7.86 (1H, m), 7.90 (1H, dd, J = 9.4, 0.5 Hz), 7.99 (1H, t, J = 1.9 Hz), 8.15 (1H, s), 10.25 (1H, s), 11.16 (1H, s).melting point 251°C.

Example 151

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-N^2,N^2-dimethylglycinamide

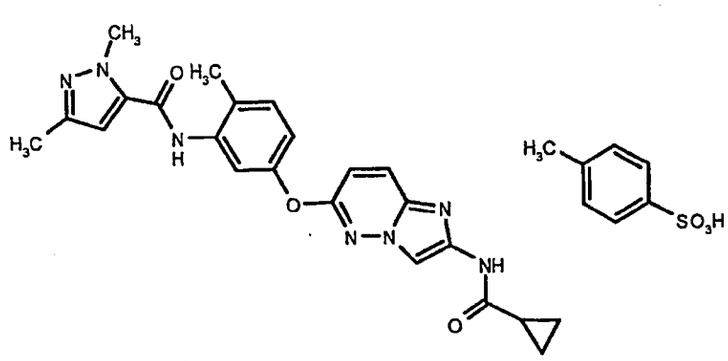


A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-N^2,N^2-dimethylglycinamide (517 mg, 1.5 mmol), 3-aminophenol (491 mg, 4.5 mmol), potassium carbonate (415 mg, 3.0 mmol) and N,N-dimethylformamide (3.0 mL) was stirred using a microwave synthesizer at 180°C for 40 min. The reaction mixture was diluted with water, and the precipitate was collected by filtration, washed with water, and dried under reduced pressure. The obtained solid was washed with ethyl acetate to give the title compound (410 mg, 84%) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.27 (6H, s), 3.13 (2H, s), 5.31 (2H, s), 6.28 - 6.33 (1H, m), 6.36 (1H, t, J = 2.1 Hz), 6.41 - 6.46 (1H, m), 6.98 (1H, d, J = 9.6 Hz), 7.05 (1H, t, J = 8.1 Hz), 8.01 (1H, d, J = 9.6 Hz), 8.04 (1H, s), 10.35 (1H, s).

Example 152

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide p-toluenesulfonate



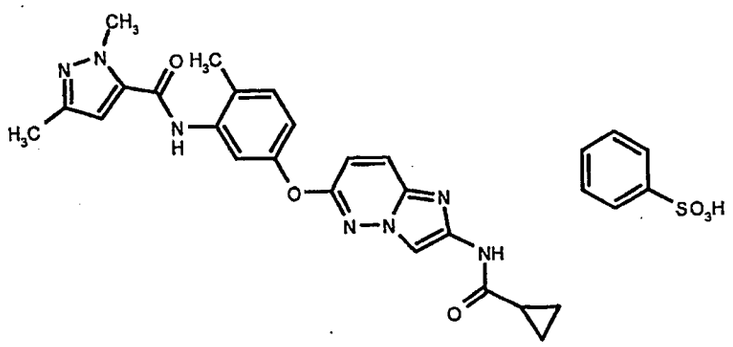
To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-

5-carboxamide (2.00 g, 4.49 mmol) was added ethanol (80 mL), and the mixture was heated to 70°C to give a uniform solution. p-Toluenesulfonic acid monohydrate (0.90 g, 4.71 mmol) was added to the mixture, and the mixture was naturally cooled to room temperature. The solvent was evaporated under reduced pressure. To the obtained residue was added hexane/ethanol (3/1, 40 mL), and the mixture was stirred at room temperature for 2 hr. The precipitated crystals were collected by filtration, and washed with hexane/ethanol (3:1). The obtained crystals were dissolved in ethanol (40 mL) by heating and the mixture was naturally cooled to room temperature. The precipitated crystals were collected by filtration and washed with ethanol. The crystals were dried at 70°C for 3 hr under reduced pressure to give the title compound (2.34 g, 84%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.87 - 1.97 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 2.29 (3H, s), 3.98 (3H, s), 6.82 (1H, s), 7.09 - 7.15 (4H, m), 7.29 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.4 Hz), 7.47 - 7.51 (2H, m), 7.96 (1H, s), 8.08 (1H, d, J = 9.6 Hz), 9.81 (1H, s), 11.17 (1H, s).

Example 153

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide benzenesulfonate



Using N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.00 g, 4.49 mmol), ethanol (100 mL) and benzenesulfonic acid monohydrate (0.83 g, 4.71 mmol), and in the

same manner as in Example 152, the title compound (2.02 g, 75%) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 3.97 (3H, s), 6.80 (1H, s), 7.06 - 7.12 (2H, m), 7.26 - 7.36 (5H, m), 7.57 - 7.61 (2H, m), 7.94 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 9.79 (1H, s), 11.13 (1H, s).

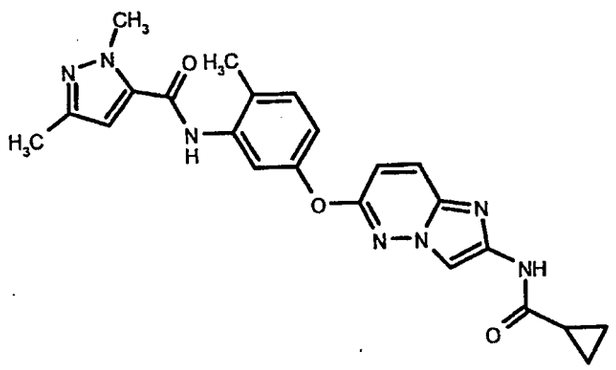
elemental analysis ($C_{23}H_{23}N_7O_3 \cdot C_6H_6O_3S$)

Calculated : C, 57.70; H, 4.84 ; N, 16.24.

Found : C, 57.73 ; H, 4.80 ; N, 16.30.

Example 154

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide methanesulfonate



Using N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.00 g, 4.49 mmol), ethanol (80 mL) and methanesulfonic acid (0.34 mL, 4.71 mmol), and in the same manner as in Example 152, the title compound (1.63 g, 67%) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 2.40 (3H, s), 3.97 (3H, s), 6.81 (1H, s), 7.07 - 7.12 (2H, m), 7.28 (1H, d, J = 2.4 Hz), 7.34 (1H, d, J = 8.7 Hz), 7.94 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 9.80 (1H, s), 11.13 (1H, s).

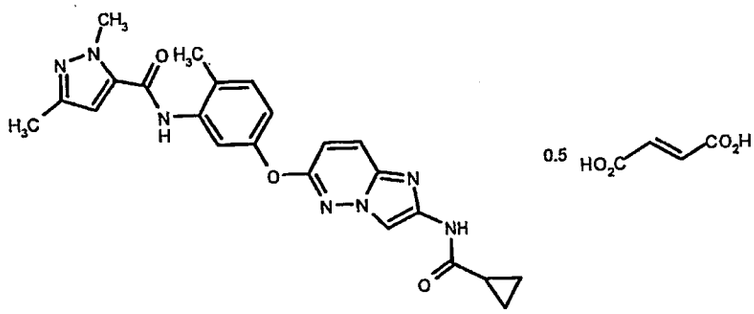
elemental analysis ($C_{23}H_{23}N_7O_3 \cdot CH_4O_3S$)

Calculated : C, 53.23 ; H, 5.03 ; N, 18.10.

Found : C, 53.14 ; H, 5.05 ; N, 18.15.

Example 155

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate



To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.00 g, 4.49 mmol) was added ethanol (100 mL) and the mixture was heated to 75°C to give a uniform solution. Fumaric acid (0.55 g, 4.71 mmol) was added to the mixture, and the mixture was naturally cooled to room temperature and stirred for 3 hr. The precipitated crystals were collected by filtration, and washed with ethanol. The obtained mother liquor was concentrated under reduced pressure, and ethanol (30 mL) was added to the obtained residue. The mixture was stirred at 60°C for 30 min. The mixture was cooled to room temperature and stood for 2 hr, and the precipitated crystals were collected by filtration, and washed with ethanol. The crystals were dried under reduced pressure at 70°C for 3 hr to give the title compound (1.73 g, 77%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.87 - 1.97 (1H, m), 2.20 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.63 (1H, s), 6.81 (1H, s), 7.05 (1H, d, J = 9.5 Hz), 7.10 (1H, dd, J = 8.6, 2.6 Hz), 7.28 (1H, d, J = 2.6 Hz), 7.35 (1H, d, J = 8.6 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.80 (1H, s), 11.08 (1H, s).

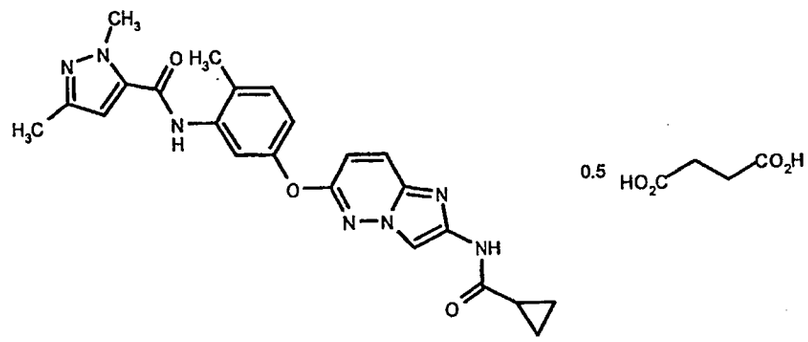
elemental analysis ($C_{23}H_{23}N_7O_3 \cdot 0.5C_4H_4O_4$)

Calculated: C, 59.63 ; H, 5.00 ; N, 19.47.

Found: C, 59.58 ; H, 4.98 ; N, 19.47.

Example 156

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 succinate



Using N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.00 g, 4.49 mmol), ethanol (100 mL) and succinic acid (0.56 g, 4.71 mmol), and in the same manner as in Example 155, the title compound (1.04 g, 46%) was obtained as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.87 - 1.96 (1H, m), 2.19 (3H, s), 2.24 (3H, s), 2.49 (2H, s), 3.97 (3H, s), 6.80 (1H, s), 7.04 (1H, d, J = 9.6 Hz), 7.09 (1H, dd, J = 8.3, 2.6 Hz), 7.27 (1H, d, J = 2.6 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.79 (1H, s), 11.06 (1H, s).

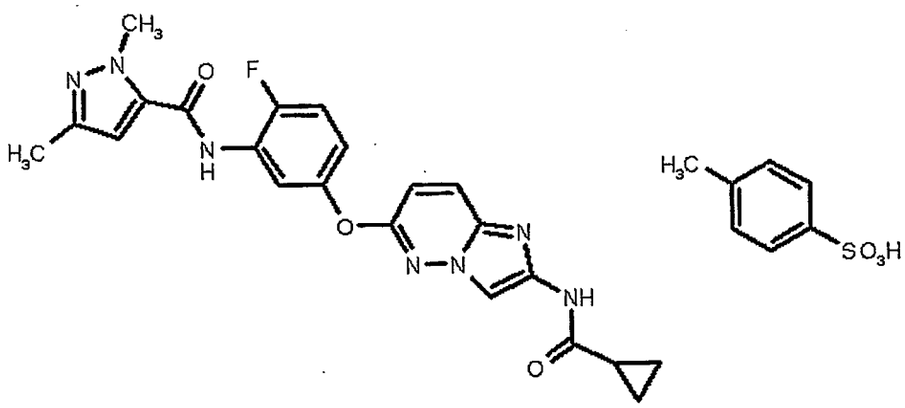
elemental analysis ($C_{23}H_{23}N_7O_3 \cdot 0.5C_4H_6O_4$)

Calculated: C, 59.52 ; H, 5.19 ; N, 19.43.

Found: C, 59.36 ; H, 5.19 ; N, 19.37.

Example 157

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide p-toluenesulfonate

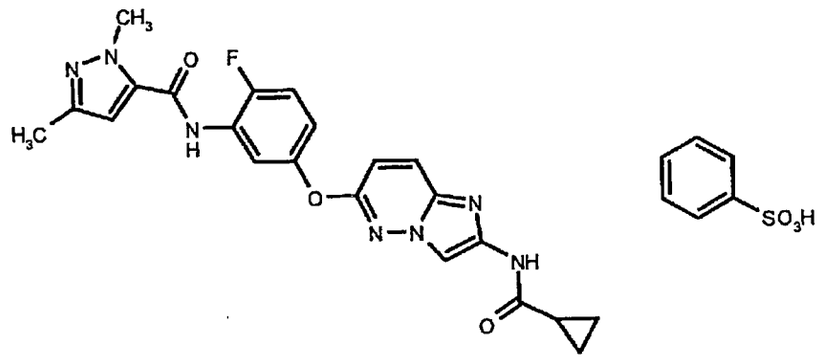


To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (225 mg, 0.5 mmol) were added tetrahydrofuran (5.0 mL) and ethanol (5.0 mL), dissolved at 70°C, and p-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol) was added thereto. Ethanol (15.0 mL) was further added to the mixture and insoluble material was filtered off. The filtrate was concentrated, ethyl acetate (10 mL) and ethanol (10 mL) were added thereto, and the mixture was concentrated again. Ethyl acetate (10 mL) and ethanol (1.0 mL) were added thereto, and the mixture was stood at room temperature for 6 hr. The precipitated crystals were collected by filtration, washed successively with a small amount of ethanol and diethyl ether, and dried under reduced pressure at 80°C for 6 hr to give the title compound (285 mg, 92%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.85 -1.95 (1H, m), 2.19 (3H, s), 2.29 (3H, s), 3.98 (3H, s), 6.85 (1H, s), 7.08 (1H, d, J = 9.6 Hz), 7.11 (2H, d, J = 7.7 Hz), 7.15 - 7.25 (1H, m), 7.40 (1H, t, J = 9.6 Hz), 7.47 (2H, d, J = 7.7 Hz), 7.50-7.55 (1H, m), 7.94 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 11.09 (1H, s).

Example 158

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide benzenesulfonate



To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (1.00 g, 2.23 mmol) was added ethanol (50 mL), and the mixture was stirred at 80°C for 20 min. Benzenesulfonic acid monohydrate (0.41 g, 2.33 mmol) was added to the mixture, and the mixture was further stirred for 10 min. Insoluble material was removed by filtration, and the mixture was naturally cooled to room temperature. The mixture was stood at room temperature for 16 hr, and the precipitated crystals were collected by filtration and washed with ethanol. The precipitated crystals were dried under reduced pressure at 80°C for 6 hr to give the title compound (1.17 g, 86%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.84 (4H, m), 1.88 -1.97 (1H, m), 2.19 (3H, s), 3.98 (3H, s), 6.85 (1H, s), 7.10 (1H, d, J = 9.6 Hz), 7.18 - 7.24 (1H, m), 7.30 - 7.34 (3H, m), 7.41 (1H, t, J = 9.5 Hz), 7.52 - 7.56 (1H, m), 7.58 - 7.62 (2H, m), 7.95 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 11.11 (1H, s).

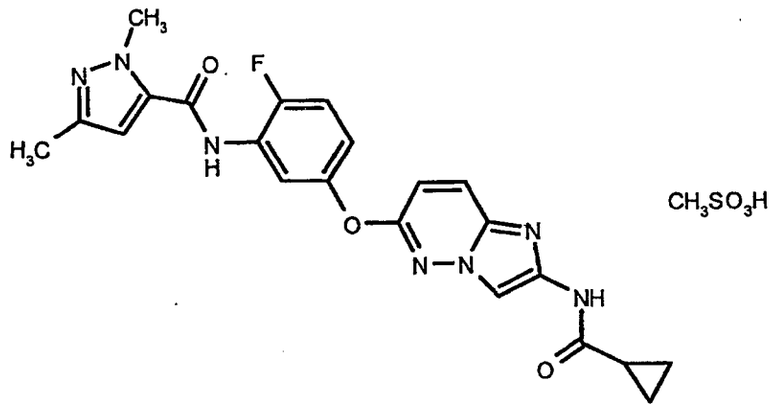
elemental analysis ($C_{22}H_{20}FN_7O_3 \cdot C_6H_6O_3S$)

Calculated: C, 55.35 ; H, 4.31 ; N, 16.14.

Found: C, 55.25 ; H, 4.33 ; N, 16.14.

Example 159

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide methanesulfonate



A solution of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (1.00 g, 2.23 mmol) in ethanol (50 mL) was stirred at 70°C for 20 min. Methanesulfonic acid (0.17 mL, 2.33 mmol) was added to the mixture, and the mixture was further stirred for 10 min. The mixture was naturally cooled to room temperature, and the solvent was evaporated under reduced pressure. To the obtained residue was added hexane/ethanol (3:1, 40 mL), and the mixture was stirred at room temperature for 2 hr. The precipitated precipitate was collected by filtration, and washed with hexane/ethanol (3:1). The obtained precipitate was dissolved in ethanol (40 mL) by heating, and the mixture was naturally cooled to room temperature. The precipitated crystals were collected by filtration, ethyl acetate (20 mL) was added to the mixture, and the mixture was stirred at 80°C by heating. After cooling the mixture to room temperature, the precipitate was collected by filtration, washed with ethyl acetate and dried under reduced pressure at 100°C for 3 hr to give the title compound (0.32 g, 26%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.86 -1.96 (1H, m), 2.19 (3H, s), 2.33 (3H, s), 3.97 (3H, s), 6.84 (1H, s), 7.08 (1H, d, J = 9.6 Hz), 7.18 - 7.23 (1H, m), 7.39 (1H, t, J = 9.6 Hz), 7.51 - 7.55 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.09 (1H, s), 11.08 (1H, s).

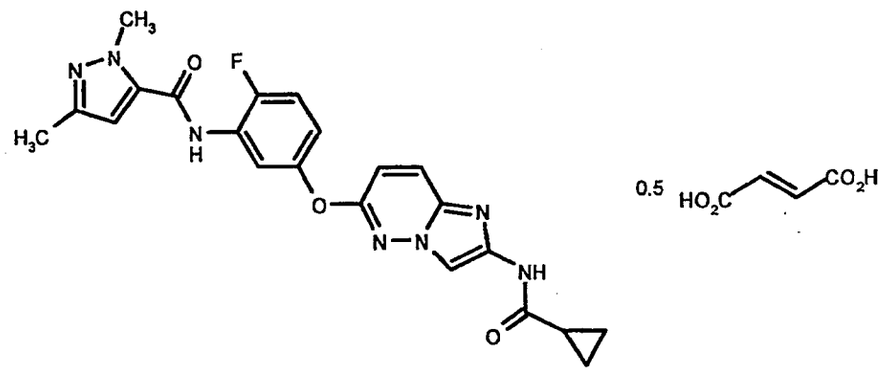
elemental analysis ($C_{22}H_{20}FN_7O_3 \cdot CH_4O_3S$)

Calculated: C, 50.64 ; H, 4.43 ; N, 17.97.

Found: C, 50.63 ; H, 4.38 ; N, 18.11.

Example 160

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide 0.5 fumarate



To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.00 g, 4.45 mmol) was added tetrahydrofuran (100 mL), and the mixture was heated to 60°C to give a uniform solution. Fumaric acid (0.54 g, 4.67 mmol) was added to the mixture and the mixture was allowed to cool to room temperature. Insoluble material was filtrated, ethyl acetate (50 mL) was added to the filtrate, and the solvent was evaporated to 1/4 under reduced pressure. The precipitated crystals were collected by filtration, washed with ethyl acetate and dried under reduced pressure at 80°C for 3 hr to give the title compound (1.88 g, 83%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.82 (4H, m), 1.87 - 1.96 (1H, m), 2.19 (3H, s), 3.97 (3H, s), 6.61 (1H, s), 6.84 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 7.18 - 7.23 (1H, m), 7.39 (1H, t, J = 9.6 Hz), 7.51 - 7.54 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.09 (1H, s), 11.06 (1H, s).

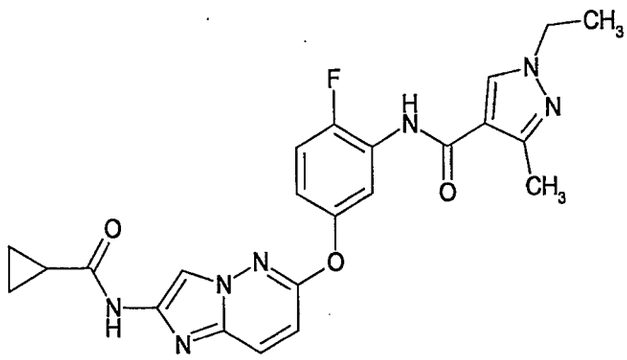
elemental analysis ($C_{22}H_{20}FN_7O_3 \cdot 0.5C_4H_4O_4$)

Calculated: C, 56.80 ; H, 4.37 ; N, 19.32.

Found: C, 56.73 ; H, 4.33 ; N, 19.24.

Example 161

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide



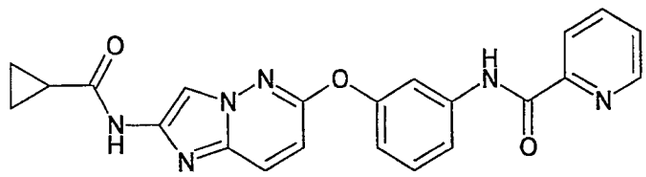
To a solution of 1-ethyl-3-methyl-1H-pyrazole-4-carboxylic acid (2.00 g, 13.0 mmol) and N,N-dimethylformamide (3 drops) in tetrahydrofuran (30 mL) was added oxalyl chloride (2.23 mL, 26.0 mmol) with stirring under ice-cooling, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylacetamide (20 mL) with stirring under ice-cooling, N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (3.27 g, 10.0 mmol) was added thereto, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution (50 mL) and extracted with a mixed solvent of ethyl acetate/tetrahydrofuran (1:1, 80 mL, 40 mL×2). The organic layer was washed with water (10 mL×3), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30) and crystallized from ethyl acetate to give the title compound (2.39 g, yield 52%) as a white solid. melting point 199°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.38 (3H, t, J = 7.3Hz), 1.86 - 1.98 (1H, m), 2.33 (3H, s), 4.09 (2H, q, J = 7.3Hz), 7.06 (1H, d, J = 9.6Hz), 7.07 - 7.15 (1H, m), 7.36 (1H,

dd, J = 10.2, 9.0Hz), 7.66 (1H, dd, J = 6.3, 3.0Hz), 7.94 (1H, s), 8.04 (1H, dd, J = 9.6, 0.6Hz), 8.39 (1H, s), 9.54 (1H, s), 11.07 (1H, s).

Example 162

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]pyridine-2-carboxamide

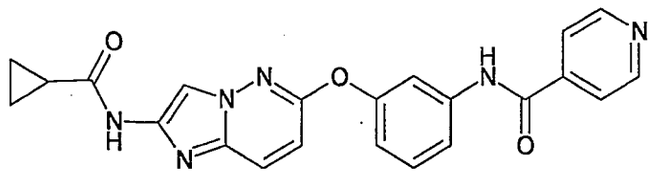


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol) in N-methylpyrrolidone (3 mL) was added pyridine-2-carbonylchloride hydrochloride (107 mg, 0.60 mmol), and the mixture was stirred at room temperature for 18 hr. A 5% aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→80/20) and crystallized from ethyl acetate to give the title compound (131 mg, yield 63%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.86 - 1.99 (1H, m), 7.02 (1H, ddd, J = 8.1, 2.5, 0.7Hz), 7.07 (1H, d, J=9.3Hz), 7.44 (1H, t, J=8.2Hz), 7.68 (1H, ddd, J=7.3, 4.7, 1.3Hz), 7.80 - 7.85 (1H, m), 7.90 (1H, t, J=2.3Hz), 7.99 (1H, s), 8.03 - 8.10 (2H, m), 8.12 - 8.18 (1H, m), 8.72 - 8.76 (1H, m), 10.81 (1H, s), 11.09 (1H, s).

Example 163

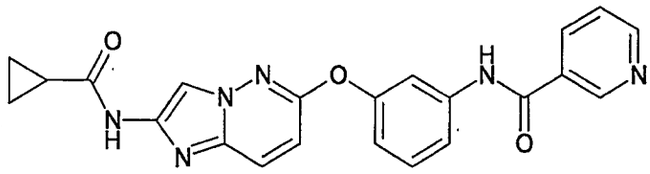
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]isonicotinamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol), N-methylpyrrolidone (3 mL) and pyridine-4-carbonylchloride hydrochloride (107 mg, 0.60 mmol), and in the same manner as in Example 162, the title compound (163 mg, yield 78%) was obtained. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.84 - 2.00 (1H, m), 7.01 - 7.07 (1H, m), 7.08 (1H, d, J = 9.6Hz), 7.46 (1H, t, J = 8.1Hz), 7.63 - 7.69 (1H, m), 7.73 (1H, t, J = 2.1Hz), 7.82 - 7.87 (2H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6Hz), 8.76 - 8.81 (2H, m), 10.62 (1H, s), 11.09 (1H, s).

Example 164

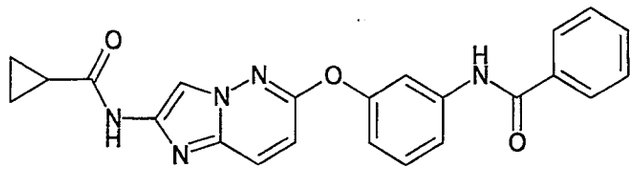
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]nicotinamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol), N-methylpyrrolidone (3 mL) and pyridine-3-carbonylchloride hydrochloride (107 mg, 0.60 mmol), and in the same manner as in Example 162, the title compound (89 mg, yield 43%) was obtained. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.87 (4H, m), 1.86 - 1.99 (1H, m), 7.03 (1H, dd, J = 7.8, 1.8Hz), 7.08 (1H, d, J = 9.6Hz), 7.45 (1H, t, J = 8.4Hz), 7.57 (1H, dd, J = 7.8, 4.8Hz), 7.66 (1H, d, J = 8.1Hz), 7.73 (1H, t, J = 1.9Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.6Hz), 8.28 (1H, dt, J = 7.9, 1.9Hz), 8.76 (1H, d, J = 3.9Hz), 9.09 (1H, s), 10.57 (1H, s), 11.09 (1H, s).

Example 165

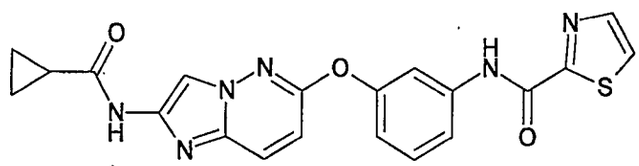
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol), N-methylpyrrolidone (3 mL) and benzoyl chloride (0.070 mL, 0.60 mmol), and in the same manner as in Example 162, the title compound (176 mg, yield 85%) was obtained. melting point 265°C. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.87 - 1.99 (1H, m), 7.00 (1H, ddd, J = 8.1, 2.4, 0.8Hz), 7.07 (1H, d, J = 9.5Hz), 7.43 (1H, t, J = 8.1Hz), 7.49 - 7.64 (3H, m), 7.68 (1H, d, J = 8.4Hz), 7.74 (1H, t, J = 2.1Hz), 7.90 - 7.97 (2H, m), 7.98 (1H, s), 8.05 (1H, d, J = 9.5Hz), 10.38 (1H, s), 11.09 (1H, s).

Example 166

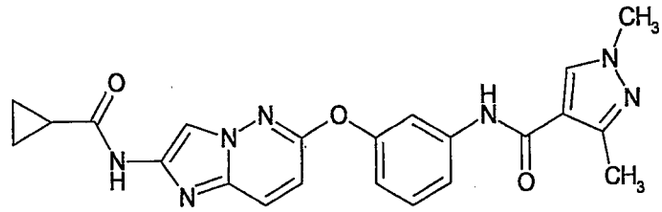
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-thiazole-2-carboxamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol), N-methylpyrrolidone (3 mL) and 1,3-thiazole-2-carbonyl chloride (89 mg, 0.60 mmol), and in the same manner as in Example 162, the title compound (136 mg, yield 65%) was obtained. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.86 - 1.99 (1H, m), 7.03 (1H, ddd, J = 8.2, 2.4, 1.0Hz), 7.07 (1H, d, J = 9.6Hz), 7.44 (1H, t, J = 8.1Hz), 7.75 - 7.83 (2H, m), 7.98 (1H, s), 8.06 (1H, dd, J = 9.6, 0.6Hz), 8.11 (1H, d, J = 3.0Hz), 8.15 (1H, d, J = 3.0Hz), 10.94 (1H, s), 11.09 (1H, s).

Example 167

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide

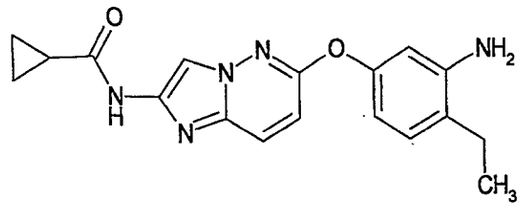


To a suspension of 1,3-dimethyl-1H-pyrazole-4-carboxylic acid (140 mg, 1.0 mmol) in dichloromethane (10 mL) were added N,N-dimethylformamide (2 drops) then oxalyl chloride (0.171 mL, 2.0 mmol), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with N-methylpyrrolidone (5 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol) was added thereto, and the mixture was stirred at room temperature for 6 hr. To the reaction mixture was added 0.5N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30). The objective fraction was concentrated under reduced pressure, and the residue was washed with diisopropyl ether to give the title compound (126 mg, yield 58%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.87 (4H, m), 1.86 - 1.99 (1H, m), 2.33 (3H, s), 3.81 (3H, s), 6.93 (1H, dd, J = 8.1, 1.8Hz), 7.05 (1H, d, J = 9.6Hz), 7.38 (1H, t, J = 8.1Hz), 7.55 (1H, d, J = 8.1Hz), 7.64 (1H, t, J = 2.1Hz), 7.97 (1H, s), 8.05 (1H, d, J = 9.6Hz), 8.27 (1H, s), 9.78 (1H, s), 11.09 (1H, s).

Example 168

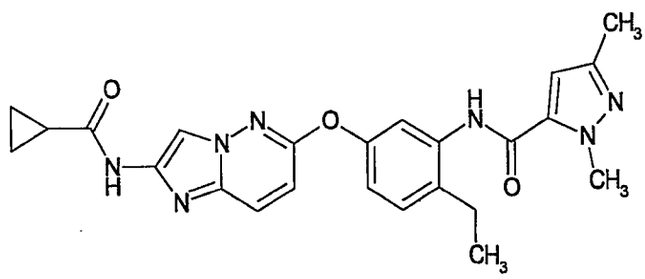
Production of N-[6-(3-amino-4-ethylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (984 mg, 3.0 mmol), 3-amino-4-ethylphenol (617 mg, 4.5 mmol), potassium carbonate (829 mg, 6.0 mmol) and N,N-dimethylformamide (9 mL) was stirred at 150°C for 24 hr. The reaction mixture was diluted with water and extracted with a mixed solvent of ethyl acetate/tetrahydrofuran (3:1). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/50→0/100) and recrystallized from a mixed solvent of ethyl acetate/diisopropyl ether to give the title compound (706 mg, yield 70%) as a khaki solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.14 (3H, t, J = 7.4Hz), 1.85 - 2.00 (1H, m), 2.43 (2H, q, J = 7.4Hz), 5.07 (2H, s), 6.31 (1H, dd, J = 8.1, 2.7Hz), 6.42 (1H, d, J = 2.7Hz), 6.93 (1H, d, J = 9.6Hz), 6.95 (1H, d, J = 7.8Hz), 7.97 (1H, s), 7.98 (1H, d, J = 9.0Hz), 11.05 (1H, s).

Example 169

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-ethylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



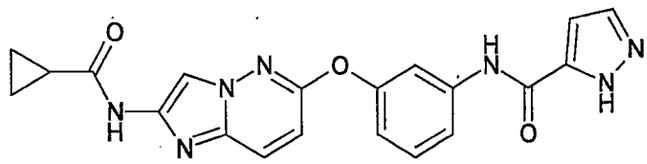
To a solution of N-[6-(3-amino-4-ethylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (202 mg, 0.60 mmol) in N-methylpyrrolidone (3 mL) was added 1,3-dimethyl-1H-pyrazole-5-

carbonyl chloride (143 mg, 0.90 mmol), and the mixture was stirred at room temperature for 8 hr. A 1N aqueous sodium hydroxide solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→80/20) and recrystallized from a mixed solvent of ethyl acetate/diisopropyl ether to give the title compound (167 mg, yield 61%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.15 (3H, t, J = 7.6Hz), 1.84 - 2.00 (1H, m), 2.19 (3H, s), 2.63 (2H, q, J = 7.6Hz), 3.97 (3H, s), 6.80 (1H, s), 7.04 (1H, d, J = 9.6Hz), 7.15 (1H, dd, J = 8.6, 2.6Hz), 7.23 (1H, d, J = 2.6Hz), 7.37 (1H, d, J = 8.6Hz), 7.94 (1H, s), 8.03 (1H, dd, J = 9.6, 0.6Hz), 9.82 (1H, s), 11.07 (1H, s).

Example 170

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-pyrazole-5-carboxamide



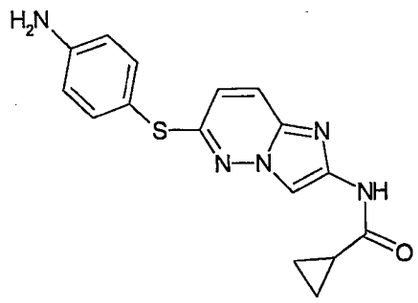
To a mixture of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol), 1H-pyrazole-5-carboxylic acid (84 mg, 0.75 mmol), 1-hydroxybenzotriazole(101 mg, 0.75 mmol) and N,N-dimethylformamide (5 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192 mg, 1.0 mmol), triethylamine (0.279 mL, 2.0 mmol), and the mixture was stirred at room temperature for 18 hr. Water was added to the reaction mixture, and the mixture was extracted with a mixed solvent of ethyl acetate/tetrahydrofuran. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl

acetate/methanol=100/0→70/30) and crystallized from ethyl acetate to give the title compound (43 mg, yield 21%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.87 - 1.99 (1H, m), 6.76 (1H, s), 6.95 (1H, dd, J = 8.1, 1.8Hz), 7.05 (1H, d, J = 9.6Hz), 7.39 (1H, t, J = 8.4Hz), 7.73 (1H, d, J = 8.4Hz), 7.79 (1H, s), 7.89 (1H, s), 7.98 (1H, s), 8.04 (1H, d, J = 9.6Hz), 10.20 (1H, s), 11.07 (1H, s), 13.42 (1H, s).

Example 171

Production of N-{6-[(4-aminophenyl)thio]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

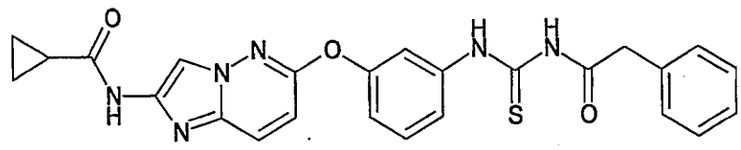


To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)-2-methylcyclopropanecarboxamide (2.0 g, 6.10 mmol) in N,N-dimethylformamide (20.0 mL) were added potassium carbonate (1.27 g, 9.14 mmol) and 4-aminothiophenol (0.92 g, 7.31 mmol), and the mixture was stirred at 80°C for 4 hr. After cooling the mixture to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was collected by filtration and washed with ethyl acetate to give the title compound (1.53 g, 77%) as brown crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.85 (4H, m), 1.87 - 1.97 (1H, m), 5.68 (2H, s), 6.60 - 6.67 (3H, m), 7.24 - 7.29 (2H, m), 7.78 (1H, d, J = 9.5 Hz), 8.06 (1H, s), 11.09 (1H, s).

Example 172

Production of N-{6-[3-({[(phenylacetyl)amino]thiocarbonyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

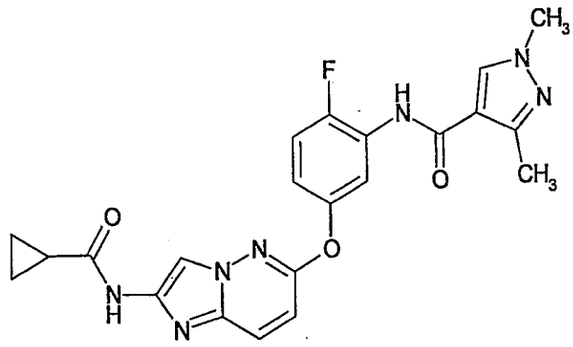


To a solution of phenylacetyl chloride (155 mg, 1.0 mmol) in acetonitrile (20 mL) was added potassium thiocyanate (292 mg, 3.0 mmol), and the mixture was stirred at 60°C for 3 hr and concentrated under reduced pressure. The residue was diluted with tetrahydrofuran (20 mL). N-[6-(3-Aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (155 mg, 0.50 mmol) was added to the mixture, and the mixture was stirred at room temperature for 18 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 concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30) and precipitated from diisopropyl ether to give the title compound (142 mg, yield 58%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.86 - 1.98 (1H, m), 3.81 (2H, s), 7.04 (1H, d, J = 9.6Hz), 7.10 - 7.19 (1H, m), 7.23 - 7.38 (5H, m), 7.45 (2H, d, J = 5.1Hz), 7.74 (1H, s), 7.96 (1H, s), 8.03 (1H, d, J = 9.6Hz), 11.07 (1H, s), 11.72 (1H, s), 12.46 (1H, s).

Example 173

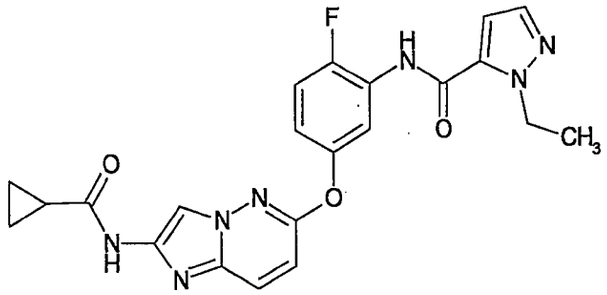
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide



To a solution of 1,3-dimethyl-1H-pyrazole-4-carboxylic acid (140 mg, 1.0 mmol) and N,N-dimethylformamide (2 drops) in tetrahydrofuran (10 mL) was added oxalyl chloride (0.171 mL, 2.0 mmol) with stirring under ice-cooling, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in N-methylpyrrolidone (5 mL) with stirring under ice-cooling, N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol) was added, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was diluted with ethyl acetate (80 mL), and washed with 1N aqueous sodium hydroxide solution (10 mL) and water (10 mL×3). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→70/30) and recrystallized from ethyl acetate to give the title compound (88 mg, yield 39%) as a white solid. melting point 205°C.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.86 - 1.99 (1H, m), 2.32 (3H, s), 3.81 (3H, s), 7.06 (1H, d, J = 9.5Hz), 7.06 - 7.14 (1H, m), 7.36 (1H, dd, J = 10.2, 9.0Hz), 7.66 (1H, dd, J = 6.4, 3.2Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.5Hz), 8.32 (1H, s), 9.53 (1H, s), 11.06 (1H, s).

Example 174

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide

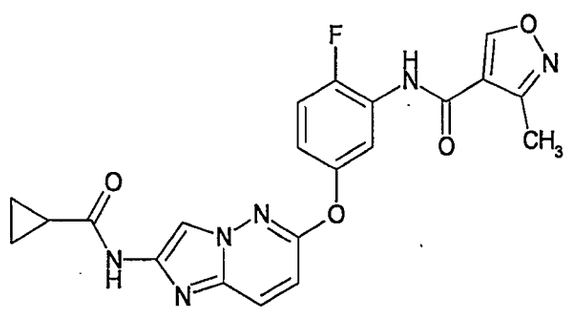


Using 1-ethyl-1H-pyrazole-5-carboxylic acid (140 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (10 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (119 mg, yield 53%) was obtained. melting point 209°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.31 (3H, t, J = 7.2Hz), 1.86 - 1.98 (1H, m), 4.50 (2H, q, J = 7.2Hz), 7.07 (1H, d, J = 2.0Hz), 7.08 (1H, d, J = 9.5Hz), 7.22 (1H, ddd, J = 9.0, 3.9, 3.0Hz), 7.41 (1H, dd, J = 10.2, 9.0Hz), 7.52 - 7.57 (1H, m), 7.55 (1H, d, J = 2.0Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.5Hz), 10.19 (1H, s), 11.06 (1H, s).

Example 175

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methylisoxazole-4-carboxamide



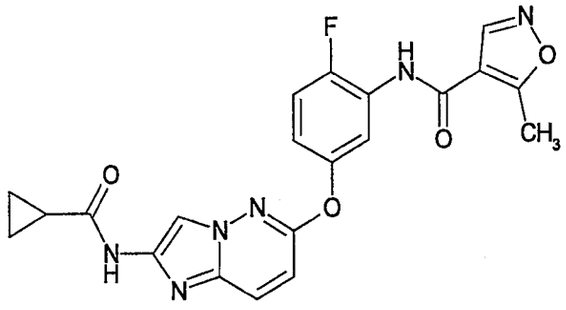
Using 3-methylisoxazole-4-carboxylic acid (127 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (10 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL)

and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (143 mg, yield 65%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.86 - 1.99 (1H, m), 2.40 (3H, s), 7.07 (1H, d, J = 9.3Hz), 7.14 - 7.21 (1H, m), 7.40 (1H, dd, J = 10.2, 9.0Hz), 7.66 (1H, dd, J = 6.3, 2.7Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.3Hz), 9.48 (1H, s), 10.19 (1H, s), 11.06 (1H, s).

Example 176

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-5-methylisoxazole-4-carboxamide



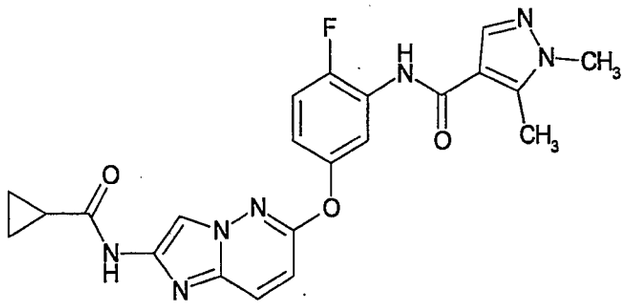
Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), N-methylpyrrolidone (5 mL) and 5-methylisoxazole-4-carbonyl chloride (146 mg, 1.00 mmol), and in the same manner as in Example 162, the title compound (112 mg, yield 51%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.86 - 1.98 (1H, m), 2.66 (3H, s), 7.08 (1H, d, J = 9.6Hz), 7.19 (1H, ddd, J = 9.0, 3.9, 3.0Hz), 7.41 (1H, dd, J = 9.9, 9.0Hz), 7.62 (1H, dd, J = 6.3, 3.0Hz), 7.94 (1H, s), 8.05 (1H, dd, J = 9.6, 0.6Hz), 9.06 (1H, s), 10.09 (1H, s), 11.08 (1H, s).

Example 177

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,5-dimethyl-1H-pyrazole-

4-carboxamide

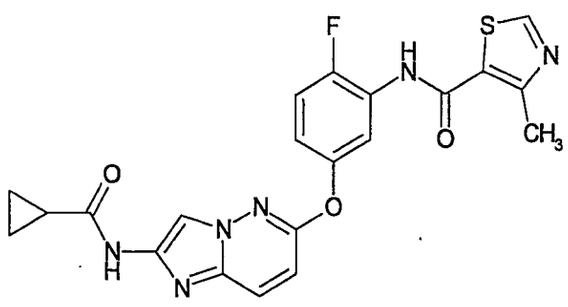


Using 1,5-dimethyl-1H-pyrazole-4-carboxylic acid (140 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (10 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (106 mg, yield 47%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 2.48 (3H, s), 3.75 (3H, s), 7.06 (1H, d, J = 9.6Hz), 7.13 (1H, ddd, J = 8.9, 3.8, 3.1Hz), 7.36 (1H, dd, J = 10.2, 9.0Hz), 7.58 (1H, dd, J = 6.3, 3.0Hz), 7.94 (1H, s), 8.04 (1H, s), 8.04 (1H, dd, J = 9.6, 0.6Hz), 9.63 (1H, s), 11.07 (1H, s).

Example 178

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-4-methyl-1,3-thiazole-5-carboxamide



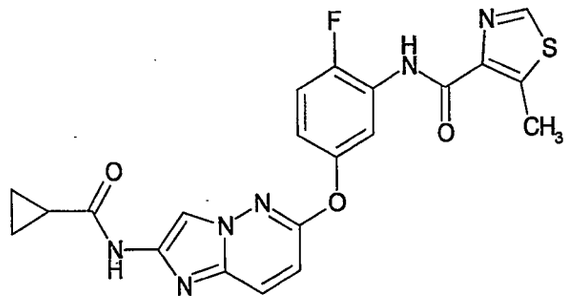
Using 4-methyl-1,3-thiazole-5-carboxylic acid (143 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (10 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL)

and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (179 mg, yield 79%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73-0.86 (4H, m), 1.85 - 1.98 (1H, m), 2.63 (3H, s), 7.08 (1H, d, J = 9.5Hz), 7.20 (1H, ddd, J = 8.8, 3.7, 3.2Hz), 7.40 (1H, dd, J = 9.9, 9.3Hz), 7.59 (1H, dd, J = 6.6, 3.0Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.5Hz), 9.14 (1H, s), 10.13 (1H, s), 11.07 (1H, s).

Example 179

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-5-methyl-1,3-thiazole-4-carboxamide

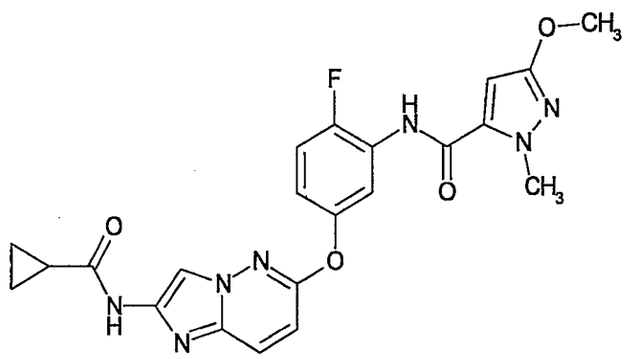


Using 5-methyl-1,3-thiazole-4-carboxylic acid (143 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (10 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (107 mg, yield 47%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.86 - 1.98 (1H, m), 2.78 (3H, s), 7.08 (1H, d, J = 9.6Hz), 7.08 - 7.16 (1H, m), 7.42 (1H, dd, J = 10.5, 9.0Hz), 7.95 (1H, s), 8.00 (1H, dd, J = 6.6, 3.0Hz), 8.05 (1H, d, J = 9.6Hz), 9.02 (1H, s), 9.94 (1H, s), 11.08 (1H, s).

Example 180

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide

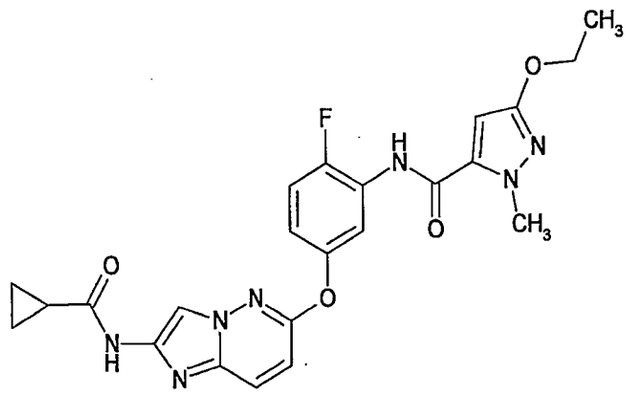


Using 3-methoxy-1-methyl-1H-pyrazole-5-carboxylic acid (156 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (15 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (85 mg, yield 36%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 3.80 (3H, s), 3.92 (3H, s), 6.50 (1H, s), 7.08 (1H, d, J = 9.6Hz), 7.21 (1H, ddd, J = 9.1, 4.0, 3.1Hz), 7.40 (1H, dd, J = 10.0, 9.1Hz), 7.53 (1H, dd, J = 6.3, 3.0Hz), 7.94 (1H, s), 8.05 (1H, dd, J = 9.6, 0.6Hz), 10.14 (1H, s), 11.07 (1H, s).

Example 181

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethoxy-1-methyl-1H-pyrazole-5-carboxamide

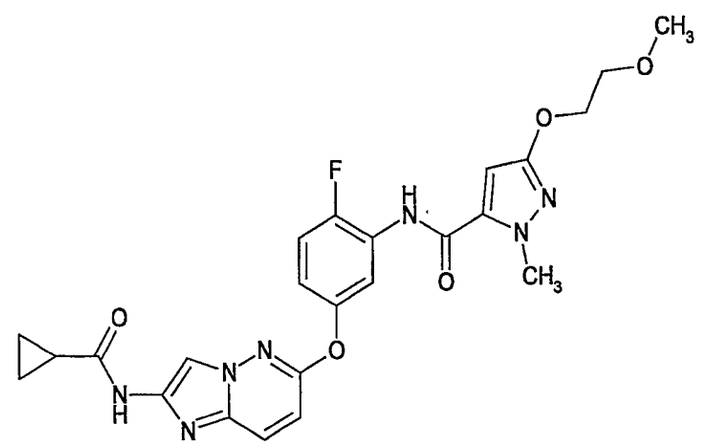


Using 3-ethoxy-1-methyl-1H-pyrazole-5-carboxylic acid (170 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (15 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (92 mg, yield 38%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.30 (3H, t, J = 7.0Hz), 1.85 - 1.99 (1H, m), 3.91 (3H, s), 4.12 (2H, q, J = 7.0Hz), 6.48 (1H, s), 7.08 (1H, d, J = 9.6Hz), 7.18 - 7.25 (1H, m), 7.36 - 7.45 (1H, m), 7.53 (1H, dd, J = 6.5, 3.1Hz), 7.94 (1H, s), 8.05 (1H, dd, J = 9.6, 0.4Hz), 10.12 (1H, s), 11.07 (1H, s).

Example 182

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carboxamide

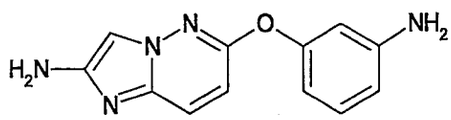


Using 3-(2-methoxyethoxy)-1-methyl-1H-pyrazole-5-carboxylic acid (200 mg, 1.0 mmol), N,N-dimethylformamide (2 drops), tetrahydrofuran (15 mL), oxalyl chloride (0.172 mL, 2.0 mmol), N-methylpyrrolidone (5 mL) and N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (164 mg, 0.50 mmol), and in the same manner as in Example 173, the title compound (128 mg, yield 50%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.85 - 1.99 (1H, m), 3.29 (3H, s), 3.59 - 3.67 (2H, m), 3.91 (3H, s), 4.15 - 4.23 (2H, m), 6.49 (1H, s), 7.08 (1H, d, J = 9.5Hz), 7.18 - 7.25 (1H, m), 7.41 (1H, dd, J = 10.1, 9.1Hz), 7.53 (1H, dd, J = 6.4, 2.9Hz), 7.94 (1H, s), 8.05 (1H, dd, J = 9.5, 0.7Hz), 10.14 (1H, s), 11.07 (1H, s).

Example 183

Production of 6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-amine



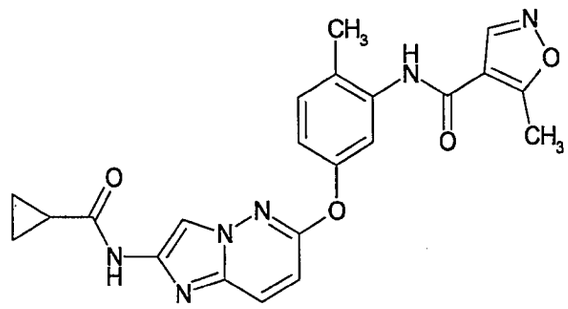
A mixture of 6-iodoimidazo[1,2-b]pyridazin-2-amine (390 mg, 1.5 mmol), 3-aminophenol (491 mg, 4.5 mmol), potassium carbonate (415 mg, 3.0 mmol) and N,N-dimethylformamide (3 mL) was stirred using a microwave synthesizer at 180°C for 40 min. The reaction mixture was diluted with water and extracted with a mixed solvent of ethyl acetate/tetrahydrofuran (1:1). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→60/40). The objective fraction was concentrated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/methanol=100/0→80/20) and precipitated from ethyl acetate to give the title compound (133 mg, yield 37%) as a purple solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.27 (2H, s), 5.31 (2H, s), 6.23 (1H,

ddd, J = 7.8, 2.4, 0.9Hz), 6.27 (1H, t, J = 2.1Hz), 6.38 (1H, ddd, J = 8.1, 2.1, 0.9Hz), 6.69 (1H, d, J = 9.3Hz), 7.02 (1H, t, J = 7.9Hz), 7.14 (1H, s), 7.68 (1H, dd, J = 9.3, 0.6Hz).

Example 184

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-5-methylisoxazole-4-carboxamide

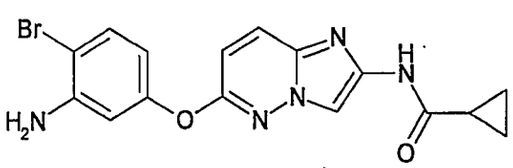


Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (162 mg, 0.50 mmol), N-methylpyrrolidone (5 mL) and 5-methylisoxazole-4-carbonyl chloride (146 mg, 1.0 mmol), and in the same manner as in Example 162, the title compound (174 mg, yield 80%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.86 - 1.99 (1H, m), 2.26 (3H, s), 2.66 (3H, s), 7.04 (1H, d, J = 9.6Hz), 7.09 (1H, dd, J = 8.6, 2.6Hz), 7.29 (1H, d, J = 2.6Hz), 7.35 (1H, d, J = 8.6Hz), 7.93 (1H, s), 8.03 (1H, dd, J = 9.6, 0.4Hz), 9.02 (1H, s), 9.75 (1H, s), 11.07 (1H, s).

Example 185

Production of N-[6-(3-amino-4-bromophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



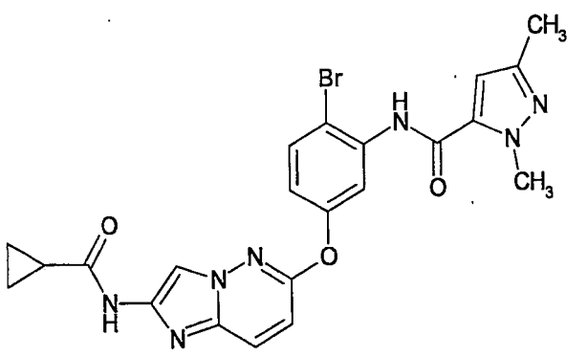
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (3.28 g, 10 mmol), 3-amino-4-

bromophenol (2.82 g, 15 mmol), potassium carbonate (2.76 g, 20 mmol) and N,N-dimethylformamide (20 mL) was stirred at 110°C for 24 hr, then at 150°C for 24 hr. The reaction mixture was diluted with water and extracted with a mixed solvent of ethyl acetate/tetrahydrofuran (1:1). The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/50→0/100) and recrystallized from ethyl acetate to give the title compound (1.85 g, yield 48%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.86 - 1.98 (1H, m), 5.51 (2H, s), 6.35 (1H, dd, J = 8.6, 2.8Hz), 6.62 (1H, d, J = 2.8Hz), 7.01 (1H, d, J = 9.6Hz), 7.37 (1H, d, J = 8.6Hz), 7.99 (1H, s), 8.02 (1H, d, J = 9.6Hz), 11.08 (1H, s).

Example 186

Production of N-[2-bromo-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

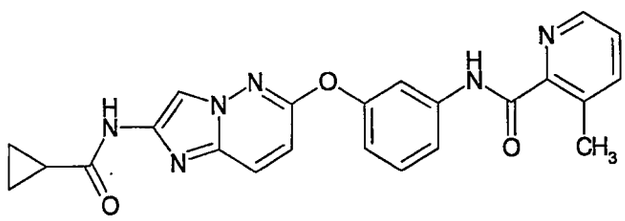


To a solution of N-[6-(3-amino-4-bromophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (582 mg, 1.50 mmol) in N-methylpyrrolidone (5 mL) was added 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (310 mg, 1.95 mmol), and the mixture was stirred at room temperature for 18 hr. A 5% aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with a mixed solvent of ethyl acetate/tetrahydrofuran (1:1). The organic layer was washed with

water, dried over anhydrous sodium sulfate, filtrated, and concentrated under reduced pressure. The residue was suspended in ethyl acetate, and the mixture was stirred with heating under reflux for 15 min. After allowing the reaction mixture to cool to room temperature, the precipitate was collected by filtration, washed with ethyl acetate, and dried under reduced pressure to give the title compound (658 mg, yield 86%) as a cream solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.86 - 1.98 (1H, m), 2.20 (3H, s), 3.98 (3H, s), 6.83 (1H, s), 7.10 (1H, d, J = 9.6Hz), 7.20 (1H, dd, J = 8.9, 2.9Hz), 7.51 (1H, dd, J = 2.9Hz), 7.79 (1H, d, J = 8.9Hz), 7.95 (1H, s), 8.06 (1H, dd, J = 9.6, 0.6Hz), 9.97 (1H, s), 11.09 (1H, s).

Example 187

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methylpyridine-2-carboxamide



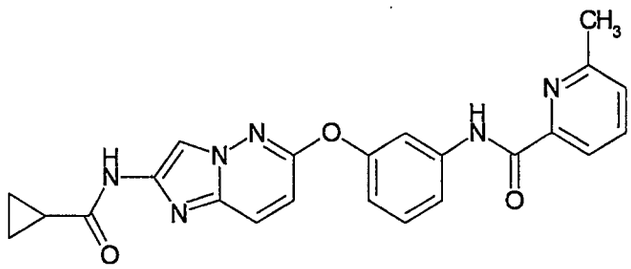
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.323 mmol), 3-methylpyridine-2-carboxylic acid (66 mg, 0.485 mmol) and 1-hydroxybenzotriazole (71 mg, 0.522 mmol) in N,N-dimethylformamide (4.0 mL) were added triethylamine (0.08 mL, 0.549 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.517 mmol) under ice-cooling, and the mixture was stirred at room temperature for 20 hr. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl

acetate/hexane=80/20→100/0) and recrystallized from ethyl acetate/methanol to give the title compound (98 mg, 71%) as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70-0.90 (4H, m), 1.85 - 2.00 (1H, m), 2.55 (3H, s), 6.95 - 7.05 (1H, m), 7.05 (1H, d, J = 9.6 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.45 - 7.55 (1H, m), 7.71 (1H, d, J = 8.4 Hz), 7.75 - 7.85 (2H, m), 8.04 (1H, d, J = 8.7 Hz), 8.50 - 8.55 (1H, m), 10.68 (1H, s), 11.07 (1H, s).

Example 188

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-6-methylpyridine-2-carboxamide



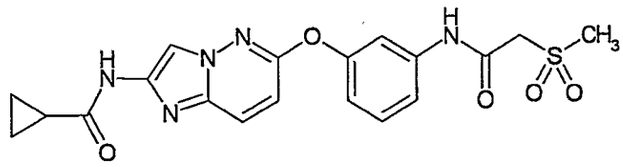
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.323 mmol), 6-methylpyridine-2-carboxylic acid (66 mg, 0.485 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.517 mmol), 1-hydroxybenzotriazole (71 mg, 0.522 mmol), triethylamine (0.08 mL, 0.549 mmol) and N,N-dimethylformamide (4.0 mL), and by a reaction in the same manner as in Example 187, the title compound (100 mg, 72%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.85 - 1.95 (1H, m), 2.62 (3H, s), 7.00 - 7.05 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.50 - 7.55 (1H, m), 7.79 (1H, d, J = 7.8 Hz), 7.85 - 7.95 (3H, m), 8.05 (1H, d, J = 9.6 Hz), 7.97 (1H, s), 10.56 (1H, s), 11.08 (1H, s).

Example 189

Production of N-[6-(3-

{[(methylsulfonyl)acetyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

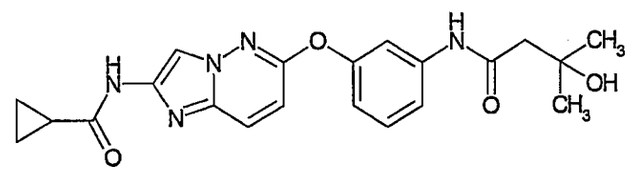


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.323 mmol), (methylsulfonyl)acetic acid (67 mg, 0.485 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.517 mmol), 1-hydroxybenzotriazole (71 mg, 0.522 mmol), triethylamine (0.08 mL, 0.549 mmol) and N,N-dimethylformamide (4.0 mL), and by a reaction in the same manner as in Example 187, the title compound (87 mg, 63%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.90 - 2.00 (1H, m), 3.15 (3H, s), 4.27 (2H, s), 6.95 - 7.05 (1H, m), 7.05 (1H, d, J = 9.3 Hz), 7.35 - 7.45 (2H, m), 7.57 (1H, s), 7.95 (1H, s), 8.04 (1H, d, J = 9.3 Hz), 10.58 (1H, s), 11.08 (1H, s).

Example 190

Production of N-(6-{3-[(3-hydroxy-3-methylbutanoyl)amino]phenoxy}imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



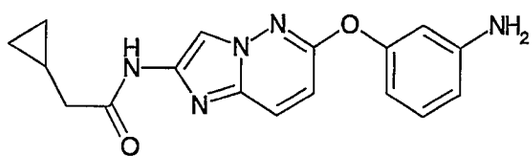
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.323 mmol), 3-hydroxy-3-methylbutanoic acid (57 mg, 0.485 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.517 mmol), 1-hydroxybenzotriazole (71 mg, 0.522 mmol), triethylamine (0.08 mL, 0.549 mmol) and N,N-dimethylformamide (4.0 mL), and by a reaction in the same manner as in Example 187,

the title compound (22 mg, 16%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.21 (6H, s), 1.90 - 2.00 (1H, m), 2.41 (2H, s), 4.69 (1H, s), 6.90 - 6.95 (1H, m), 7.03 (1H, d, J = 9.4 Hz), 7.30 - 7.45 (2H, m), 7.55 - 7.60 (1H, m), 7.96 (1H, s), 8.04 (1H, d, J = 9.4 Hz), 9.97 (1H, s), 11.09 (1H, s).

Example 191

Production of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-cyclopropylacetamide



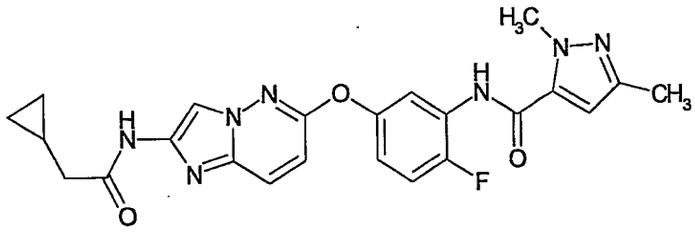
A mixture of 2-cyclopropyl-N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (501 mg, 1.46 mmol), 3-aminophenol (479 mg, 4.39 mmol), potassium carbonate (807 mg, 5.84 mmol) and N,N-dimethylformamide (5 mL) was stirred at 120°C for 12 hr. Tetrahydrofuran/ethyl acetate and saturated brine were added to the reaction mixture, and insoluble material was filtered off. The filtrate was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=20/80→0/100) to give the title compound (156 mg, 33%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.10 - 0.25 (2H, m), 0.45 - 0.55 (2H, m), 1.00 - 1.10 (1H, m), 2.25 (2H, d, J = 7.2 Hz), 5.31 (2H, s), 6.30 (1H, d, J = 8.1 Hz), 6.35 (1H, s), 6.43 (1H, d, J = 8.1 Hz), 6.95 (1H, d, J = 9.6 Hz), 7.05 (1H, t, J = 8.1 Hz), 7.99 (1H, d, J = 9.6 Hz), 8.03 (1H, s), 10.70 (1H, s).

Example 192

Production of N-[5-({2-[(cyclopropylacetyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

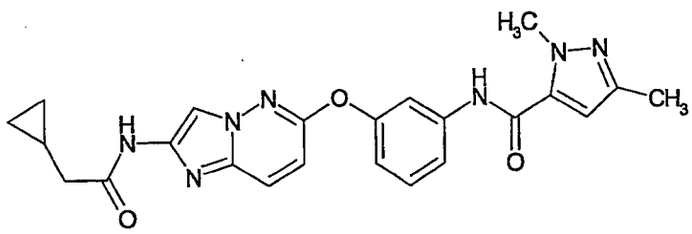


Using 2-cyclopropyl-N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (171 mg, 0.5 mmol), N-(2-fluoro-5-hydroxyphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (150 mg, 0.6 mmol), potassium carbonate (104 mg, 0.75 mmol) and N,N-dimethylformamide (4 mL), and by a reaction in the same manner as in Example 191, the title compound (53 mg, 23%) was obtained as pale-pink crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.10 - 0.20 (2H, m), 0.40 - 0.50 (2H, m), 1.00 - 1.15 (1H, m), 2.19 (3H, s), 2.24 (2H, d, J = 7.2 Hz), 3.97 (3H, s), 6.84 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.40 (1H, t, J = 9.6 Hz), 7.50 - 7.60 (1H, m), 7.98 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 10.09 (1H, s), 10.68 (1H, s).

Example 193

Production of N-[3-({2-[(cyclopropylacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



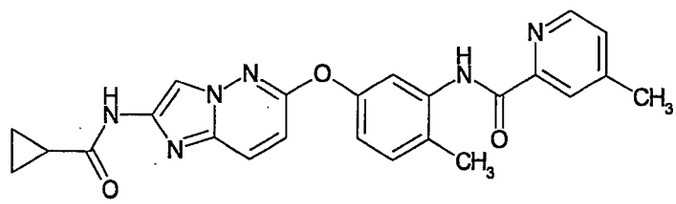
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-cyclopropylacetamide (100 mg, 0.309 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (64 mg, 0.404 mmol) and N,N-dimethylacetamide (5.0 mL), and by a reaction in the same manner as in Example 148, the title compound (85 mg, 62%) was obtained

as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.15 - 0.25 (2H, m), 0.40 - 0.50 (2H, m), 1.00 - 1.15 (1H, m), 2.19 (3H, s), 2.25 (2H, d, J = 6.9 Hz), 3.97 (3H, s), 6.82 (1H, s), 7.00 (1H, d, J = 8.1 Hz), 7.05 (1H, d, J = 9.6 Hz), 7.42 (1H, t, J = 8.1 Hz), 7.60 (1H, d, J = 8.1 Hz), 7.67 (1H, s), 8.02 (1H, s), 8.05 - 8.10 (1H, m), 10.23 (1H, s), 10.70 (1H, s).

Example 194

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methylpyridine-2-carboxamide

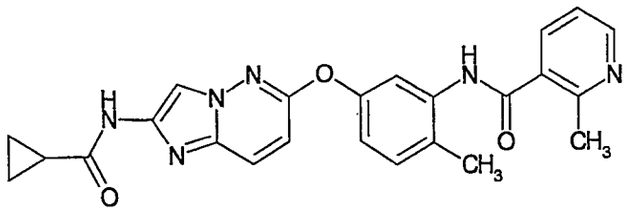


Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (120 mg, 0.371 mmol), 4-methylpyridine-2-carboxylic acid (76 mg, 0.557 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (114 mg, 0.594 mmol), 1-hydroxybenzotriazole (81 mg, 0.600 mmol), triethylamine (0.09 mL, 0.631 mmol) and N,N-dimethylformamide (6.0 mL), and by a reaction in the same manner as in Example 187, the title compound (40 mg, 24%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75-0.85 (4H, m), 1.85-2.00 (1H, m), 2.35 (3H, s), 2.44 (3H, s), 7.00 - 7.10 (2H, m), 7.34 (1H, d, J = 8.7 Hz), 7.50 - 7.55 (1H, m), 7.85 - 8.00 (3H, m), 8.02 (1H, d, J = 9.3 Hz), 8.58 (1H, d, J = 4.8 Hz), 10.31 (1H, s), 11.07 (1H, s).

Example 195

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2-methylnicotinamide

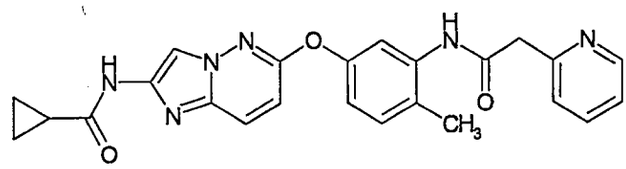


Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (120 mg, 0.371 mmol), 2-methylpyridine-3-carboxylic acid (76 mg, 0.557 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (114 mg, 0.594 mmol), 1-hydroxybenzotriazole (81 mg, 0.600 mmol), triethylamine (0.09 mL, 0.631 mmol) and N,N-dimethylformamide (6.0 mL), and by a reaction in the same manner as in Example 187, the title compound (52 mg, 31%) was obtained as pale-pink crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75-0.85 (4H, m), 1.85 - 1.95 (1H, m), 2.30 (3H, s), 2.59 (3H, s), 7.00 - 7.10 (2H, m), 7.30 - 7.35 (2H, m), 7.40 - 7.45 (1H, m), 7.85 - 7.90 (1H, m), 7.93 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 8.54 (1H, d, J = 3.0 Hz), 9.98 (1H, s), 11.06 (1H, s).

Example 196

Production of N-(6-{4-methyl-3-[(pyridin-2-ylacetyl)amino]phenoxy}imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



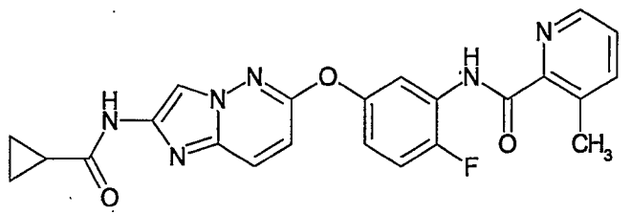
To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (120 mg, 0.371 mmol) and pyridin-2-ylacetic acid hydrochloride (129 mg, 0.742 mmol) in N,N-dimethylformamide (4.0 mL) were added dropwise triethylamine (0.21 mL, 1.484 mmol) and diethyl cyanophosphate (0.12 mL, 0.816 mmol) under ice-cooling, and the mixture was stirred at room

temperature for 3 hr. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→95/5) and recrystallized from ethyl acetate to give the title compound (67 mg, 41%) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.90-2.00 (1H, m), 2.25 (3H, s), 3.90 (2H, s), 6.90 - 7.00 (1H, m), 7.00 (1H, d, J = 9.6 Hz), 7.20 - 7.30 (2H, m), 7.40 (1H, t, J = 7.8 Hz), 7.50 - 7.55 (1H, m), 7.70 - 7.80 (1H, m), 7.91 (1H, s), 7.99 (1H, d, J = 9.6 Hz), 8.50 - 8.55 (1H, m), 9.79 (1H, s), 11.05 (1H, s).

Example 197

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methylpyridine-2-carboxamide



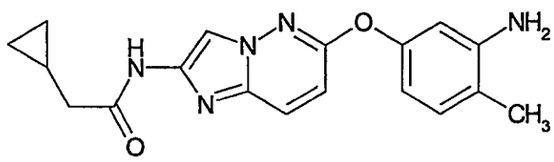
Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.611 mmol), 3-methylpyridine-2-carboxylic acid (126 mg, 0.917 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (187 mg, 0.978 mmol), 1-hydroxybenzotriazole (133 mg, 0.988 mmol), triethylamine (0.14 mL, 1.039 mmol) and N,N-dimethylformamide (6.0 mL), and by a reaction in the same manner as in Example 187, the title compound (128 mg, 47%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.90 (4H, m), 1.85 - 2.00 (1H, m), 2.63 (3H, s), 7.05 - 7.20 (2H, m), 7.35 - 7.50 (1H, m), 7.50

- 7.60 (1H, m), 7.84 (1H, d, J = 7.5 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.9 Hz), 8.10 - 8.15 (1H, m), 8.55 - 8.60 (1H, m), 10.57 (1H, s), 11.07 (1H, s).

Example 198

Production of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-cyclopropylacetamide

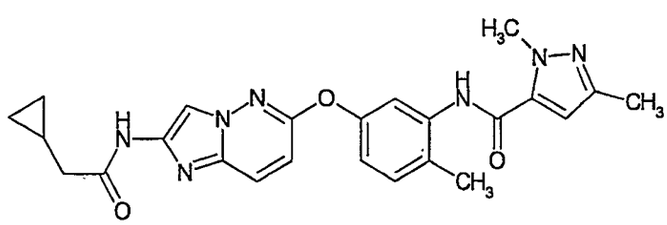


Using 2-cyclopropyl-N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (300 mg, 0.877 mmol), 3-amino-4-methylphenol (216 mg, 1.754 mmol), potassium carbonate (182 mg, 1.316 mmol) and N,N-dimethylformamide (3 mL), and by a reaction in the same manner as in Example 191, the title compound (138 mg, 47%) was obtained as a orange powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.15 - 0.25 (2H, m), 0.40 - 0.50 (2H, m), 1.00 - 1.10 (1H, m), 2.05 (3H, s), 2.25 (2H, d, J = 6.9 Hz), 5.07 (2H, s), 6.28 (1H, d, J = 7.5 Hz), 6.42 (1H, s), 6.90 - 7.00 (2H, m), 7.97 (1H, d, J = 9.6 Hz), 8.01 (1H, s), 10.68 (1H, s).

Example 199

Production of N-[5-({2-[(cyclopropylacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



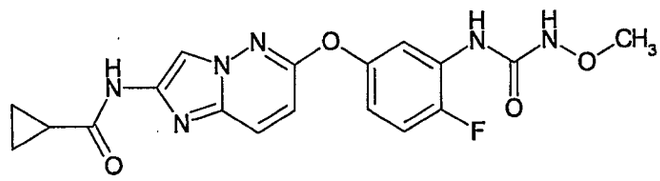
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-cyclopropylacetamide (120 mg, 0.356 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (59 mg, 0.374 mmol) and N,N-

dimethylacetamide (4.0 mL), and by a reaction in the same manner as in Example 148, the title compound (99 mg, 61%) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.15 - 0.25 (2H, m), 0.40 - 0.50 (2H, m), 1.00 - 1.15 (1H, m), 2.19 (3H, s), 2.25 - 2.30 (5H, m), 3.97 (3H, s), 6.80 (1H, s), 7.04 (1H, d, J = 9.8 Hz), 7.05 - 7.15 (1H, m), 7.25 - 7.30 (1H, m), 7.34 (1H, d, J = 8.1 Hz), 7.98 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 9.80 (1H, s), 10.68 (1H, s).

Example 200

Production of N-[6-(4-fluoro-3-{[(methoxyamino)carbonyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



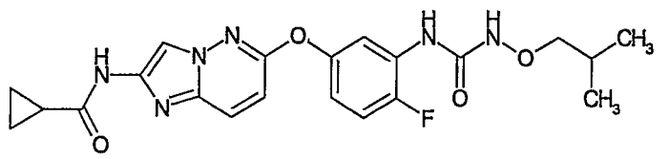
A solution of 1,1'-carbonyldiimidazole (297 mg, 1.833 mmol), O-methylhydroxyammonium chloride (153 mg, 1.833 mmol) and triethylamine (0.25 mL, 1.833 mmol) in N,N-dimethylformamide (4.0 mL) was stirred at room temperature for 30 min. A solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.611 mmol) in N,N-dimethylformamide (2.0 mL) was further added to the mixture, and the mixture was stirred at room temperature for 2 days. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was recrystallized from tetrahydrofuran/ethanol to give the title compound (67 mg, 27%) as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.85 - 2.00 (1H, m), 3.63 (3H, s), 6.95 - 7.05 (1H, m), 7.05 (1H, d, J = 9.3 Hz), 7.25 - 7.40 (1H, m), 7.70 - 7.75 (1H, m), 7.93 (1H, s), 8.03 (1H,

d, J = 9.3 Hz), 8.55 (1H, s), 9.76 (1H, s), 11.07 (1H, s).

Example 201

Production of N-[6-(4-fluoro-3-{[(isobutoxyamino)carbonyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

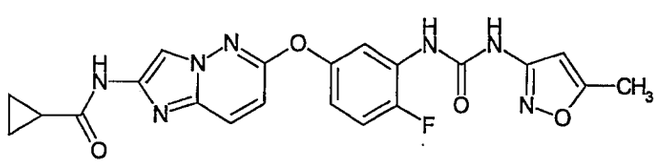


Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.611 mmol), 1,1'-carbonyldiimidazole (297 mg, 1.833 mmol), 1-(aminooxy)-2-methylpropane hydrochloride (230 mg, 1.833 mmol), triethylamine (0.25 mL, 1.833 mmol) and N,N-dimethylformamide (6.0 mL), and by a reaction in the same manner as in Example 200, the title compound (170 mg, 63%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 0.92 (6H, d, J = 6.9 Hz), 1.85-2.00 (1H, m), 3.58 (2H, d, J = 6.9 Hz), 6.95 - 7.05 (1H, m), 7.04 (1H, d, J = 9.9 Hz), 7.33 (1H, t, J = 9.9 Hz), 7.80 - 7.90 (1H, m), 7.92 (1H, s), 8.02 (1H, d, J = 9.9 Hz), 8.31 (1H, s), 9.80 (1H, s), 11.06 (1H, s).

Example 202

Production of N-{6-[4-fluoro-3-({[(5-methylisoxazol-3-yl)amino]carbonyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



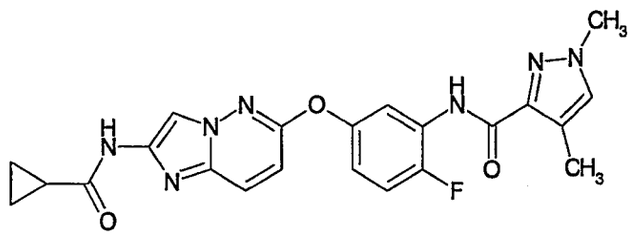
To a solution of pyridine (475 mg, 6 mmol) and 3-amino-5-methylisoxazole (147 mg, 1.5 mmol) in N,N-dimethylformamide (2.0 mL) was added dropwise a solution of phenyl chlorocarbonate (235 mg, 1.5 mmol) in N,N-dimethylformamide (2.0 mL) under ice-

cooling. After the mixture was stirred at room temperature for 2 hr, N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (327 mg, 1.0 mmol) was added to the mixture, and the mixture was stirred at 80°C for 15 hr and at 100°C for 2 hr. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by basic silica gel column chromatography (ethyl acetate/hexane=80/20→100/0) and recrystallized from tetrahydrofuran/ethanol to give the title compound (101 mg, 22%) as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.90 (4H, m), 1.85 - 2.00 (1H, m), 2.34 (3H, s), 6.48 (1H, s), 6.90 - 7.00 (1H, m), 7.04 (1H, d, J = 9.3 Hz), 7.35 (1H, t, J = 9.9 Hz), 7.90 (1H, s), 8.03 (1H, d, J = 9.3 Hz), 9.00 (1H, br s), 9.85 (1H, br s), 11.06 (1H, s).

Example 203

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,4-dimethyl-1H-pyrazole-3-carboxamide



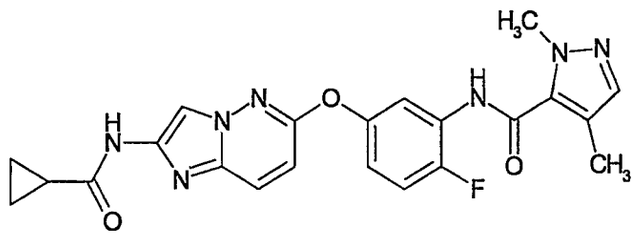
To a suspension of 1,4-dimethyl-1H-pyrazole-3-carboxylic acid (151 mg, 1.08 mmol) in tetrahydrofuran (2.0 mL) were added N,N-dimethylformamide (1 drop) and thionyl chloride (0.08 mL, 1.1 mmol), and the mixture was stirred at room temperature for 50 min. The reaction mixture was concentrated under reduced pressure and dissolved in N,N-dimethylacetamide (2.0 mL). On the other hand, to a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (327 mg, 1.0 mmol) in N,N-dimethylacetamide (6.0 mL) was added dropwise the above-mentioned solution under ice-cooling, and the mixture was stirred at room temperature for 2 hr. Under ice-cooling, aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by basic silica gel column chromatography (ethyl acetate/hexane=80/20→100/0) and recrystallized from tetrahydrofuran/ethanol to give the title compound (283 mg, 63%) as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75-0.85 (4H, m), 1.85-2.00 (1H, m), 2.21 (3H, s), 3.89 (3H, s), 7.05-7.15 (2H, m), 7.38 (1H, t, J = 9.6 Hz), 7.65 (1H, s), 7.90-8.00 (2H, m), 8.03 (1H, d, J = 9.6 Hz), 9.40 (1H, s), 11.06 (1H, s).

Example 204

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,4-dimethyl-1H-pyrazole-5-carboxamide

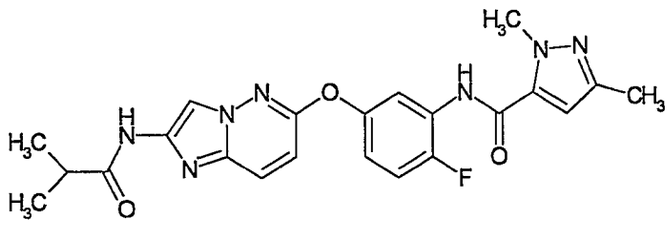


Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (327 mg, 1.0 mmol), 1,4-dimethyl-1H-pyrazole-5-carboxylic acid (154 mg, 1.1 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (1 drop), thionyl chloride (0.08 mL, 1.1 mmol) and N,N-dimethylacetamide (6.0 mL), and by a reaction in the same manner as in Example 203, the title compound (300 mg, 67%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.85 - 2.00 (1H, m), 2.19 (3H, s), 3.90 (3H, s), 7.07 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.33 (1H, s), 7.40 (1H, t, J = 9.6 Hz), 7.75 - 7.80 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.06 (1H, s), 11.06 (1H, s).

Example 205

Production of N-(2-fluoro-5-{[2-(isobutyrylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide

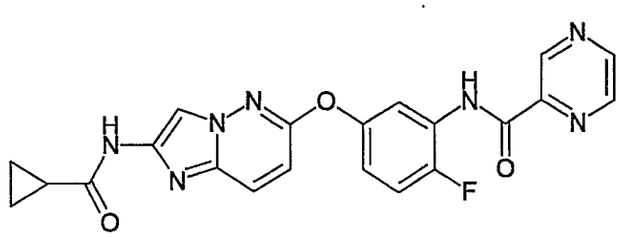


Using N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol), 2-methylpropanoyl chloride (53 mg, 0.50 mmol) and N,N-dimethylacetamide (5.0 mL), and by a reaction in the same manner as in Example 148, the title compound (98 mg, 45%) was obtained as pale-blue crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.08 (6H, d, J = 6.9 Hz), 2.19 (3H, s), 2.65 - 2.75 (1H, m), 3.97 (3H, s), 6.84 (1H, s), 7.06 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.40 (1H, t, J = 9.6 Hz), 7.50 - 7.60 (1H, m), 7.98 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 10.09 (1H, s), 10.72 (1H, s).

Example 206

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]pyrazine-2-carboxamide

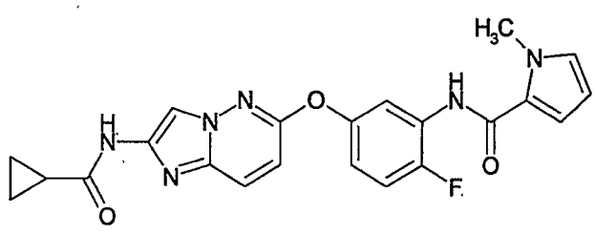


Using a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (327 mg, 1.0 mmol) and 2-pyrazinecarbonylchloride (171 mg, 1.2 mmol) in N,N-dimethylacetamide (6.0 mL), and by a reaction in the same manner as in Example 148, the title compound (113 mg, 26%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.85 (4H, m), 1.85 - 2.00 (1H, m), 7.09 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.44 (1H, t, J = 9.6 Hz), 7.90 - 8.00 (2H, m), 8.05 (1H, d, J = 9.6 Hz), 8.83 (1H, s), 8.96 (1H, s), 9.28 (1H, s), 10.44 (1H, s), 11.07 (1H, s).

Example 207

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrrole-2-carboxamide



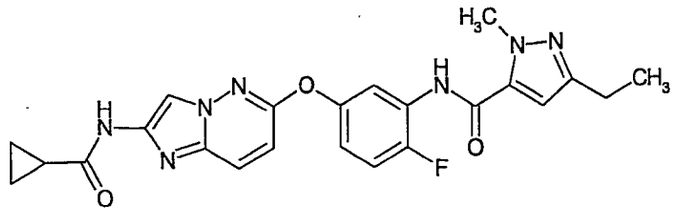
Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (327 mg, 1.0 mmol), 1-methyl-1H-pyrrole-2-carbonyl chloride (151 mg, 1.05 mmol) and N,N-dimethylacetamide (6.0 mL), and by a reaction in the same manner as in Example 148, the title compound (268 mg, 62%) was obtained as colorless crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.90 - 2.00 (1H, m), 3.84 (3H, s), 6.05 - 6.10 (1H, m), 7.00 - 7.20 (4H, m), 7.35 (1H, t, J = 9.6 Hz), 7.50 - 7.60 (1H, m), 7.93 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.63 (1H, s), 11.06 (1H, s).

Example 208

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide

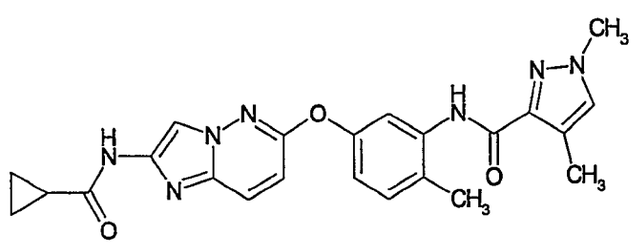


Using N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (327 mg, 1.0 mmol), 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (170 mg, 1.1 mmol) tetrahydrofuran (2.0 mL), N,N-dimethylformamide (1 drop), thionyl chloride (0.08 mL, 1.1 mmol) and N,N-dimethylacetamide (6.0 mL), and by a reaction in the same manner as in Example 203, the title compound (256 mg, 55%) was obtained as colorless crystals. melting point 236°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.19 (3H, t, J = 7.5 Hz), 1.90 - 2.00 (1H, m), 2.56 (2H, q, J = 7.5 Hz), 3.98 (3H, s), 6.89 (1H, s), 7.06 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.39 (1H, t, J = 9.6 Hz), 7.50 - 7.55 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 11.07 (1H, s).

Example 209

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,4-dimethyl-1H-pyrazole-3-carboxamide



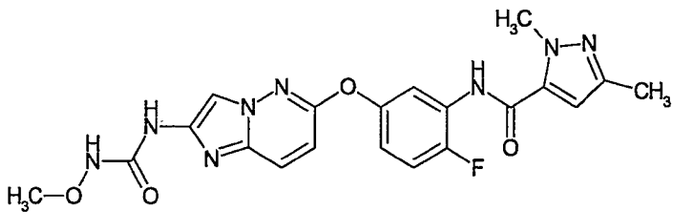
Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (323 mg, 1.0 mmol), 1,4-dimethyl-1H-pyrazole-3-carboxylic acid (154 mg, 1.1 mmol) tetrahydrofuran (2.0 mL), N,N-dimethylformamide (1 drop), thionyl chloride (0.08 mL, 1.1 mmol) and N,N-dimethylacetamide

(6.0 mL), and by a reaction in the same manner as in Example 203, the title compound (208 mg, 47%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.85 - 2.00 (1H, m), 2.20 (3H, s), 2.28 (3H, s), 3.88 (3H, s), 6.95 - 7.05 (1H, m), 7.02 (1H, d, J = 9.6 Hz), 7.30 (1H, d, J = 8.7 Hz), 7.63 (1H, s), 7.65 - 7.70 (1H, m), 7.93 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.28 (1H, s), 11.06 (1H, s).

Example 210

Production of N-{2-fluoro-5-[(2-{[(methoxyamino)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide



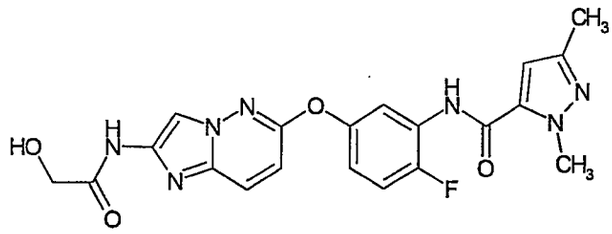
Using N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol), 1,1'-carbonylimidazole (233 mg, 1.44 mmol), O-methylhydroxyammonium chloride (120 mg, 1.44 mmol), triethylamine (0.27 mL, 1.92 mmol) and N,N-dimethylformamide (6.0 mL), and by a reaction in the same manner as in Example 200, the title compound (117 mg, 54%) was obtained as pale-yellow crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.60 (3H, s), 3.97 (3H, s), 6.84 (1H, s), 7.05 (1H, d, J = 9.6 Hz), 7.15 - 7.25 (1H, m), 7.39 (1H, t, J = 9.0 Hz), 7.50 - 7.55 (1H, m), 7.83 (1H, s), 8.01 (1H, d, J = 9.6 Hz), 9.46 (1H, s), 9.67 (1H, s), 10.09 (1H, s).

Example 211

Production of N-(2-fluoro-5-{[2-(glycoloylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-

carboxamide

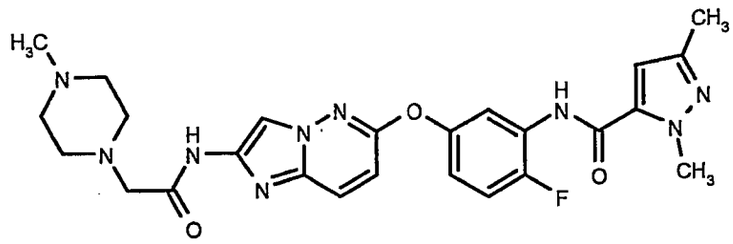


To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (507 mg, 1.13 mmol) was added 10% hydrogen chloride methanol solution (30 mL), and the mixture was stirred at 50°C for 23 hr. The solvent was evaporated under reduced pressure. To the residue were added acetoxyacetic acid (242 mg, 2.05 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (336 mg, 1.75 mmol), 1-hydroxybenzotriazole (167 mg, 1.24 mmol), N-ethyldiisopropylamine (0.60 mL, 3.51 mmol) and N,N-dimethylformamide (10 mL), and the mixture was stirred at room temperature for 62 hr. Methanol (10 mL), water (10 mL) and saturated aqueous sodium carbonate solution (2 mL) were added to the mixture, and the mixture was stirred at room temperature for 2 hr and 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 concentrated under reduced pressure. The residue was separated and purified by NH silica gel column chromatography (ethyl acetate/hexane=0/100→100/0→methanol/ethyl acetate=2/98) and crystallized from ethanol to give the title compound (94 mg, 19%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.98 (3H, s), 4.05 (2 H, d, J = 6.0 Hz), 5.51 (1H, t, J = 6.0 Hz), 6.85 (1H, s), 7.11 (1H, d, J = 9.8 Hz), 7.18 - 7.27 (1H, m), 7.41 (1H, m), 7.55 (1H, dd, J = 6.4, 3.0 Hz), 8.01 (1H, s), 8.07 (1H, d, J = 9.0 Hz), 10.11 (1H, s), 10.23 (1H, s).

Example 212

Production of N-{2-fluoro-5-[(2-{[(4-methylpiperazin-1-yl)acetyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide dihydrochloride



2HCl

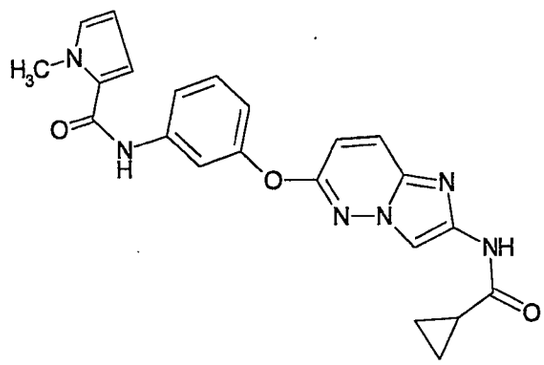
To N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (1.05 mg, 2.33 mmol) was added 10% hydrogen chloride methanol solution (120 mL), and the mixture was stirred at 50°C for 44 hr. The solvent was evaporated under reduced pressure. To a half of the residue were added (4-methylpiperazin-1-yl)acetic acid (205 mg, 1.30 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (284 mg, 1.48 mmol), 1-hydroxybenzotriazole (167 mg, 1.24 mmol), N-ethyldiisopropylamine (0.60 mL, 3.51 mmol) and N,N-dimethylformamide (10 mL), and the mixture was stirred at room temperature for 11 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=0/100→70/30) and the objective fraction was concentrated under reduced pressure. The residue was dissolved in methanol and treated with a 4N hydrogen chloride ethyl acetate solution to give the title compound (43 mg, 6%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 2.78 (3H, s), 3.21 (1H, brs), 3.34 (1H, brs), 3.67 (1H, br), 3.98 (3H, s), 6.87 (1H, s), 7.13 (1H, d, J = 9.5 Hz), 7.18 - 7.27 (1H, m), 7.41 (1H, t, J =

9.7 Hz), 7.51 - 7.60 (1H, m), 8.02 (1H, s), 8.09 (1H, d, J = 9.5 Hz), 10.13 (1H, s), 11.03 (1H, s).

Example 213

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-1H-pyrrole-2-carboxamide

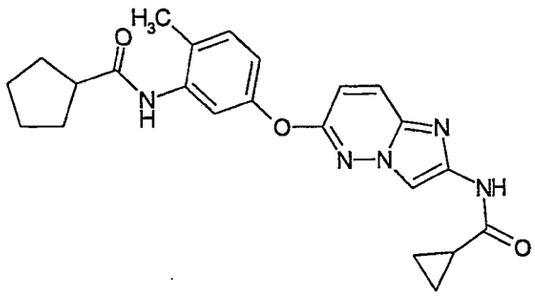


Using 1-methyl-1H-pyrrole-2-carboxylic acid (97 mg, 0.78 mmol), tetrahydrofuran(4.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (135 μL, 1.55 mmol), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 119, the title compound (133 mg, 49%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.88 - 1.96 (1H, m), 3.85 (3H, s), 6.09 (1H, dd, J = 3.9, 2.7 Hz), 6.91 - 6.95 (1H, m), 7.01 - 7.07 (3H, m), 7.35 - 7.41 (1H, m), 7.58 - 7.62 (1H, m), 7.66 - 7.68 (1H, m), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 9.87 (1H, s), 11.09 (1H, s).

Example 214

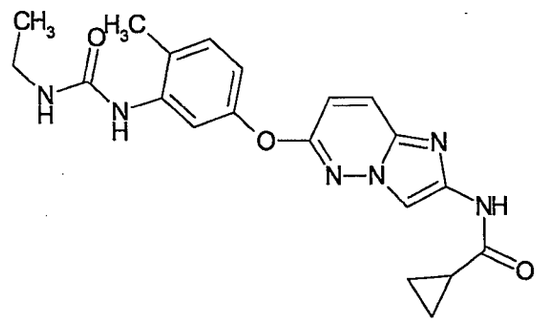
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]cyclopentanecarboxamide



Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), N,N-dimethylacetamide (3.0 mL) and cyclopentanecarbonyl chloride (90 μL, 0.74 mmol), and in the same manner as in Example 120, the title compound (119 mg, 46%) was obtained as a white powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.48 - 1.96 (9H, m), 2.22 (3H, s), 2.82 - 2.93 (1H, m), 6.97 (1H, dd, J = 8.4, 2.6 Hz), 7.01 (1H, d, J = 9.6 Hz), 7.26 (1H, d, J = 8.4 Hz), 7.37 (1H, d, J = 2.6 Hz), 7.93 (1H, s), 8.01 (1H, d, J = 9.6 Hz), 9.24 (1H, s), 11.07 (1H, s).

Example 215

Production of N-[6-(3-{[(ethylamino)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



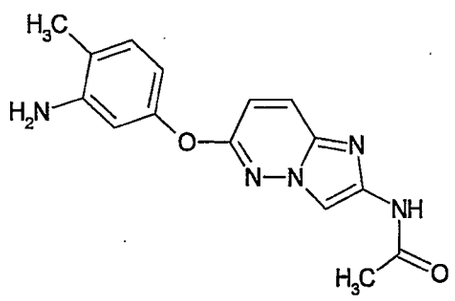
To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) in pyridine (4.0 mL) was added ethyl isocyanate (490 μL, 6.19 mmol), and the mixture was stirred at room temperature for 16 hr. The solvent was evaporated under reduced pressure and water was added to the

residue. The mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/ethanol and filtrated to give the title compound (142 mg, 58%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.04 (3H, t, J = 7.1 Hz), 1.86 - 1.95 (1H, m), 2.19 (3H, s), 3.02 - 3.14 (2H, m), 6.64 - 6.75 (2H, m), 6.98 (1H, d, J = 9.6 Hz), 7.16 (1H, d, J = 8.1 Hz), 7.71 (1H, s), 7.86 (1H, d, J = 2.7 Hz), 7.93 (1H, s), 8.00 (1H, d, J = 9.6 Hz), 11.07 (1H, s).

Example 216

Production of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide



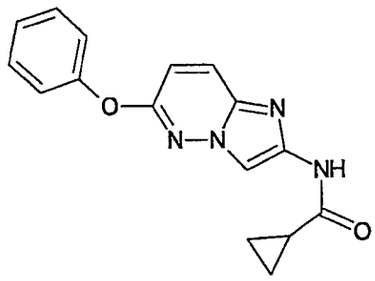
To a solution of 3-amino-4-methylphenol (1.22 g, 9.93 mmol) in N,N-dimethylformamide (25.0 mL) was added potassium tert-butoxide (1.16 g, 10.3 mmol), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture were added N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (2.5 g, 8.28 mmol) and potassium carbonate (0.57 g, 4.14 mmol), and the mixture was stirred at 140°C for 16 hr. Saturated brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone) and the obtained residue was washed with hexane/ethyl acetate, and filtrated to give the title compound (1.04 g, 42%)

as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 2.07 (3H, s), 5.06 (2H, s), 6.28 (1H, d, J = 8.1, 2.4 Hz), 6.42 (1H, d, J = 2.4 Hz), 6.94 (1H, d, J = 9.6 Hz), 6.95 (1H, d, J = 8.1 Hz), 7.97 (1H, d, J = 8.1 Hz), 7.98 (1H, s), 10.78 (1H, s).

Example 217

Production of N-(6-phenoxyimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

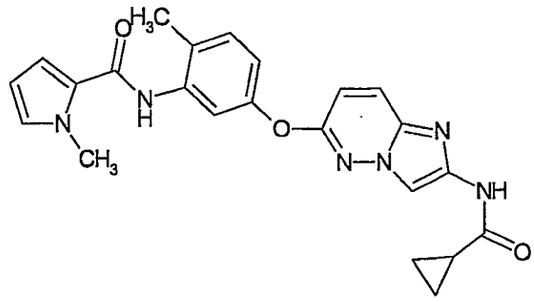


Using phenol (69 mg, 0.73 mmol), N,N-dimethylformamide (25.0 mL), potassium tert-butoxide (1.16 g, 10.3 mmol), N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (200 mg, 0.61 mmol) and potassium carbonate (42 mg, 0.31 mmol), and in the same manner as in Example 216, the title compound (98 mg, 54%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.86 - 1.96 (1H, m), 7.03 (1H, d, J = 9.6 Hz), 7.23 - 7.29 (3H, m), 7.42 - 7.49 (2H, m), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 11.06 (1H, s).

Example 218

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-pyrrole-2-carboxamide

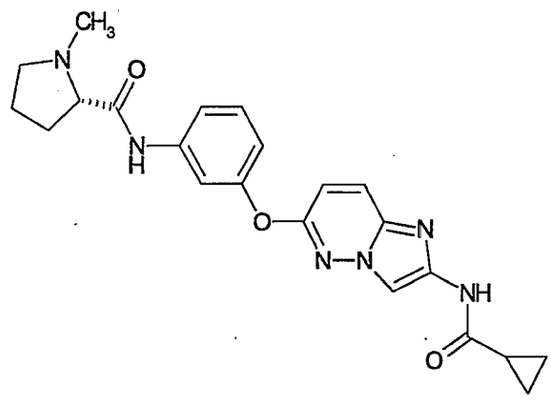


Using 1-methyl-1H-pyrrole-2-carboxylic acid (93 mg, 0.74 mmol), tetrahydrofuran (4.0 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (135 μL, 1.48 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 119, the title compound (15 mg, 6%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.87 - 1.95 (1H, m), 2.25 (3H, s), 3.84 (3H, s), 6.06 - 6.09 (1H, m), 6.96 - 7.03 (3H, m), 7.03 (1H, d, J = 9.6 Hz), 7.26 - 7.32 (2H, m), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.35 (1H, s), 11.07 (1H, s).

Example 219

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-methyl-L-prolinamide



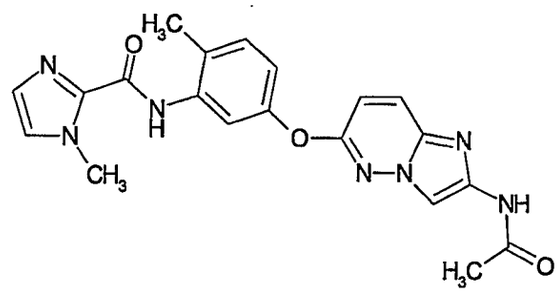
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropylcarboxamide (200 mg, 0.65 mmol) in N,N-dimethylformamide (4.0 mL) were added 1-methyl-L-proline(167

mg, 1.29 mmol), O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate (736 mg, 1.94 mmol), hydroxybenzotriazole (262 mg, 1.94 mmol) and N,N-diisopropylethylamine (338 μL, 1.94 mmol), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/ethanol=8/1), and the obtained residue was recrystallized from ethyl acetate to give the title compound (86 mg, 32%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.68 - 1.84 (3H, m), 1.87 - 1.95 (1H, m), 2.06 - 2.18 (1H, m), 2.25 - 2.36 (1H, m), 2.32 (3H, s), 2.85 - 2.92 (1H, m), 3.05 - 3.13 (1H, m), 6.91 - 6.95 (1H, m), 7.03 (1H, d, J = 9.8 Hz), 7.32 - 7.39 (1H, m), 7.54 - 7.58 (1H, m), 7.65 - 7.68 (1H, m), 7.95 (1H, s), 8.03 (1H, d, J = 9.8 Hz), 9.81 (1H, s), 11.08 (1H, s).

Example 220

Production of N-(5-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1-methyl-1H-imidazole-2-carboxamide



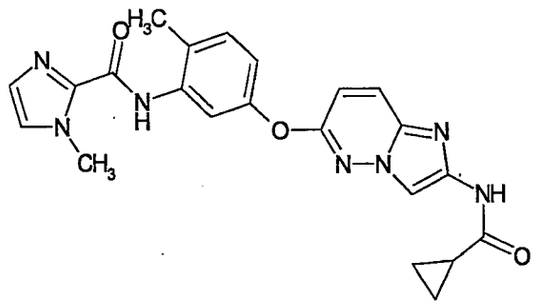
To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (150 mg, 0.50 mmol) in N,N-dimethylformamide (3.0 mL) were added 1-methyl-1H-imidazole-2-carboxylic acid (127 mg, 1.01 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (290 mg, 1.51 mmol) and 1-hydroxybenzotriazole (205 mg, 1.51 mmol),

and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the obtained residue was recrystallized from ethyl acetate/ethanol to give the title compound (115 mg, 56%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 2.30 (3H, s), 3.97 (3H, s), 6.96 - 7.09 (3H, m), 7.33 (1H, d, J = 8.4 Hz), 7.45 (1H, s), 7.68 (1H, d, J = 2.4 Hz), 7.95 (1H, s), 8.02 (1H, d, J = 9.9 Hz), 9.77 (1H, s), 10.78 (1H, s).

Example 221

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-imidazole-2-carboxamide



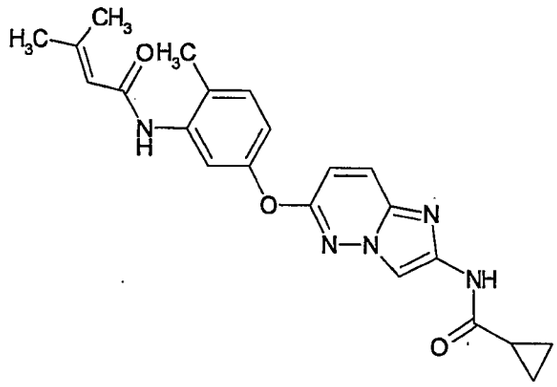
To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) in N,N-dimethylformamide (3.0 mL) were added 1-methyl-1H-imidazole-2-carboxylic acid (117 mg, 0.93 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (267 mg, 1.39 mmol) and 1-hydroxybenzotriazole (188 mg, 1.39 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over

anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the obtained residue was washed with ethyl acetate/hexane to give the title compound (66 mg, 32%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.85 - 1.96 (1H, m), 2.30 (3H, s), 3.96 (3H, s), 6.98 - 7.03 (2H, m), 7.07 (1H, d, J = 9.5 Hz), 7.32 (1H, d, J = 8.4 Hz), 7.42 (1H, s), 7.68 (1H, d, J = 2.7 Hz), 7.93 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.76 (1H, s), 11.06 (1H, s).

Example 222

Production of N-(6-{4-methyl-3-[(3-methylbut-2-enoyl)amino]phenoxy}imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide



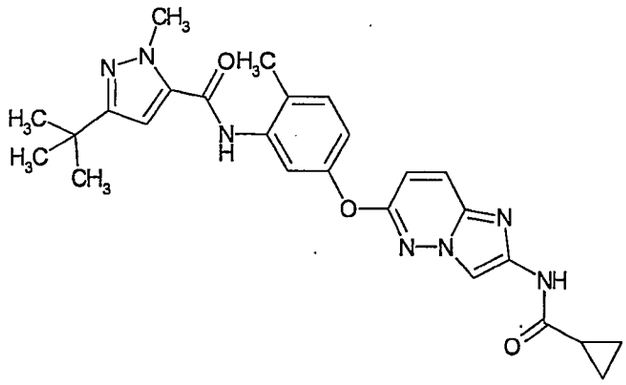
Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), N,N-dimethylacetamide (2.0 mL) and 3,3-dimethylacryloyl chloride (83 μL, 0.74 mmol), and in the same manner as in Example 120, the title compound (142 mg, 57%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.86 (3H, s), 1.87 - 1.93 (1H, m), 2.11 (3H, s), 2.22 (3H, s), 5.99 (1H, s), 6.94 (1H, dd, J = 8.3, 2.6 Hz), 7.01 (1H, d, J = 9.6 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.49 (1H, d, J = 2.6 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.14 (1H, s), 11.05 (1H, s).

Example 223

Production of 3-tert-butyl-N-[5-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-pyrazole-5-carboxamide

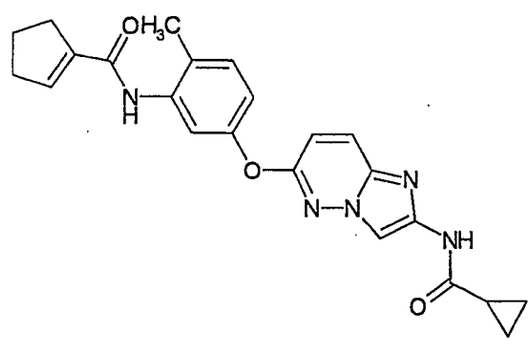


Using 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (61 mg, 0.33 mmol), tetrahydrofuran (1.8 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (44 μL, 0.50 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (90 mg, 0.28 mmol) and N,N-dimethylacetamide (1.8 mL), and in the same manner as in Example 119, the title compound (55 mg, 41%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.27 (9H, s), 1.86 - 1.94 (1H, m), 2.25 (3H, s), 3.99 (3H, s), 6.92 (1H, s), 7.04 (1H, d, J = 9.5 Hz), 7.09 (1H, dd, J = 8.4, 2.4 Hz), 7.25 (1H, d, J = 2.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.84 (1H, s), 11.07 (1H, s).

Example 224

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]cyclopent-1-ene-1-carboxamide

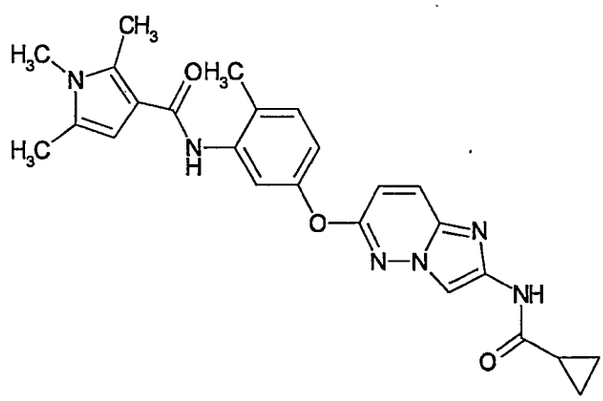


Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), N,N-dimethylacetamide (4.0 mL), 1-cyclopentenecarboxylic acid (139 mg, 1.24 mmol), O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate (704 mg, 1.86 mmol), 1-hydroxybenzotriazole (251 mg, 1.86 mmol) and N, N-diisopropylethylamine (323 μL, 1.86 mmol), and in the same manner as in Example 219, the title compound (69 mg, 21%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.84 - 1.95 (3H, m), 2.21 (3H, s), 2.40 - 2.61 (4H, m), 6.67 - 6.70 (1H, m), 7.00 - 7.04 (2H, m), 7.23 - 7.30 (2H, m), 7.91 (1H, s), 8.01 (1H, d, J = 9.3 Hz), 9.18 (1H, s), 11.06 (1H, s).

Example 225

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,2,5-trimethyl-1H-pyrrole-3-carboxamide



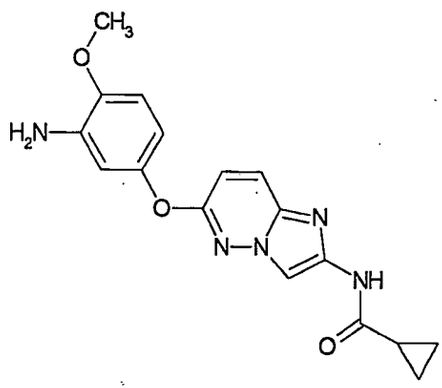
To a solution of 1,2,5-trimethylpyrrole-3-carboxylic acid (142 mg, 0.93 mmol) in tetrahydrofuran (4.0 mL) were added N,N-dimethylformamide (20 μL, 0.26 mmol) and oxalyl chloride (108 μL, 1.24 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and triethylamine (259 μL, 1.86 mmol) in N,N-dimethylacetamide (4.0 mL), and the mixture was stirred at 50°C for 16 hr. Water was added to the

reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/3→ethyl acetate alone), washed with hexane/ethyl acetate and filtrated to give the title compound (68 mg, 24%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.83 (4H, m), 1.86 - 1.94 (1H, m), 2.17 (3H, s), 2.23 (3H, s), 2.44 (3H, s), 3.37 (3H, s), 6.35 (1H, s), 6.96 (1H, dd, J = 8.1, 2.4 Hz), 7.01 (1H, d, J = 9.6 Hz), 7.26 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 2.4 Hz), 7.92 (1H, s), 8.01 (1H, d, J = 9.6 Hz), 8.73 (1H, s), 11.05 (1H, s).

Example 226

Production of N-[6-(3-amino-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

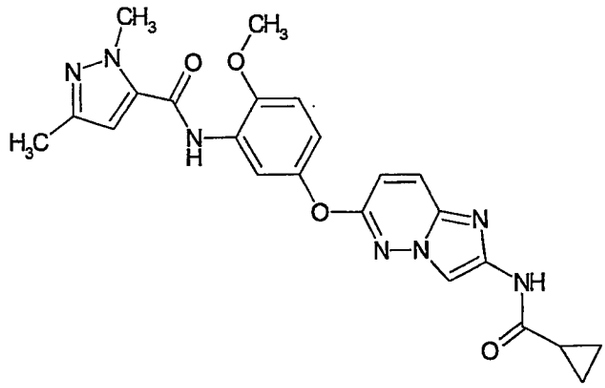


Using 3-amino-4-methoxyphenol (408 mg, 2.93 mmol), N,N-dimethylformamide (16 mL), potassium tert-butoxide (343 mg, 3.05 mmol), N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (800 mg, 2.44 mmol) and potassium carbonate (169 mg, 1.22 mmol), and in the same manner as in Example 216, the title compound (1.04 g, 42%) was obtained as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.86 - 1.94 (1H, m), 3.77 (3H, s), 4.95 (2H, s), 6.33 (1H, dd, J = 8.7, 2.9 Hz), 6.46 (1H, d, J = 2.9 Hz), 6.79 (1H, d, J = 8.7 Hz), 6.91 (1H, d, J = 9.6 Hz), 7.93 (1H, s), 7.96 (1H, d, J = 9.6 Hz), 11.04 (1H, s).

Example 227

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methoxyphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

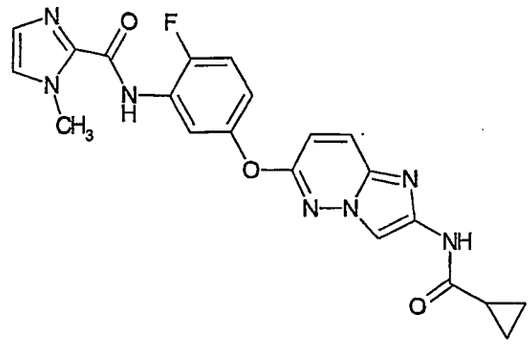


Using N-[6-(3-amino-4-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.59 mmol), N,N-dimethylacetamide (4.0 mL) and 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (113 mg, 0.71 mmol), and in the same manner as in Example 120, the title compound (146 mg, 54%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.87 - 1.96 (1H, m), 2.19 (3H, s), 3.88 (3H, s), 3.97 (3H, s), 6.82 (1H, s), 7.03 (1H, d, J = 9.6 Hz), 7.07 - 7.19 (2H, m), 7.70 (1H, d, J = 3.0 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.35 (1H, s), 11.06 (1H, s).

Example 228

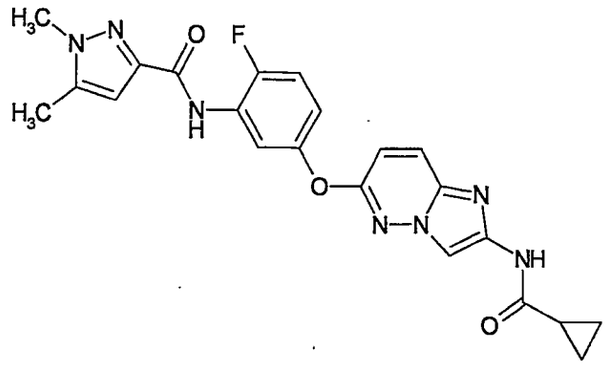
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-imidazole-2-carboxamide



To a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) in N,N-dimethylformamide (4.0 mL) were added 1-methyl-1H-imidazole-2-carboxylic acid (154 mg, 1.22 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (351 mg, 1.83 mmol) and 1-hydroxybenzotriazole (248 mg, 1.83 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl acetate alone) to give the title compound (31 mg, 12%) as a white powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.86 - 1.96 (1H, m), 3.97 (3H, s), 7.03 - 7.17 (3H, m), 7.37 - 7.48 (2H, m), 7.88 (1H, dd, J = 6.5, 2.9 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.9 Hz), 9.91 (1H, s), 11.07 (1H, s).

Example 229

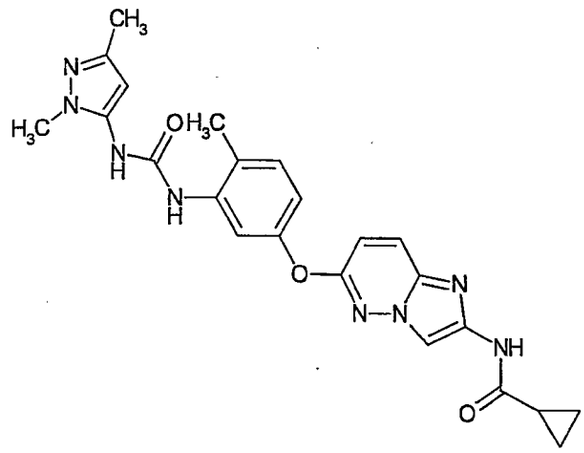
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,5-dimethyl-1H-pyrazole-3-carboxamide



To a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) in N,N-dimethylformamide (4.0 mL) were added 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (171 mg, 1.22 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (351 mg, 1.83 mmol), 1-hydroxybenzotriazole (248 mg, 1.83 mmol) and triethylamine (256 μL, 1.83 mmol), and the mixture was stirred at 60°C for 36 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) to give the title compound (72 mg, 26%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.82 (4H, m), 1.87 - 1.96 (1H, m), 2.30 (3H, s), 3.84 (3H, s), 6.57 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 7.07 - 7.14 (1H, m), 7.35 - 7.43 (1H, m), 7.89 (1H, dd, J = 6.3, 3.0 Hz), 7.95 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 9.46 (1H, s), 11.08 (1H, s).

Example 230

Production of N-{6-[3-({[(1,3-dimethyl-1H-pyrazol-5-yl)amino]carbonyl}amino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

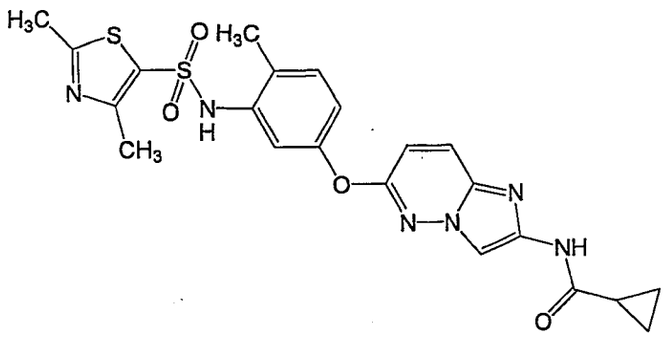


To a solution of 1,3-dimethyl-1H-pyrazol-5-amine (104 mg, 0.93 mmol) in N,N-dimethylformamide (4.0 mL) was added N,N-carbonyldiimidazole (150 mg, 0.93 mmol), and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethanol/ethyl acetate=1/20→1/10) to give the title compound (58 mg, 20%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.82 (4H, m), 1.87 - 1.95 (1H, m), 2.05 (3H, s), 2.27 (3H, s), 3.59 (3H, s), 5.94 (1H, s), 6.83 (1H, dd, J = 8.0, 2.6 Hz), 7.00 (1H, d, J = 9.5 Hz), 7.24 (1H, d, J = 8.4 Hz), 7.80 (1H, d, J = 2.6 Hz), 7.92 (1H, s), 8.00 (1H, d, J = 9.5 Hz), 8.25 (1H, s), 8.99 (1H, s), 11.05 (1H, s).

Example 231

Production of N-[6-(3-{[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

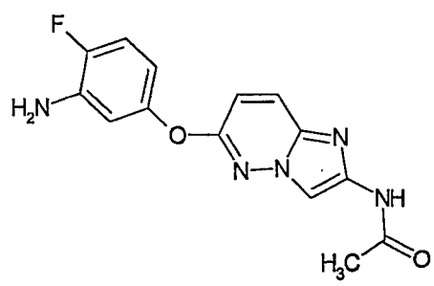


To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) in pyridine (4.0 mL) was added 2,4-dimethyl-1,3-thiazole-5-sulfonyl chloride (157 mg, 0.74 mmol), and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) and washed with hexane/ethyl acetate to give the title compound (196 mg, 64%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.88 - 1.95 (1H, m), 2.07 (3H, s), 2.20 (3H, s), 2.55 (3H, s), 6.92 (1H, d, J = 2.7 Hz), 7.01 (1H, d, J = 9.8 Hz), 7.07 - 7.12 (1H, dd, J = 8.4, 2.7 Hz), 7.27 (1H, d, J = 8.4 Hz), 7.93 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 10.10 (1H, s), 11.08 (1H, s).

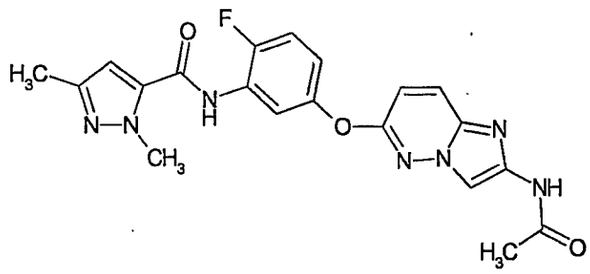
Example 232

Production of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide



To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)acetamide (12 g, 39.7 mmol) in N,N-dimethylformamide (120 mL) were added 3-amino-4-fluorophenol (7.6 g, 59.6 mmol) and potassium carbonate (11.0 g, 79.5 mmol), and the mixture was stirred at 140°C for 12 hr. After cooling the mixture to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) to give the title compound (9.5 g, 79%) as a brown powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 5.36 (2H, s), 6.30 - 6.37 (1H, m), 6.58 (1H, dd, J = 7.8, 2.7 Hz), 6.97 (1H, d, J = 9.6 Hz), 6.98 - 7.06 (1H, m), 7.99 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 10.78 (1H, s).

Example 233
Production of N-(5-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-fluorophenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



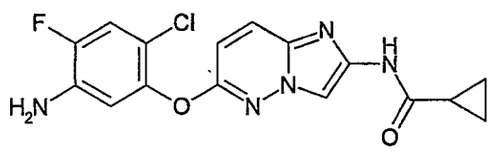
To a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (5.6 g, 18.6 mmol) in N,N-dimethylacetamide (44.8 mL) was added 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (3.25 g, 20.4 mmol). After stirring at room temperature for 2 hr, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed

with ethyl acetate/ethanol to give the title compound (6.1 g, 78%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.06 (3H, s), 2.19 (3H, s), 3.97 (3H, s), 6.85 (1H, s),7.07 (1H, d, J = 9.6 Hz), 7.17 - 7.25 (1H, m), 7.34 - 7.44 (1H, m), 7.50 - 7.58 (1H, m), 7.96 (1H, s), 8.04 (1H, d), 10.10 (1H, s), 10.79 (1H, s).

Example 234

Production of N-[6-(5-amino-2-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

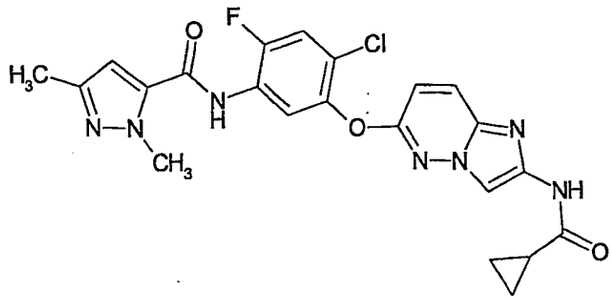


To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (600 mg, 1.83 mmol) in N,N-dimethylformamide (12 mL) were added 3-amino-6-chloro-4-fluorophenol (443 mg, 2.74 mmol) and potassium carbonate (505 mg, 3.66 mmol). In the same manner as in Example 232, the title compound (372 mg, 56%) was obtained as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.83 (4H, m), 1.87 - 1.95 (1H, m), 5.56 (2H, s), 6.74 (1H, d, J = 8.4 Hz), 7.07 (1H, d, J = 9.5 Hz), 7.34 (1H, d, J = 10.5 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.5 Hz), 11.07 (1H, s).

Example 235

Production of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

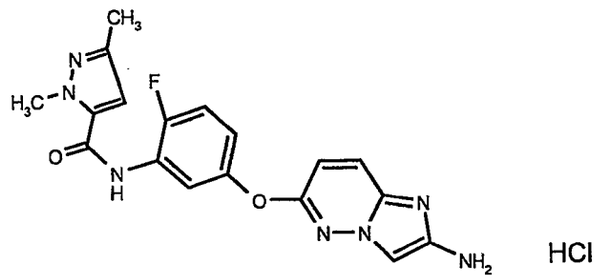


Using N-[6-(5-amino-2-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.55 mmol), N,N-dimethylacetamide (4.0 mL) and 1,3-dimethyl-1H-pyrazole-5-carbonyl chloride (105 mg, 0.66 mmol), and in the same manner as in Example 120, the title compound (108 mg, 40%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.84 (4H, m), 1.85 - 1.96 (1H, m), 2.19 (3H, s), 3.97 (3H, s), 6.84 (1H, s), 7.16 (1H, d, J = 9.6 Hz), 7.74 - 7.81 (2H, m), 7.90 (1H, s), 8.08 (1H, d, J = 9.6 Hz), 10.19 (1H, s), 11.07 (1H, s).

Example 236

Production of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride



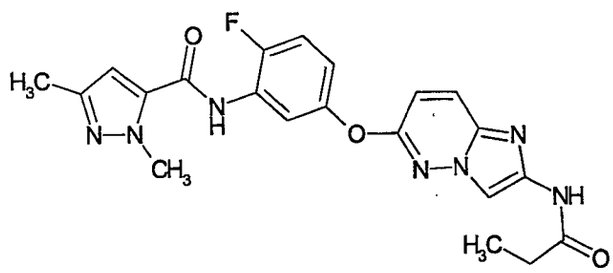
To a suspension of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide (2.0 g, 4.72 mmol) in methanol (20 mL) was added 4N hydrochloric acid/ethyl acetate (16 mL) solution. After stirring at room temperature for 4 hr, the mixture was stirred at 50°C for 12 hr. The solvent was evaporated under reduced pressure, and

diisopropyl ether/ethanol (8 mL/2 mL) was added to the residue. The mixture was stirred at room temperature for 2 hr. The precipitate was collected by filtration and washed with diisopropyl ether to give the title compound (2.0 g, quant.) as a brown powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 3.98 (3H, s), 6.91 (1H, s), 7.18 - 7.26 (1H, m), 7.37 (1H, d, J = 9.6 Hz), 7.39 - 7.48 (2H, m), 7.54 - 7.60 (1H, m), 8.20 (1H, d, J = 9.6 Hz), 10.24 (1H, s).

Example 237

Production of N-(2-fluoro-5-{[2-(propionylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



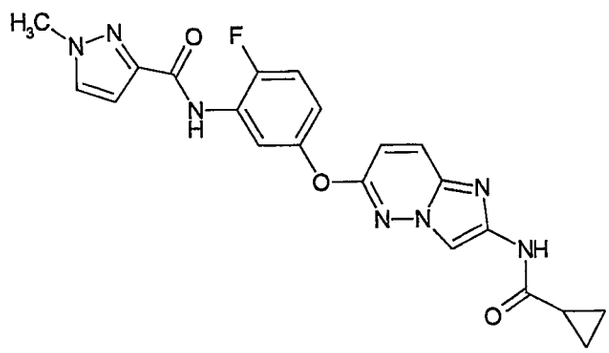
To a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (200 mg, 0.48 mmol) in N,N-dimethylacetamide (2.0 mL) was added propionyl chloride (49.9 μL, 0.57 mmol), and the mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1→ethyl acetate alone) and washed with ethyl acetate to give the title compound (78 mg, 37%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.06 (3H, t, J = 7.5 Hz), 2.19 (3H, s), 2.37 (2H, q, J = 7.5 Hz), 3.98 (3H, s), 6.85 (1H, s), 7.07

(1H, d, J = 9.6 Hz), 7.18 - 7.24 (1H, m), 7.37 - 7.44 (1H, m), 7.55 (1H, dd, J = 6.3, 3.3 Hz), 7.98 (1H, s), 8.08 (1H, d, J = 9.6 Hz), 10.11 (1H, s), 10.74 (1H, s).

Example 238

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-3-carboxamide



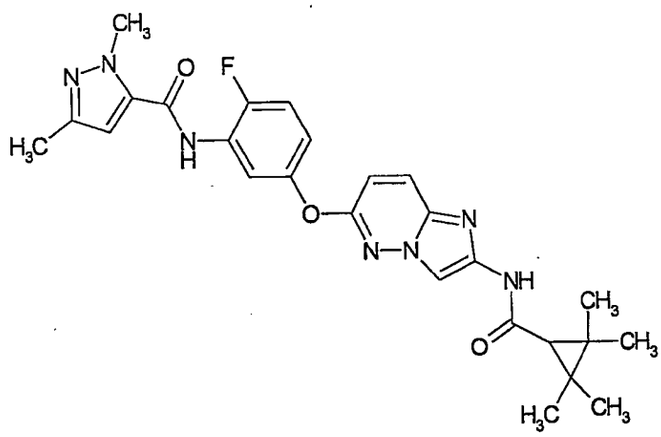
To a solution of 1-methyl-1H-pyrazole-3-carboxylic acid (115 mg, 0.92 mmol) in tetrahydrofuran (4.0 mL) were added N,N-dimethylformamide (20 μL, 0.26 mmol) and oxalyl chloride (80 μL, 0.92 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) in N,N-dimethylacetamide (4.0 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure and ethanol (10 mL) was added to the residue. The mixture was stirred with heating at 75°C and cooled to room temperature, and the precipitate was collected by filtration to give the title compound (144 mg, 54%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.87 - 1.97 (1H, m), 3.97 (3H, s), 6.77 (1H, d, J = 2.4 Hz), 7.06 - 7.16 (2H, m),

7.36 - 7.43 (1H, m), 7.82 - 7.89 (2H, m), 7.95 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 9.59 (1H, s), 11.08 (1H, s).

Example 239

Production of N-{2-fluoro-5-[(2-{[(2,2,3,3-tetramethylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide



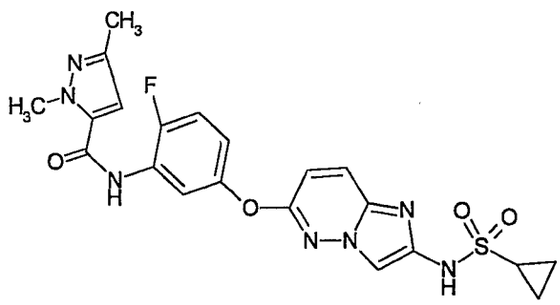
To a solution of 2,2,3,3-tetramethylcyclopropanecarboxylic acid (102 mg, 0.72 mmol) in tetrahydrofuran (4.0 mL) were added N,N-dimethylformamide (20 μL, 0.26 mmol) and oxalyl chloride (63 μL, 0.72 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (200 mg, 0.48 mmol) in N,N-dimethylacetamide (4.0 mL), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/1) and precipitated from hexane/ethyl acetate to give the title compound (46 mg, 19%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.16 (6H, s), 1.22 (6H, s), 1.47 (1H, s), 2.19 (3H, s), 3.97 (3H, s), 6.83 (1H, s), 7.04 (1H, d, J =

9.5 Hz), 7.17 - 7.22 (1H, m), 7.34 - 7.42 (1H, m), 7.51 - 7.55 (1H, m), 7.95 (1H, s), 8.01 (1H, d, J = 9.5 Hz), 10.09 (1H, s), 11.70 (1H, s).

Example 240

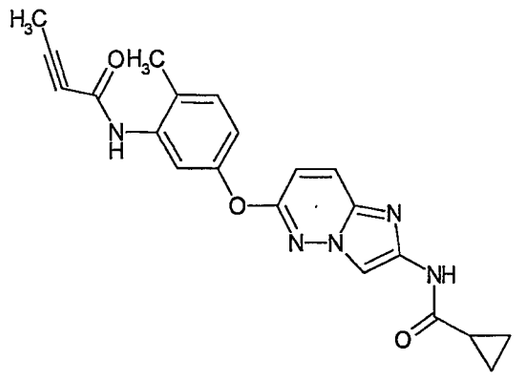
Production of N-[5-({2-[(cyclopropylsulfonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



To a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (400 mg, 0.97 mmol) in 1-methyl-2-pyrrolidone (4.0 mL) were added triethylamine (404 μL, 2.90 mmol) and cyclopropanesulfonyl chloride (204 mg, 1.45 mmol), and the mixture was stirred at 70°C for 16 hr. After cooling the mixture to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone) and precipitated from hexane/ethyl acetate to give the title compound (74 mg, 16%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.92 - 1.03 (4H, m), 2.19 (3H, s), 2.75 - 2.86 (1H, m), 3.97 (3H, s), 6.84 (1H, s), 7.10 (1H, d, J = 9.6 Hz), 7.18 - 7.25 (1H, m), 7.36 - 7.43 (1H, m), 7.52 - 7.56 (1H, m), 7.63 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.09 (1H, s), 10.30 (1H, s).

Example 241

Production of N-{6-[3-(but-2-ynoylamino)-4-methylphenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

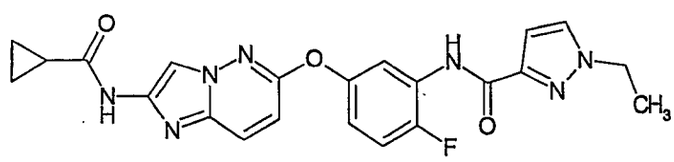


Using 2-butynoic acid (78 mg, 0.93 mmol), tetrahydrofuran (4.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (81 μL, 0.93 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 238, the title compound (47 mg, 20%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.85 - 1.95 (1H, m), 2.03 (3H, s), 2.21 (3H, s), 6.96 - 7.04 (2H, m), 7.25 - 7.29 (2H, m), 7.92 (1H, s), 8.10 (1H, d, J = 9.3 Hz), 10.05 (1H, s), 11.05 (1H, s).

Example 242

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-3-carboxamide



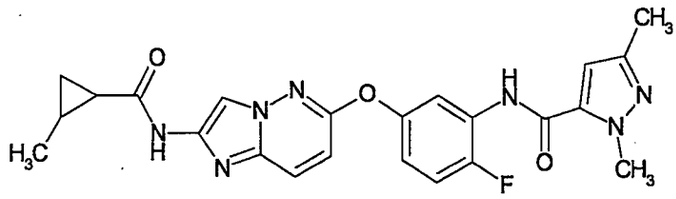
Using 1-ethyl-1H-pyrazole-3-carboxylic acid (128 mg, 0.92 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (80 μL, 0.92 mmol), N-[6-(3-amino-4-

fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 238, the title compound (111 mg, 40%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.44 (3H, t, J = 7.2 Hz), 1.87 - 1.97 (1H, m), 4.26 (2H, q, J = 7.2 Hz), 6.77 (1H, d, J = 2.1 Hz), 7.07 (1H, d, J = 9.6 Hz), 7.09 - 7.16 (1H, m), 7.39 (1H, dd, J = 11.4, 8.7 Hz), 7.84 (1H, dd, J = 6.5, 2.9 Hz), 7.91 - 7.96 (2H, m), 8.04 (1H, d, J = 9.6 Hz), 9.57 (1H, s), 11.07 (1H, s).

Example 243

Production of N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

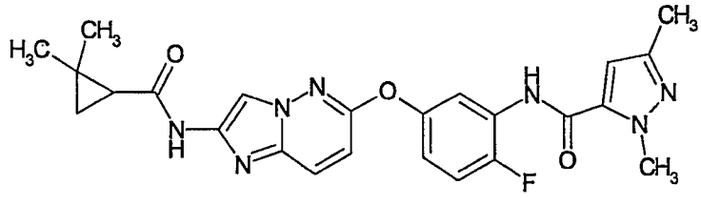


Using 2-methylcyclopropanecarboxylic acid (72 mg, 0.72 mmol), tetrahydrofuran (2.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (63 μL, 0.72 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 239, the title compound (55 mg, 25%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.72 (1H, m), 0.95 - 1.05 (1H, m), 1.06 - 1.09 (3H, m), 1.18 - 1.27 (1H, m), 1.64 - 1.73 (1H, m), 2.19 (3H, s), 3.98 (3H, s), 6.84 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 7.09 - 7.24 (1H, m), 7.36 - 7.43 (1H, m), 7.52 - 7.56 (1H, m), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 10.99 (1H, s).

Example 244

Production of N-{5-[(2-{[(2,2-dimethylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

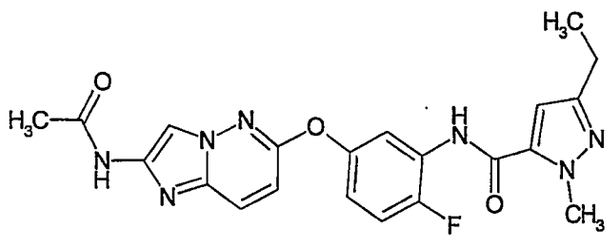


Using 2,2-dimethylcyclopropanecarboxylic acid (82 mg, 0.72 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (63 μL, 0.72 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 239, the title compound (37 mg, 16%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 1.27 (2H, m), 1.12 (3H, s), 1.14 (3H, s), 1.75 - 1.84 (1H, m), 2.19 (3H, s), 3.97 (3H, s), 6.83 (1H, s), 7.05 (1H, d, J = 8.7 Hz), 7.16 - 7.24 (1H, m), 7.35 - 7.42 (1H, m), 7.50 - 7.55 (1H, m), 7.95 (1H, s), 8.03 (1H, d, J = 8.7 Hz), 10.09 (1H, s), 10.90 (1H, s).

Example 245

Production of N-(5-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-fluorophenyl)-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide



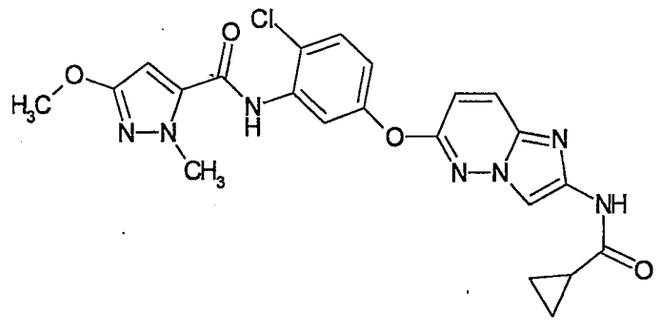
Using 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (215 mg, 1.39 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide

(30 μL, 0.39 mmol), oxalyl chloride (122 μL, 1.39 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (300 mg, 1.00 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 238, the title compound (219 mg, 50%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.19 (3H, t, J = 7.5 Hz), 2.06 (3H, s), 2.55 (2H, q, J = 7.5 Hz), 3.99 (3H, s), 6.89 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 7.18 - 7.25 (1H, m), 7.36 - 7.43 (1H, m), 7.52 - 7.56 (1H, m), 7.95 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 10.10 (1H, s), 10.78 (1H, s).

Example 246

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide

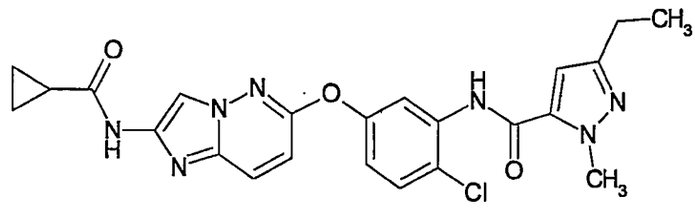


Using 3-methoxy-1-methyl-1H-pyrazole-5-carboxylic acid (191 mg, 1.22 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (107 μL, 1.22 mmol), N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.87 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 238, the title compound (259 mg, 62%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.87 (4H, m), 1.86 - 1.99 (1H, m), 3.79 (3H, s), 3.91 (3H, s), 6.47 (1H, s), 7.09 (1H, d, J = 9.9 Hz), 7.23 - 7.28 (1H, m), 7.49 - 7.53 (1H, m), 7.62 (1H, d, J = 8.7 Hz), 7.94 (1H, s), 8.05 (1H, d, J = 9.9 Hz), 10.05 (1H, s), 11.07 (1H, s).

Example 247

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide

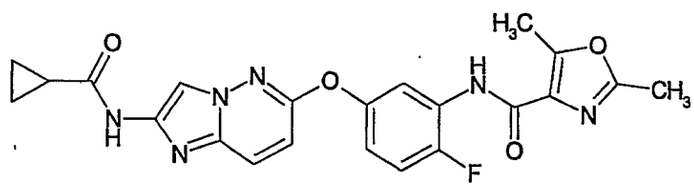


Using 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (188 mg, 1.22 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (107 μL, 1.22 mmol), N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.87 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 238, the title compound (268 mg, 64%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.19 (3H, t, J = 7.7 Hz), 1.84 - 1.97 (1H, m), 2.55 (2H, q, J = 7.7 Hz), 3.99 (3H, s), 6.88 (1H, s), 7.09 (1H, d, J = 9.6 Hz), 7.25 (1H, dd, J = 8.7, 2.9 Hz), 7.53 (1H, d, J = 2.9 Hz), 7.62 (1H, d, J = 8.7 Hz), 7.95 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.00 (1H, s), 11.07 (1H, s).

Example 248

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide

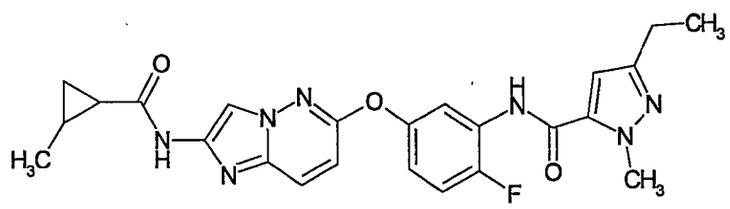


To a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) in N,N-dimethylacetamide (4.0 mL) was added 2,5-dimethyl-1,3-oxazole-4-carbonyl chloride (127 mg, 0.79 mmol), 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, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethanol to give the title compound (198 mg, 72%) as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 2.45 (3H, s), 2.55 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.08 - 7.15 (1H, m), 7.35 - 7.42 (1H, m), 7.87 (1H, dd, J = 6.5, 2.9 Hz), 7.93 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.48 (1H, s), 11.06 (1H, s).

Example 249

Production of 3-ethyl-N-{2-fluoro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1-methyl-1H-pyrazole-5-carboxamide



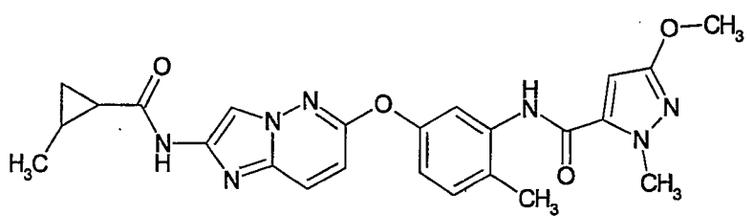
To a solution of 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (158 mg, 1.03 mmol) in tetrahydrofuran (3.8 mL) were added N,N-dimethylformamide (20 μL, 0.26 mmol) and oxalyl chloride (90 μL, 1.03 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide (250 mg, 0.73 mmol) in N,N-dimethylacetamide (5.0 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with

saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate alone) and recrystallized from hexane/ethyl acetate to give the title compound (201 mg, 57%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.71 (1H, m), 0.95 - 1.04 (1H, m), 1.06 - 1.10 (3H, m), 1.19 (3H, t, J = 7.7 Hz), 1.17 - 1.29 (1H, m), 1.61 - 1.72 (1H, m), 2.57 (2H, q, J = 7.7 Hz), 3.98 (3H, s), 6.89 (1H, s), 7.06 (1H, d, J = 9.3 Hz), 7.18 - 7.22 (1H, m), 7.35 - 7.42 (1H, m), 7.50 - 7.53 (1H, m), 7.92 (1H, s), 8.03 (1H, d, J = 9.3 Hz), 10.10 (1H, s), 10.98 (1H, s).

Example 250

Production of 3-methoxy-1-methyl-N-{2-methyl-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1H-pyrazole-5-carboxamide



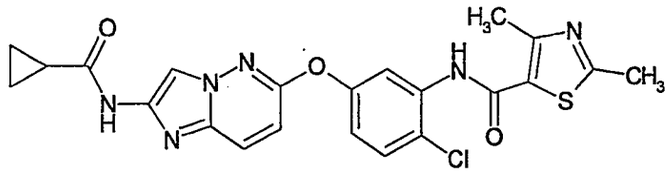
Using 3-methoxy-1-methyl-1H-pyrazole-5-carboxylic acid (194 mg, 1.24 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (109 μL, 1.22 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide (300 mg, 0.89 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (291 mg, 69%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.71 (1H, m), 0.95 - 1.04 (1H, m), 1.06 - 1.09 (3H, m), 1.19 -1.26 (1H, m), 1.62 - 1.72 (1H, m), 2.24 (3H, s), 3.79 (3H, s), 3.91 (3H, s), 6.45 (1H, s), 7.03 (1H, d, J = 9.3 Hz), 7.09 (1H, dd, J = 8.3, 2.6 Hz), 7.25 (1H, d, J = 2.6 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.91 (1H, s), 8.02 (1H, d, J

= 9.6 Hz), 9.84 (1H, s), 10.97 (1H, s).

Example 251

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide

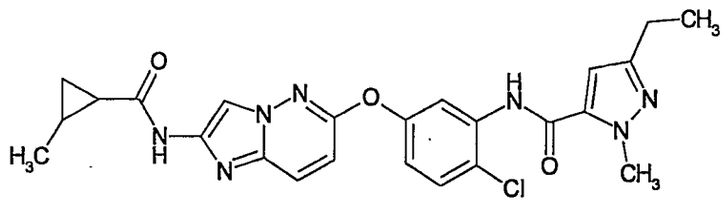


Using 2,4-dimethyl-1,3-thiazole-5-carboxylic acid (192 mg, 1.22 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (107 μL, 1.22 mmol), N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.87 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (206 mg, 49%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.82 (4H, m), 1.83 - 1.97 (1H, m), 2.59 (3H, s), 2.64 (3H, s), 7.08 (1H, d, J = 9.5 Hz), 7.20 - 7.24 (1H, m), 7.59 - 7.63 (2H,m), 7.94 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 9.78 (1H, s), 11.07 (1H, s).

Example 252

Production of N-{2-chloro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide



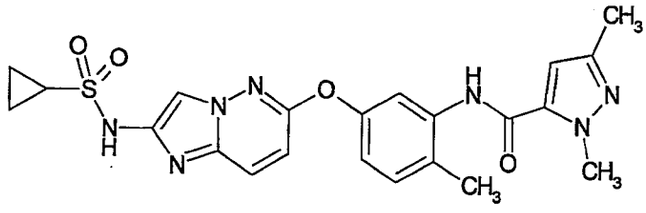
Using 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (181 mg, 1.17 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (102 μL, 1.17 mmol), N-[6-

(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide (300 mg, 0.84 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (207 mg, 50%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.73 (1H, m), 0.97 - 1.04 (1H, m), 1.05 - 1.09 (3H, m), 1.16 - 1.25 (1H, m), 1.19 (3H, t, J = 7.5 Hz), 1.62 -1.73 (1H, m), 2.55 (2H, q, J = 7.5 Hz), 3.99 (3H, s), 6.88 (1H, s), 7.08 (1H, d, J = 9.5 Hz), 7.21 - 7.27 (1H, m), 7.53 (1H, d, J = 3.0 Hz), 7.62 (1H, d, J = 8.7 Hz), 7.94 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 10.00 (1H, s), 10.99 (1H, s).

Example 253

Production of N-[5-({2-[(cyclopropylsulfonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

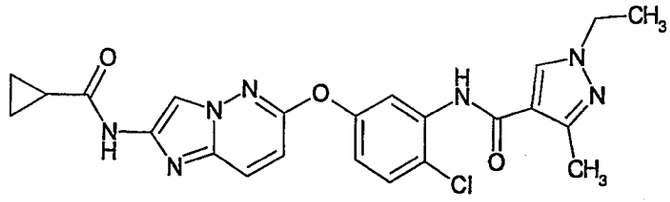


To a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-fluorophenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide·hydrochloride (400 mg, 0.97 mmol) in 1-methyl-2-pyrrolidone (4.0 mL) were added triethylamine(404 μL, 2.90 mmol) and cyclopropanesulfonyl chloride (204 mg, 1.45 mmol), and the mixture was stirred at 70°C for 16 hr. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate alone) and recrystallized from hexane/ethyl acetate to give the title compound (74 mg, 16%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.84 - 1.03 (4H, m), 2.19 (3H,s), 2.25 (3H, s), 2.72 - 2.86 (1H, m), 3.97 (3H, s), 6.80 (1H, s), 7.05 - 7.12 (2H, m), 7.26 - 7.29 (1H, m), 7.34 (1H, d, J = 8.4 Hz), 7.61 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 9.79 (1H, s), 10.29 (1H, s).

Example 254

Production of N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide

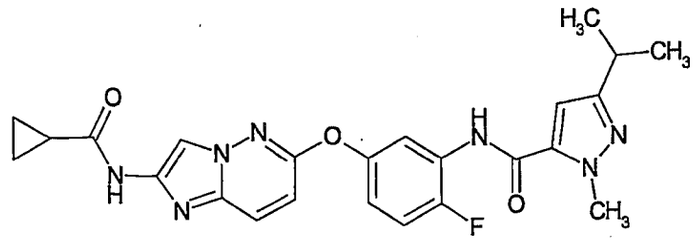


Using 1-ethyl-3-methyl-1H-pyrazole-4-carboxylic acid (188 mg, 1.22 mmol), tetrahydrofuran(4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (107 μL, 1.22 mmol), N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.87 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (135 mg, 33%) was obtained as a white powder. melting point 200°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.83 (4H, m), 1.38 (3H, t, J = 7.2 Hz), 1.78 -1.96 (1H, m), 2.35 (3H, s), 4.09 (2H, q, J = 7.2 Hz), 7.08 (1H, d, J = 9.6 Hz), 7.15 (1H, dd, J = 8.9, 3.0 Hz), 7.62 (1H, d, J = 8.9 Hz), 7.65 (1H, d, J = 3.0 Hz), 7.95 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 8.36 (1H, s), 9.30 (1H, s), 11.06 (1H, s).

Example 255

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-isopropyl-1-methyl-1H-pyrazole-5-carboxamide

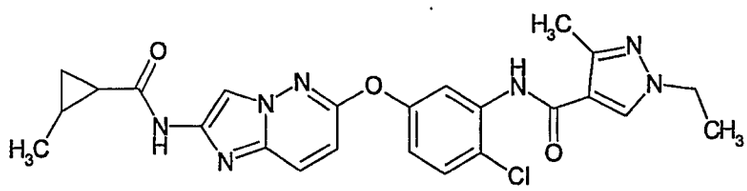


To a solution of 3-isopropyl-1-methyl-1H-pyrazole-5-carboxylic acid (144 mg, 0.86 mmol) in tetrahydrofuran (3.0 mL) were added N,N-dimethylformamide (30 μL, 0.39 mmol) and oxalyl chloride (75 μL, 0.86 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) in N,N-dimethylacetamide (4.0 mL), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran, washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate to give the title compound (216 mg, 74%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.21 (6H, d, J = 6.6 Hz), 1.85 - 1.96 (1H, m), 2.83 -2.96 (1H, m), 3.98 (3H, s), 6.91 (1H, s), 7.06 (1H, d, J = 9.3 Hz), 7.17 - 7.22 (1H, m), 7.35 - 7.42 (1H, m), 7.50 - 7.54 (1H, m), 7.93 (1H, s), 8.03 (1H, d, J = 9.3 Hz), 10.10 (1H, s), 11.06 (1H, s).

Example 256

Production of N-{2-chloro-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide



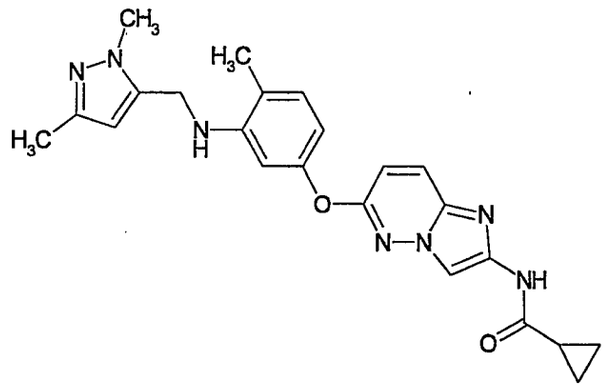
Using 1-ethyl-3-methyl-1H-pyrazole-4-carboxylic acid (181

mg, 1.17 mmol), tetrahydrofuran (4.5 mL), N,N-dimethylformamide (30 μL, 0.39 mmol), oxalyl chloride (102 μL, 1.17 mmol), N-[6-(3-amino-4-chlorophenoxy)imidazo[1,2-b]pyridazin-2-yl]-2-methylcyclopropanecarboxamide (300 mg, 0.84 mmol) and N,N-dimethylacetamide (6.0 mL), and in the same manner as in Example 249, the title compound (118 mg, 28%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.61 - 0.69 (1H, m), 0.96 - 1.04 (1H, m), 1.06 - 1.10 (3H, m), 1.18 - 1.29 (1H, m), 1.38 (3H, t, J = 7.2 Hz), 1.62 -1.71 (1H, m), 2.35 (3H, s), 4.09 (2H, q, J = 7.2 Hz), 7.07 (1H, d, J = 9.6 Hz), 7.15 (1H, dd, J = 8.9, 3.2 Hz), 7.58 (1H, d, J = 8.9 Hz), 7.64 (1H, d, J = 3.2 Hz), 7.93 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 8.36 (1H, s), 9.30 (1H, s), 10.99 (1H, s).

Example 257

Production of N-[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



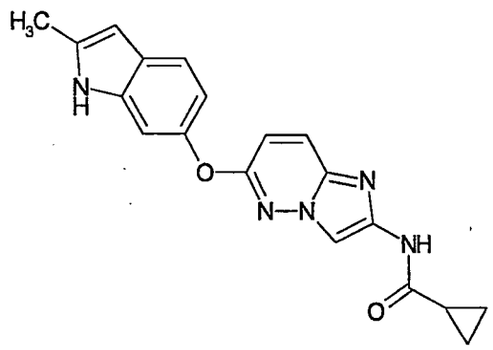
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (210 mg, 0.64 mmol), 3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}-4-methylphenol (220 mg, 0.96 mmol), potassium carbonate (220 mg, 1.6 mmol) and N,N-dimethylformamide (1.5 mL) was stirred under microwave irradiation at 150°C for 40 min. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue, the aqueous layer was extracted with

ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methanol/ethyl acetate=0/100→5/95) to give the title compound (200 mg, 72%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.87 - 1.96 (1H, m), 2.00 (3H, s), 2.11 (3H, s), 3.68 (3H, s), 4.26 (2H, d, J = 5.7 Hz), 5.64 (1H, t, J = 5.7 Hz), 5.80 (1H, s), 6.34 (1H, dd, J = 7.9, 2.3 Hz), 6.40 (1H, d, J = 2.3 Hz), 6.89 (1H, d, J = 9.8 Hz), 7.01 (1H, d, J = 8.5 Hz), 7.91 - 8.01 (2H, m), 11.07 (1H, s).

Example 258

Production of N-{6-[(2-methyl-1H-indol-6-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



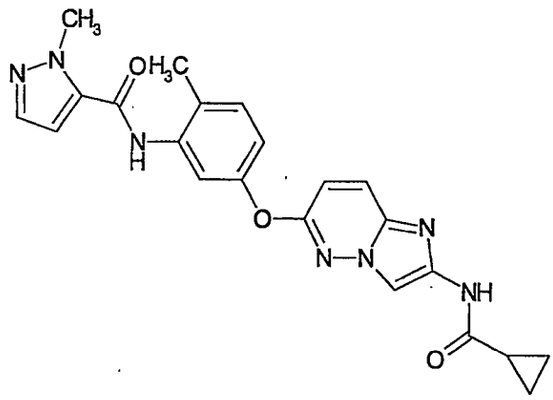
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (360 mg, 1.1 mmol), 2-methyl-1H-indole-6-ol (320 mg, 2.2 mmol), potassium carbonate (450 mg, 3.3 mmol) and N,N-dimethylformamide (4 mL) was stirred at 120°C for 24 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography

(ethyl acetate/hexane=20/80→90/10) to give the title compound (140 mg, 36%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.84 - 1.97 (1H, m), 2.39 (3H, s), 6.15 (1H, s), 6.81 (1H, dd, J = 8.5, 2.1 Hz), 6.96 (1H, d, J = 9.8 Hz), 7.13 (1H, d, J = 2.1 Hz), 7.42 (1H, d, J = 8.5 Hz), 7.90 (1H, s), 7.97 (1H, d, J = 9.8 Hz), 11.00 (1H, s), 11.04 (1H, s).

Example 259

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-pyrazole-5-carboxamide

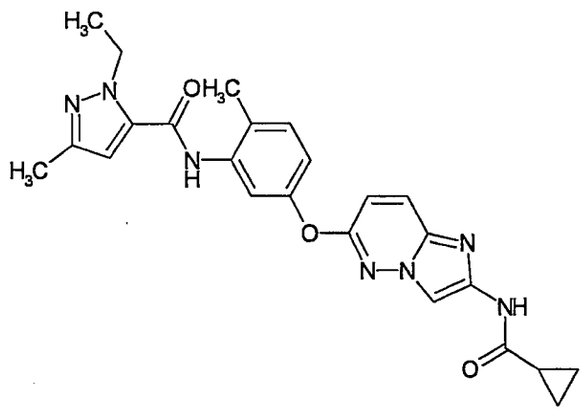


To a solution of 1-methyl-1H-pyrazole-5-carboxylic acid (106 mg, 0.84 mmol) in tetrahydrofuran (5 mL) were added N,N-dimethylformamide (1 drop), oxalyl chloride (91 μL, 1.0 mmol), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, and the obtained 1-methyl-1H-pyrazole-5-carbonylchloride was dissolved in N, N-dimethylacetamide (2 mL). This was added to a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (210 mg, 0.65 mmol) in N,N-dimethylacetamide (5 mL), and the mixture was stirred at room temperature for 30 min. To the mixture were added ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer

was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→90/10) to give the title compound (230 mg, 83%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.87 - 1.97 (1H, m), 2.25 (3H, s), 4.05 (3H, s), 7.00 - 7.07 (2H, m), 7.11 (1H, dd, J = 8.3, 2.3 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.36 (1H, d, J = 8.3 Hz), 7.53 (1H, d, J = 2.3 Hz), 7.93 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.91 (1H, s), 11.07 (1H, s).

Example 260

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide

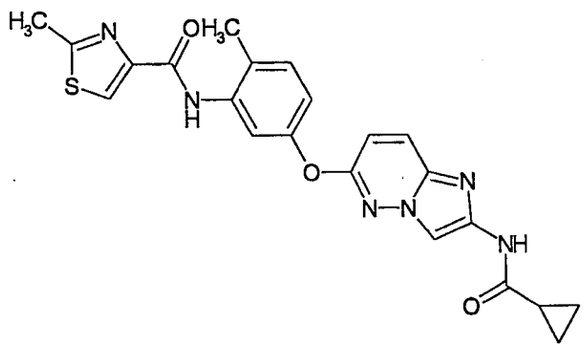


In the same manner as in Example 259 and using 1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid (130 mg, 0.84 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (91 μL, 1.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (210 mg, 0.65 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (220 mg, 75%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.83 (4H, m), 1.26 (3H, t, J = 7.1 Hz), 1.84 - 1.95 (1H, m), 2.18 (3H, s), 2.23 (3H, s), 4.39 (2H, q, J = 7.1 Hz), 6.78 (1H, s), 7.02 (1H, d, J = 9.6 Hz),

7.08 (1H, dd, J = 8.2, 2.7 Hz), 7.26 (1H, d, J = 2.7 Hz), 7.32 (1H, d, J = 8.2 Hz), 7.91 (1H, s), 8.01 (1H, d, J = 9.6 Hz), 9.79 (1H, s), 11.05 (1H, s).

Example 261

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2-methyl-1,3-thiazole-4-carboxamide



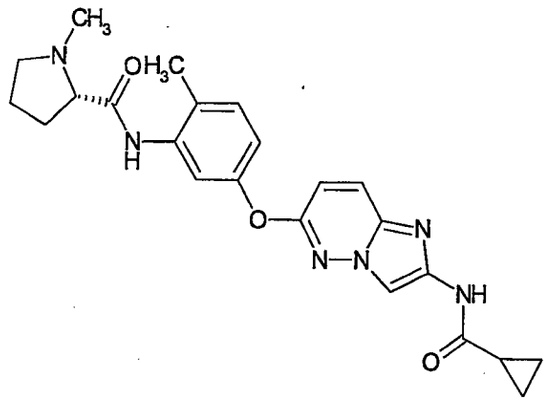
A mixture of 2-methyl-1,3-thiazole-4-carboxylic acid (120 mg, 0.84 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (210 mg, 0.65 mmol), 1-hydroxybenzotriazole (110 mg, 0.84 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (160 mg, 0.84 mmol), triethylamine (85 mg, 0.84 mmol) and N,N-dimethylformamide (5 mL) was stirred at room temperature for 16 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→100/0) to give the title compound (180 mg, 62%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.82 (4H, m), 1.82 - 1.94 (1H, m), 2.27 (3H, s), 2.72 (3H, s), 6.95 - 7.07 (2H, m), 7.32 (1H, d, J = 8.8 Hz), 7.65 (1H, d, J = 2.7 Hz), 7.93 (1H, s), 8.01 (1H, d,

J = 9.6 Hz), 8.25 (1H, s), 9.73 (1H, s), 11.06 (1H, s).

Example 262

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-L-prolinamide



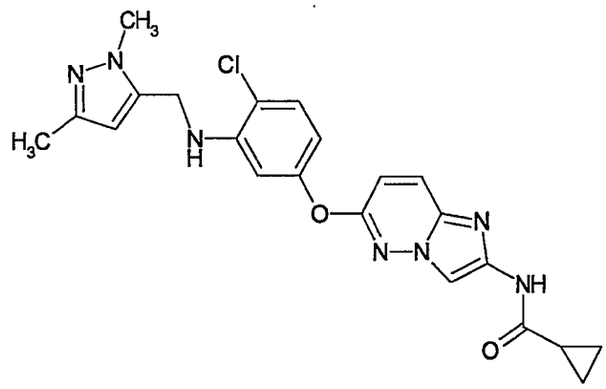
A mixture of 1-methyl-L-proline (170 mg, 1.3 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (210 mg, 0.65 mmol), 1-hydroxybenzotriazole (175 mg, 1.3 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (490 mg, 1.3 mmol), N,N-diisopropylethylamine (330 mg, 2.6 mmol) and N,N-dimethylformamide (15 mL) was stirred at room temperature for 18 hr, and then at 40°C for 4 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue, the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (methanol/ethyl acetate=0/100→10/90) to give the title compound (15 mg, 5%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.69 - 1.86 (3H, m), 1.87 - 1.99 (1H, m), 2.11 - 2.22 (1H, m), 2.23 (3H, s), 2.38 (1H, d, J = 8.0 Hz), 2.43 (3H, s), 2.95 (1H, dd, J = 10.0, 4.7 Hz), 3.16 (1H, dd, J = 7.4, 4.7 Hz), 6.95 (1H, dd, J = 8.3, 2.7 Hz), 7.02 (1H, d, J = 9.5 Hz), 7.29 (1H, d, J = 8.3 Hz), 7.77

(1H, d, J = 2.7 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.61 (1H, s), 11.07 (1H, s).

Example 263

Production of N-[6-(4-chloro-3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

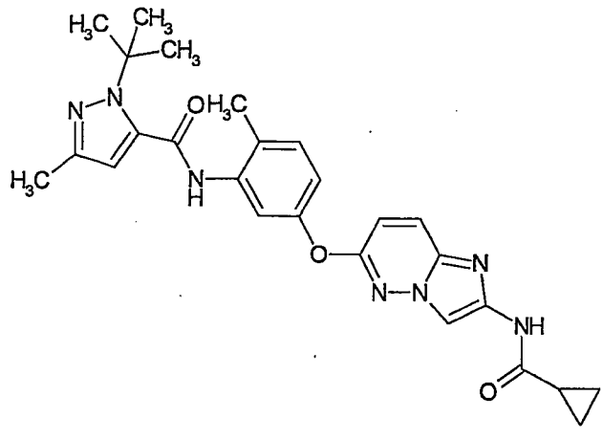


In the same manner as in Example 257 and using N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (210 mg, 0.65 mmol), 4-chloro-3-{[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]amino}phenol(240 mg, 0.97 mmol), potassium carbonate (220 mg, 1.6 mmol) and N,N-dimethylformamide (1.5 mL) as starting materials, the title compound (180 mg, 61%) was obtained as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.86 - 1.91 (1H, m), 1.98 (3H, s), 3.68 (3H, s), 4.35 (2H, d, J = 6.1 Hz), 5.78 (1H, s), 6.11 (1H, t, J = 6.1 Hz), 6.46 (1H, dd, J = 8.7, 2.7 Hz), 6.61 (1H, d, J = 2.7 Hz), 6.96 (1H, d, J = 9.5 Hz), 7.30 (1H, d, J = 8.7 Hz), 7.93 - 8.03 (2H, m), 11.06 (1H, s).

Example 264

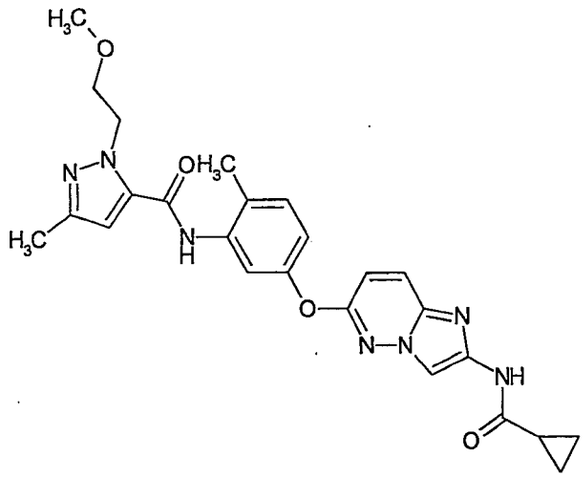
Production of 1-tert-butyl-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methyl-1H-pyrazole-5-carboxamide



To a solution of N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (210 mg, 0.65 mmol) in N,N-dimethylacetamide (5 mL) was added a solution of 1-tert-butyl-3-methyl-1H-pyrazole-5-carbonylchloride (160 mg, 0.78 mmol) in N,N-dimethylacetamide (1 mL), and the mixture was stirred at room temperature for 30 min. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the mixture, the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→90/10) to give the title compound (14 mg, 4%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.60 (9H, s), 1.86 - 1.98 (1H, m), 2.19 (3H, s), 2.27 (3H, s), 6.45 (1H, s), 6.99 - 7.15 (2H, m), 7.27 - 7.41 (2H, m), 7.91 - 7.97 (1H, m), 8.02 (1H, d, J = 9.8 Hz), 10.05 (1H, s), 11.05 (1H, s).

Example 265

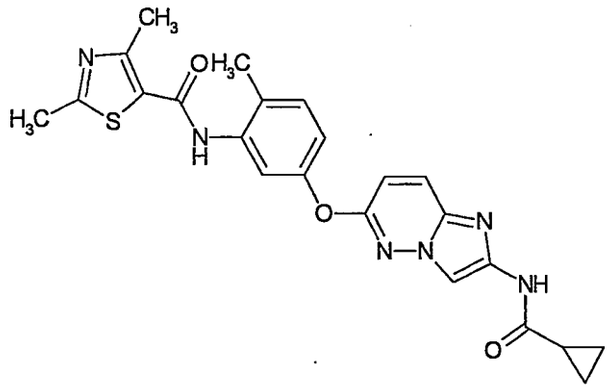
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxamide



In the same manner as in Example 259 and using 1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxylic acid (150 mg, 0.80 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (83 μL, 0.97 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (230 mg, 77%) was obtained as a pale-green solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.85 - 1.98 (1H, m), 2.20 (3H, s), 2.25 (3H, s), 3.17 (3H, s), 3.62 (2H, t, J = 5.5 Hz), 4.56 (2H, t, J = 5.5 Hz), 6.76 (1H, s), 7.04 (1H, d, J = 9.5 Hz), 7.10 (1H, dd, J = 8.3, 2.3 Hz), 7.26 (1H, d, J = 2.3 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.93 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.82 (1H, s), 11.05 (1H, s).

Example 266

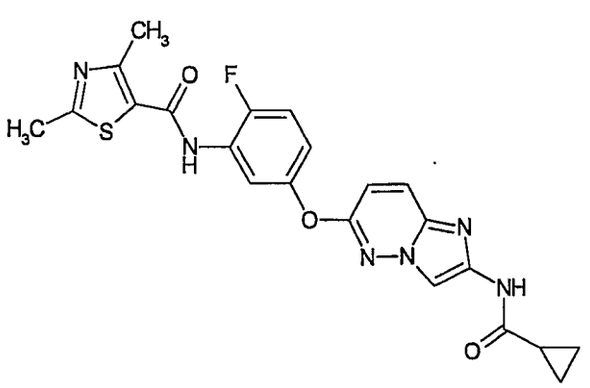
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide



In the same manner as in Example 261 and using 2,4-dimethyl-1,3-thiazole-5-carboxylic acid (130 mg, 0.80 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), 1-hydroxybenzotriazole(110 mg, 0.80 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (150 mg, 0.80 mmol), triethylamine (94 mg, 0.93 mmol) and N,N-dimethylformamide (5 mL) as starting materials, the title compound (120 mg, 41%) was obtained as a pale-yellow solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 2.26 (3H, s), 2.57 (3H, s), 2.64 (3H, s), 7.03 (1H, d, J = 9.5 Hz), 7.08 (1H, dd, J = 8.3, 2.3 Hz), 7.30 - 7.37 (2H, m), 7.93 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.62 (1H, s), 11.06 (1H, s).

Example 267

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide

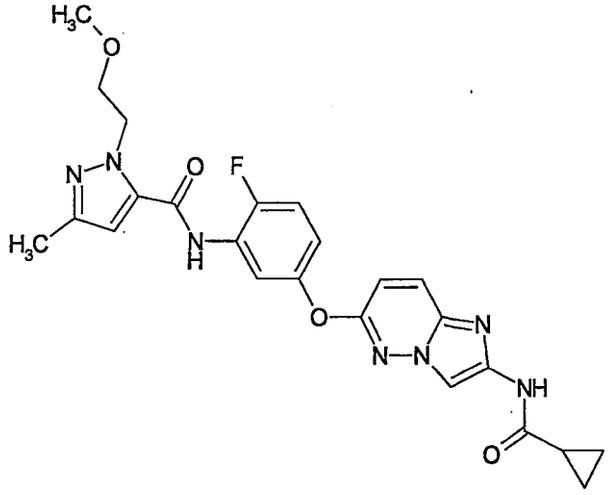


In the same manner as in Example 261 and using 2,4-dimethyl-1,3-thiazole-5-carboxylic acid (190 mg, 1.2 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), 1-hydroxybenzotriazole (170 mg, 1.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg, 1.2 mmol), N, N-diisopropylethylamine(240 mg, 1.9 mmol) and N,N-dimethylformamide (5 mL) as starting materials, the title compound (93 mg, 32%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 2.56 (3H, s), 2.65 (3H, s), 7.07 (1H, d, J = 9.8 Hz), 7.14 - 7.23 (1H, m), 7.33 - 7.44 (1H, m), 7.58 (1H, dd, J = 6.2, 2.8 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.8 Hz), 9.94 (1H, s), 11.06 (1H, s).

Example 268

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxamide

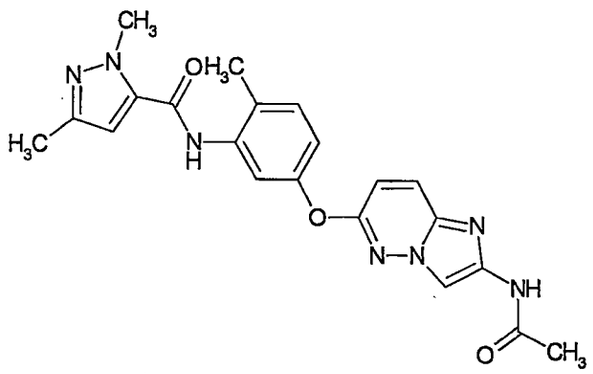


In the same manner as in Example 259 and using 1-(2-methoxyethyl)-3-methyl-1H-pyrazole-5-carboxylic acid (150 mg, 0.80 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (83 μL, 0.97 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-

dimethylacetamide (7 mL) as starting materials, the title compound (230 mg, 77%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.82 (4H, m), 1.85 - 1.97 (1H, m), 2.19 (3H, s), 3.30 (3H, s), 3.63 (2H, t, J = 5.7 Hz), 4.56 (2H, t, J = 5.7 Hz), 6.81 (1H, s), 7.07 (1H, d, J = 9.5 Hz), 7.17 - 7.25 (1H, m), 7.35 - 7.44 (1H, m), 7.54 (1H, dd, J = 6.2, 2.8 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.5 Hz), 10.12 (1H, s), 11.06 (1H, s).

Example 269

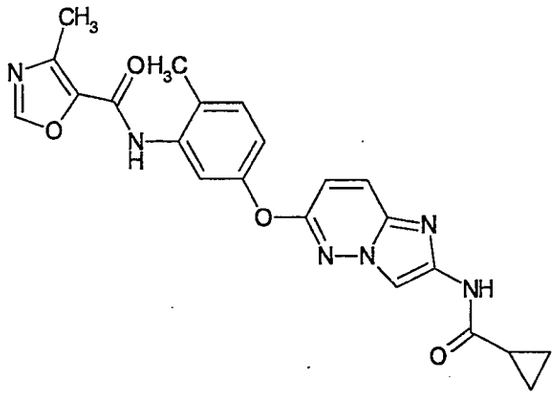
Production of N-(5-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



In the same manner as in Example 264 and using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (840 mg, 2.8 mmol), 1,3-dimethyl-1H-pyrazole-5-carbonylchloride (540 mg, 3.4 mmol) and N,N-dimethylacetamide (35 mL), the title compound (910 mg, 77%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 2.18 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.04 (1H, d, J = 9.8 Hz), 7.10 (1H, dd, J = 8.3, 2.7 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.95 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 9.79 (1H, s), 10.78 (1H, s).

Example 270

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-oxazole-5-carboxamide

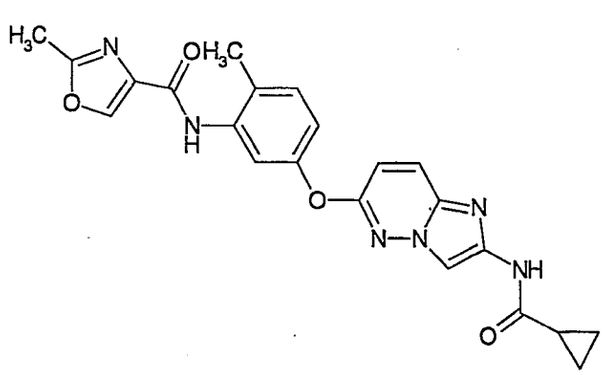


In the same manner as in Example 259 and using 4-methyl-1,3-oxazole-5-carboxylic acid (77 mg, 0.60 mmol), tetrahydrofuran (10 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (62 μL, 0.72 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (170 mg, 83%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.86 - 1.98 (1H, m), 2.25 (3H, s), 2.41 (3H, s), 7.04 (1H, d, J = 9.5 Hz), 7.09 (1H, dd, J = 8.1, 2.5 Hz), 7.29 - 7.39 (2H, m), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 8.51 (1H, s), 9.82 (1H, s), 11.06 (1H, s).

Example 271

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2-methyl-1,3-oxazole-4-carboxamide

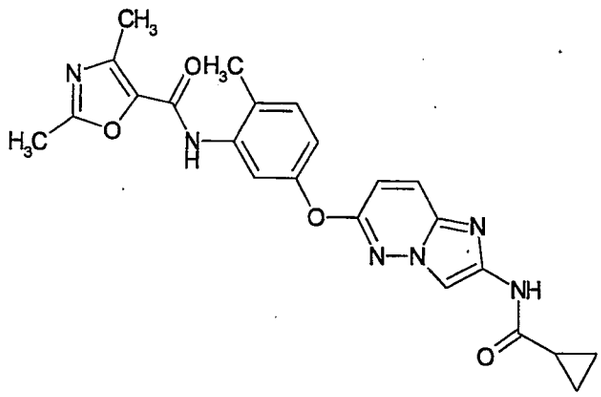


In the same manner as in Example 259 and using 2-methyl-

1,3-oxazole-4-carboxylic acid (77 mg, 0.60 mmol), tetrahydrofuran (10 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (62 μL, 0.72 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (150 mg, 74%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.87 - 1.96 (1H, m), 2.27 (3H, s), 2.51 (3H, s), 6.99 - 7.07 (2H, m), 7.32 (1H, d, J = 8.7 Hz), 7.54 (1H, d, J = 2.7 Hz), 7.94 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 8.62 (1H, s), 9.54 (1H, s), 11.06 (1H, s).

Example 272

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide

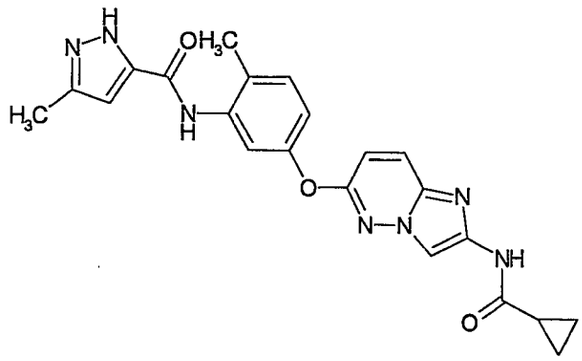


In the same manner as in Example 259 and using 2,4-dimethyl-1,3-oxazole-5-carboxylic acid (85 mg, 0.60 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (62 μL, 0.72 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (170 mg, 81%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 2.24 (3H, s), 2.34 (3H, s), 2.48 (3H, s), 7.03 (1H, d, J = 9.5 Hz), 7.08 (1H, dd, J = 8.3, 2.7 Hz), 7.29 (1H, d, J = 2.7

Hz), 7.33 (1H, d, J = 8.3 Hz), 7.94 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.70 (1H, s), 11.06 (1H, s).

Example 273

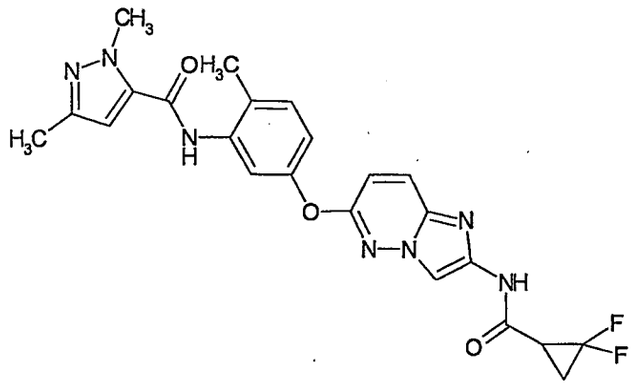
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methyl-1H-pyrazole-5-carboxamide



In the same manner as in Example 261 and using 3-methyl-1H-pyrazole-5-carboxylic acid (160 mg, 1.2 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol), 1-hydroxybenzotriazole (170 mg, 1.2 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (240 mg, 1.2 mmol), triethylamine (190 mg, 1.9 mmol) and N,N-dimethylformamide (3 mL) as starting materials, the title compound (190 mg, 70%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.87 - 1.97 (1H, m), 2.29 (6H, s), 6.49 (1H, s), 6.99 (1H, dd, J = 8.3, 2.7 Hz), 7.03 (1H, d, J = 9.5 Hz), 7.31 (1H, d, J = 8.3 Hz), 7.68 (1H, d, J = 2.7 Hz), 7.94 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.36 (1H, s), 11.06 (1H, s), 13.09 (1H, s).

Example 274

Production of N-{5-[(2-{[(2,2-difluorocyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

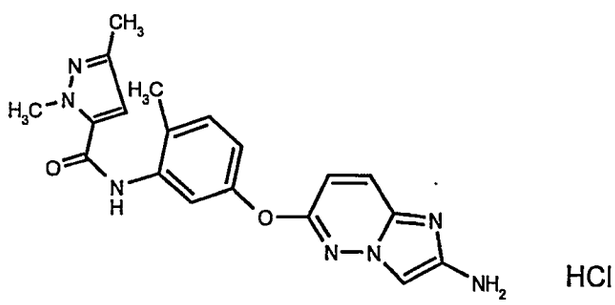


In the same manner as in Example 259 and using 2,2-difluorocyclopropanecarboxylic acid (88 mg, 0.60 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (74 μL, 0.86 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (250 mg, 0.60 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (210 mg, 73%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.95 - 2.09 (2H, m), 2.19 (3H, s), 2.25 (3H, s), 2.86 - 2.96 (1H, m), 3.98 (3H, s), 6.81 (1H, s), 7.05 - 7.13 (2H, m), 7.29 (1H, d, J = 2.3 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.96 (1H, s), 8.06 (1H, d, J = 9.8 Hz), 9.79 (1H, s), 11.29 (1H, s).

Example 275

Production of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride



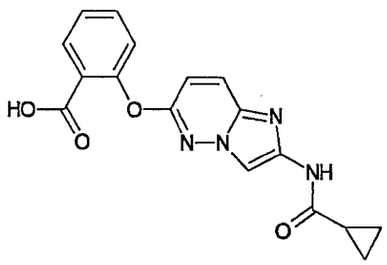
To a suspension of N-(5-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-

5-carboxamide (310 mg, 0.73 mmol) in methanol (10 mL) was added 4N hydrochloric acid/ethyl acetate (10 mL, 40 mmol), and the mixture was stirred at room temperature for 16 hr. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/tetrahydrofuran, and then with diethyl ether to give the title compound (240 mg, 78%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.18 (3H, s), 2.27 (3H, s), 3.97 (3H, s), 6.90 (1H, s), 7.12 (1H, dd, J = 8.3, 2.3 Hz), 7.29 - 7.41 (3H, m), 7.45 (1H, s), 8.20 (1H, d, J = 9.5 Hz), 9.94 (1H, s).

Example 276

Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid

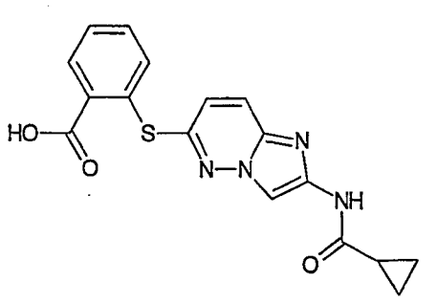


To a solution of ethyl salicylate (1010 mg, 6.1 mmol) in N,N-dimethylformamide (8 mL) was added potassium tert-butoxide (840 mg, 6.4 mmol) at 0°C, and the mixture was stirred at 0°C for 5 min and at room temperature for 25 min. To the reaction mixture were added N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (1.0 g, 3.1 mmol) and potassium carbonate (420 mg, 3.1 mmol), and the mixture was stirred at 100°C for 24 hr. The solvent was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→90/10) to give ethyl 2-({2-

[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoate (200 mg, 18%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.00 (3H, t, J = 7.2 Hz), 1.83 - 1.97 (1H, m), 4.08 (2H, q, J = 7.2 Hz), 7.09 (1H, d, J = 9.5 Hz), 7.39 - 7.51 (2H, m), 7.69 - 7.76 (1H, m), 7.80 (1H, s), 7.95 (1H, dd, J = 7.8, 1.7 Hz), 8.03 (1H, d, J = 9.5 Hz), 11.02 (1H, s).

To a solution of ethyl 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoate (200 mg, 0.54 mmol) in tetrahydrofuran (10 mL) was added 4N aqueous sodium hydroxide solution (1.5 mL), and the mixture was stirred at room temperature for 3 hr. 6N Hydrochloric acid (1.5 mL) and ethyl acetate were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (130 mg, 73%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.83 (4H, m), 1.84 - 1.96 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.35 - 7.46 (2H, m), 7.66 - 7.73 (1H, m), 7.81 (1H, s), 7.94 (1H, dd, J = 7.7, 1.7 Hz), 8.00 (1H, d, J = 9.6 Hz), 11.02 (1H, s).

Example 277
Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid



A mixture of methyl 2-mercaptobenzoate (1030 mg, 6.1 mmol), N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

(1.0 g, 3.1 mmol), potassium carbonate (1050 mg, 7.6 mmol) and N,N-dimethylformamide (10 mL) was stirred at 80°C for 7 hr. The mixture was evaporated under reduced pressure, and ethyl acetate/tetrahydrofuran and water were added to the residue. The aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→90/10) to give methyl 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoate (200 mg, 18%) as a brown solid.

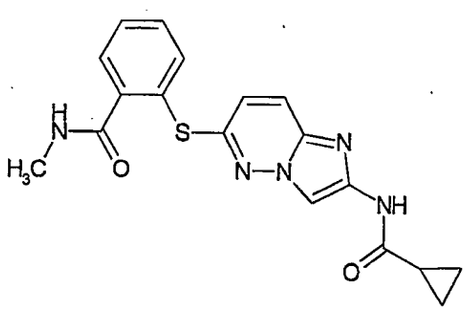
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.89 (4H, m), 1.90 - 2.00 (1H, m), 3.85 (3H, s), 7.16 (1H, d, J = 9.5 Hz), 7.28 (1H, d, J = 8.0 Hz), 7.39 - 7.46 (1H, m), 7.48 - 7.55 (1H, m), 7.90 - 8.00 (2H, m), 8.21 (1H, s), 11.21 (1H, s).

In the same manner as in Example 276 and using methyl 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoate (390 mg, 1.1 mmol) and 4N aqueous sodium hydroxide solution (2 mL) as starting materials, the title compound (340 mg, 92%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.91 (4H, m), 1.88 - 2.02 (1H, m), 7.15 - 7.21 (2H, m), 7.38 (1H, t, J = 6.8 Hz), 7.43 - 7.50 (1H, m), 7.89 - 8.01 (2H, m), 8.22 (1H, s), 11.21 (1H, s).

Example 278

Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)-N-methylbenzamide

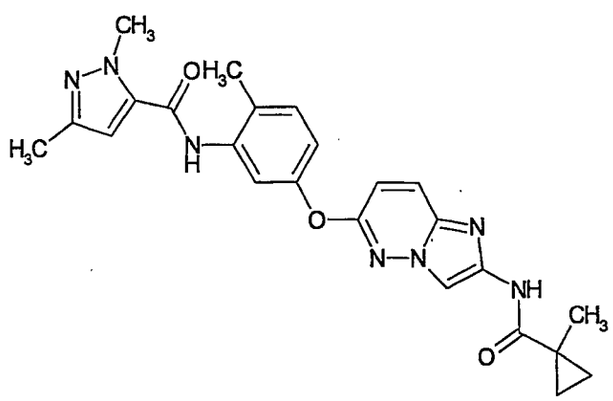


A mixture of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (120 mg, 0.35 mmol), a solution of methylamine in tetrahydrofuran (2M, 1 mL, 2.0 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (200 mg, 0.53 mmol) and N,N-dimethylformamide (4 mL) was stirred at room temperature for 5 hr. The mixture was evaporated under reduced pressure, ethyl acetate/tetrahydrofuran and water were added to the residue, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→90/10) to give the title compound (45 mg, 41%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.88 (4H, m), 1.89 - 1.97 (1H, m), 2.71 (3H, d, J = 4.5 Hz), 6.97 (1H, d, J = 9.5 Hz), 7.38 - 7.46 (3H, m), 7.49 - 7.56 (1H, m), 7.88 (1H, d, J = 9.5 Hz), 8.15 (1H, s), 8.40 (1H, t, J = 4.5 Hz), 11.15 (1H, s).

Example 279

Production of 1,3-dimethyl-N-{2-methyl-5-[(2-{[(1-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1H-pyrazole-5-carboxamide



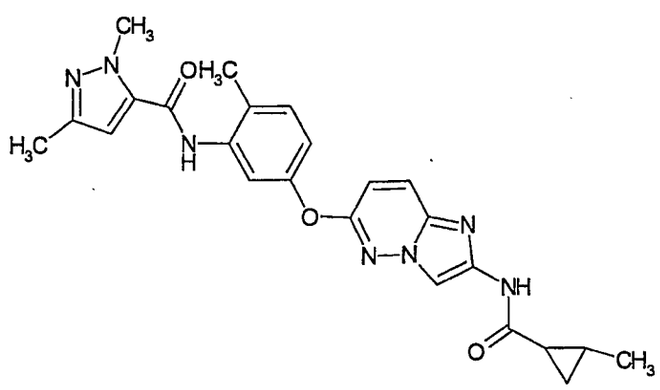
To a solution of 1-methylcyclopropanecarboxylic acid (97

mg, 0.97 mmol) in tetrahydrofuran (1.5 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (83 μL, 0.97 mmol), and the mixture was stirred at room temperature for 30 min. The reaction mixture was added to a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) in N,N-dimethylacetamide (5 mL), and the mixture was stirred at room temperature for 1 hr. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→100/0) to give the title compound (105 mg, 74%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.60 - 0.68 (2H, m), 1.09 - 1.15 (2H, m), 1.40 (3H, s), 2.19 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.05 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.7, 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.98 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 9.80 (1H, s), 10.15 (1H, s).

Example 280

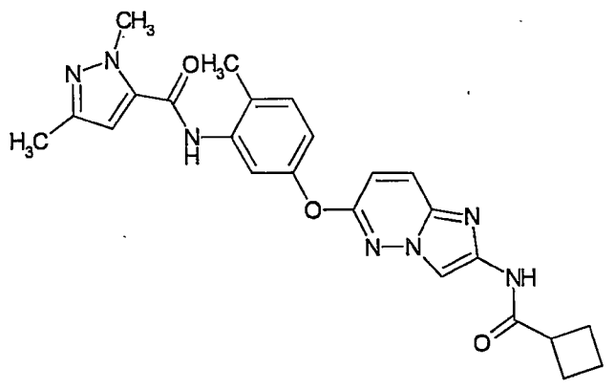
Production of 1,3-dimethyl-N-{2-methyl-5-[(2-{[(2-methylcyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1H-pyrazole-5-carboxamide



In the same manner as in Example 279 and using 2-methylcyclopropanecarboxylic acid (97 mg, 0.97 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (83 μL, 0.97 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (155 mg, 70%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.58 - 0.69 (1H, m), 0.93 - 1.04 (1H, m), 1.04 - 1.12 (3H, m), 1.17 - 1.28 (1H, m), 1.61 - 1.71 (1H, m), 2.20 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.03 (1H, d, J = 9.5 Hz), 7.09 (1H, dd, J = 8.3, 2.7 Hz), 7.27 (1H, d, J = 2.7 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.92 (1H, s), 8.02 (1H, d, J = 9.5 Hz), 9.79 (1H, s), 10.97 (1H, s).

Example 281

Production of N-[5-({2-[(cyclobutylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide

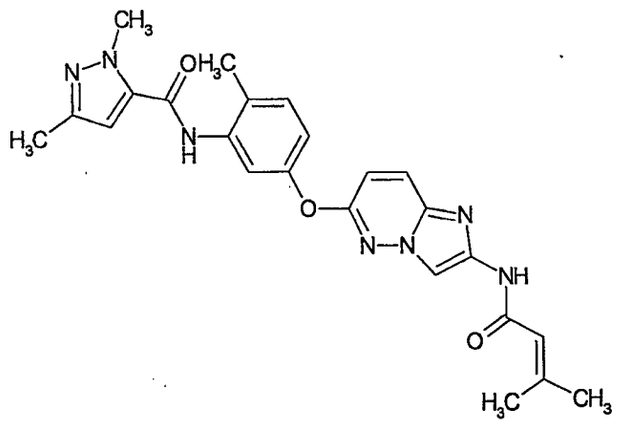


In the same manner as in Example 264 and using N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol), cyclobutanecarbonyl chloride (86 mg, 0.73 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (170 mg, 76%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.73 - 1.98 (3H, m), 2.01 - 2.22 (4H, m), 2.19 (3H, s), 2.25 (3H, s), 3.99 (3H, s), 6.81 (1H, s), 7.04

(1H, d, J = 9.8 Hz), 7.10 (1H, dd, J = 8.7, 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.96 - 8.06 (2H, m), 9.81 (1H, s), 10.64 (1H, s).

Example 282

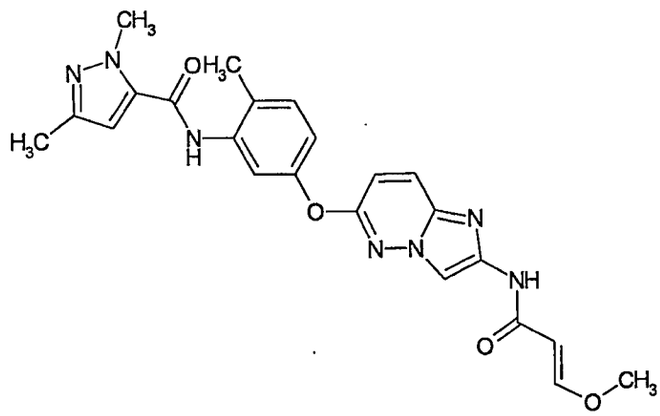
Production of 1,3-dimethyl-N-[2-methyl-5-({2-[(3-methylbut-2-enoyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-pyrazole-5-carboxamide



In the same manner as in Example 264 and using N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol), 3-methylbut-2-enoylchloride (81 μL, 0.73 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (150 mg, 68%) was obtained as a pale-yellow solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.85 (3H, s), 2.17 (3H, d, J = 0.8 Hz), 2.19 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 5.98 (1H, s), 6.81 (1H, s), 7.03 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.5, 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.35 (1H, d, J = 8.5 Hz), 7.96 - 8.05 (2H, m), 9.81 (1H, s), 10.69 (1H, s).

Example 283

Production of N-{5-[(2-{[(2E)-3-methoxyprop-2-enoyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

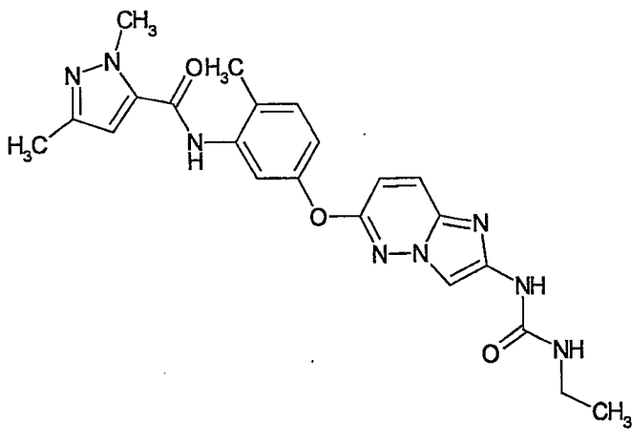


In the same manner as in Example 279 and using (2E)-3-methoxyacrylic acid (99 mg, 0.97 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (83 μL, 0.97 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (63 mg, 28%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 2.25 (3H, s), 3.68 (3H, s), 3.98 (3H, s), 5.68 (1H, d, J = 12.2 Hz), 6.83 (1H, s), 7.04 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.7, 2.6 Hz), 7.27 (1H, d, J = 2.6 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.54 (1H, d, J = 12.2 Hz), 7.96 - 8.07 (2H, m), 9.84 (1H, s), 10.61 (1H, s).

Example 284

Production of N-{5-[(2-{[(ethylamino)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

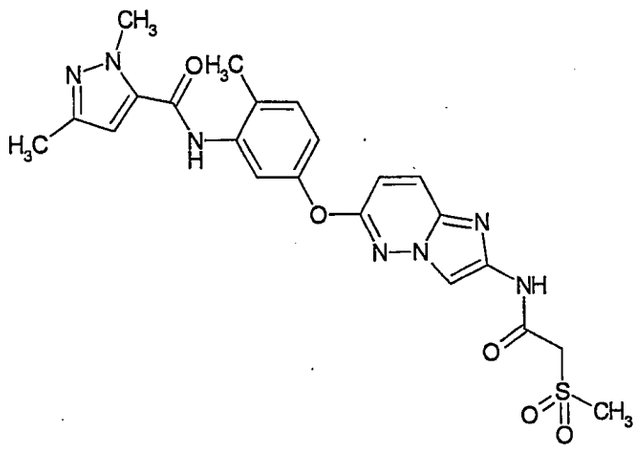


To a solution of N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) in pyridine (3 mL) was added ethyl isocyanate (380 μL, 4.8 mmol), and the mixture was stirred at room temperature for 2 hr. Ethyl acetate/tetrahydrofuran and water were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→100/0) to give the title compound (160 mg, 72%) as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.05 (3H, t, J = 7.2 Hz), 2.20 (3H, s), 2.24 (3H, s), 3.06 - 3.18 (2H, m), 3.98 (3H, s), 6.47 - 6.55 (1H, m), 6.81 (1H, s), 6.97 (1H, d, J = 9.6 Hz), 7.08 (1H, dd, J = 8.7, 2.6 Hz), 7.26 (1H, d, J = 2.6 Hz), 7.34 (1H, d, J = 8.7 Hz), 7.70 (1H, s), 7.95 (1H, d, J = 9.6 Hz), 8.99 (1H, s), 9.80 (1H, s).

Example 285

Production of 1,3-dimethyl-N-{2-methyl-5-[(2-{[(methylsulfonyl)acetyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-1H-pyrazole-5-carboxamide

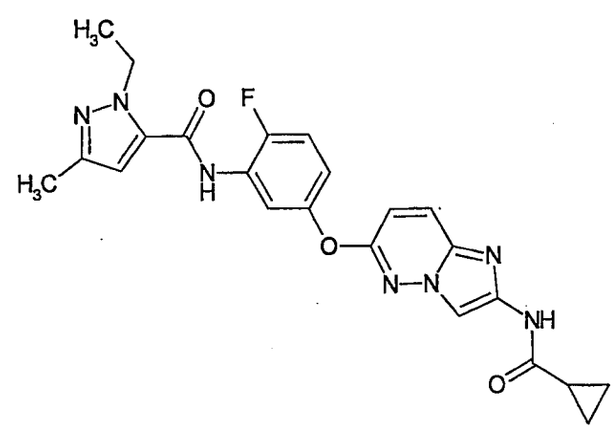


In the same manner as in Example 279 and using (methylsulfonyl)acetic acid (100 mg, 0.73 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (63 μL, 0.73 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (91 mg, 38%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.20 (3H, s), 2.25 (3H, s), 3.17 (3H, s), 3.99 (3H, s), 4.37 (2H, s), 6.81 (1H, s), 7.07 - 7.14 (2H, m), 7.29 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.7 Hz), 8.01 (1H, s), 8.08 (1H, d, J = 9.5 Hz), 9.79 (1H, s), 11.26 (1H, s).

Example 286

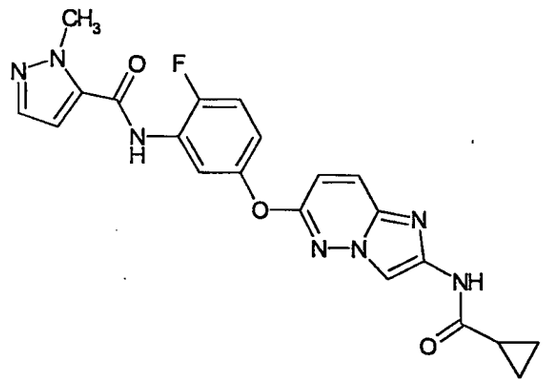
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide



365
415

In the same manner as in Example 259 and using 1-ethyl-3-methyl-1H-pyrazole-5-carboxylic acid (120 mg, 0.79 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (89 μL, 1.0 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (150 mg, 53%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.29 (3H, t, J = 7.0 Hz), 1.86 - 1.97 (1H, m), 2.21 (3H, s), 4.40 (2H, q, J = 7.0 Hz), 6.83 (1H, s), 7.07 (1H, d, J = 9.5 Hz), 7.16 - 7.25 (1H, m), 7.34 - 7.45 (1H, m), 7.54 (1H, dd, J = 6.4, 3.0 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.5 Hz), 10.08 (1H, s), 11.06 (1H, s).

Example 287
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide

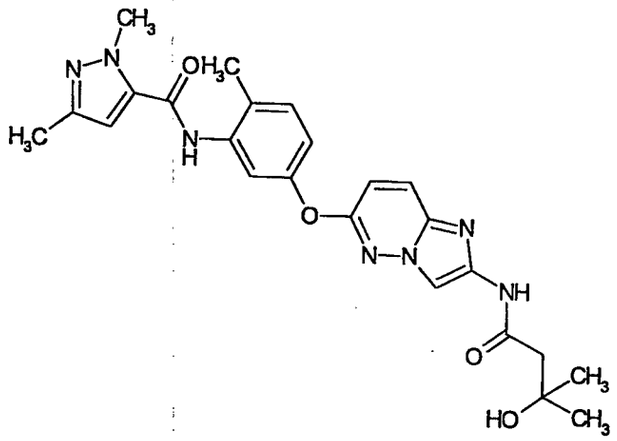


In the same manner as in Example 259 and using 1-methyl-1H-pyrazole-5-carboxylic acid (100 mg, 0.79 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (89 μL, 1.0 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (180 mg, 68%) was obtained as a white solid. melting point 253°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.87 - 1.98 (1H, m), 4.06 (3H, s), 7.07 (1H, d, J = 7.2 Hz), 7.09 (1H, s), 7.17 - 7.26 (1H, m), 7.34 - 7.46 (1H, m), 7.50 - 7.56 (2H, m), 7.94 (1H, s), 8.04 (1H, d, J = 9.8 Hz), 10.19 (1H, s), 11.06 (1H, s).

Example 288

Production of N-[5-({2-[(3-hydroxy-3-methylbutanoyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



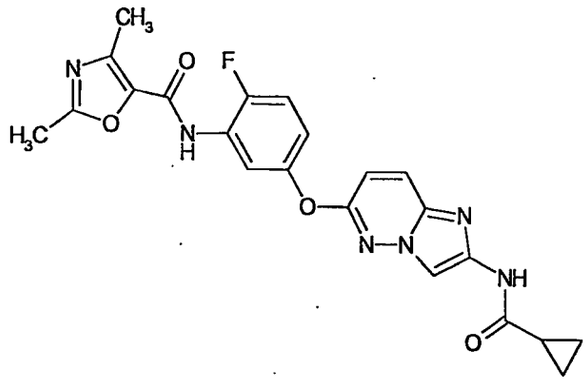
In the same manner as in Example 278 and using 3-hydroxy-3-methylbutanoic acid (74 mg, 0.63 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (240 mg, 0.63 mmol), N, N-diisopropylethylamine (190 mg, 1.5 mmol) and N,N-dimethylformamide (7 mL) as starting materials, the title compound (150 mg, 66%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.19 (6H, s), 2.19 (3H, s), 2.25 (3H, s), 2.48 (2H, s), 3.98 (3H, s), 4.76 (1H, s), 6.81 (1H, s), 6.99 - 7.14 (2H, m), 7.28 (1H, d, J = 2.3 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.94 - 8.06 (2H, m), 9.79 (1H, s), 10.58 (1H, s).

Example 289

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-

5-carboxamide

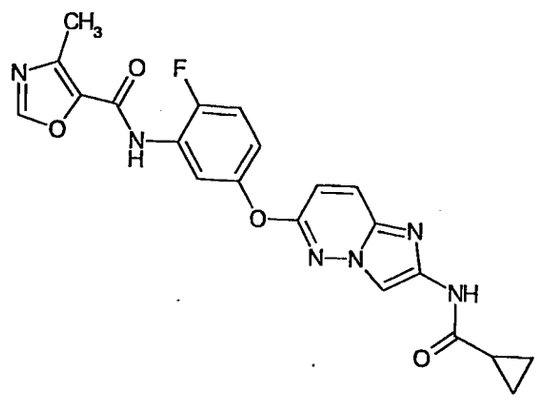


In the same manner as in Example 259 and using 2,4-dimethyl-1,3-oxazole-5-carboxylic acid (84 mg, 0.59 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (61 μL, 0.71 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (140 mg, 67%) was obtained as a white solid. melting point 202°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.84 - 1.98 (1H, m), 2.35 (3H, s), 2.48 (3H, s), 7.07 (1H, d, J = 9.6 Hz), 7.14 - 7.23 (1H, m), 7.39 (1H, dd, J = 10.0, 9.0 Hz), 7.56 (1H, dd, J = 6.4, 3.0 Hz), 7.95 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 9.95 (1H, s), 11.07 (1H, s).

Example 290

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-4-methyl-1,3-oxazole-5-carboxamide

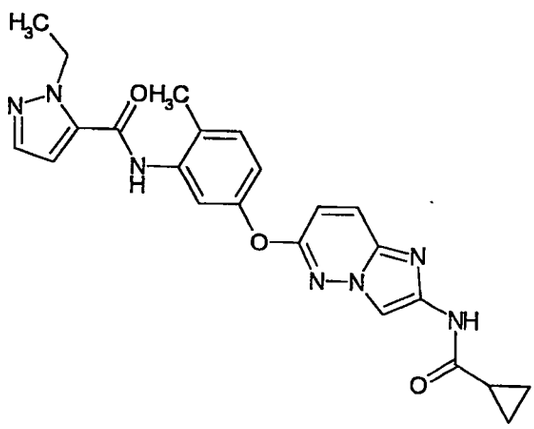


In the same manner as in Example 259 and using 4-methyl-1,3-oxazole-5-carboxylic acid (76 mg, 0.59 mmol), tetrahydrofuran (10 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (61 μL, 0.71 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N, N-dimethylacetamide (7 mL) as starting material, the title compound (170 mg, 84%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.85 - 1.97 (1H, m), 2.41 (3H, s), 7.07 (1H, d, J = 9.4 Hz), 7.16 - 7.25 (1H, m), 7.40 (1H, dd, J = 10.0, 9.0 Hz), 7.57 (1H, dd, J = 6.4, 3.0 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.4 Hz), 8.54 (1H, s), 10.10 (1H, s), 11.07 (1H, s).

Example 291

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-ethyl-1H-pyrazole-5-carboxamide

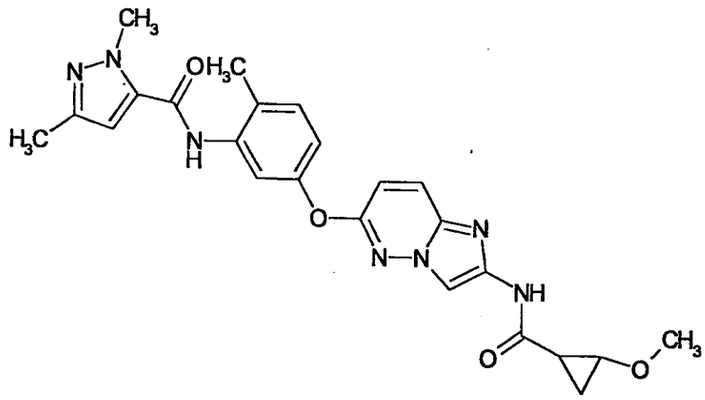


In the same manner as in Example 259 and using 1-ethyl-1H-pyrazole-5-carboxylic acid (110 mg, 0.80 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (83 μL, 0.97 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (210 mg, 75%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.32 (3H, t, J = 7.2 Hz), 1.86 - 1.96 (1H, m), 2.25 (3H, s), 4.50 (2H, q, J = 7.2 Hz), 7.02 - 7.07 (2H, m), 7.11 (1H, dd, J = 8.3, 2.4 Hz), 7.28 (1H, d, J = 2.4 Hz), 7.36 (1H, d, J = 8.3 Hz), 7.54 (1H, d, J = 2.1 Hz), 7.93 (1H, s), 8.03 (1H, d, J = 10.0 Hz), 9.92 (1H, s), 11.10 (1H, s).

Example 292

Production of N-{5-[(2-{[(2-methoxycyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide

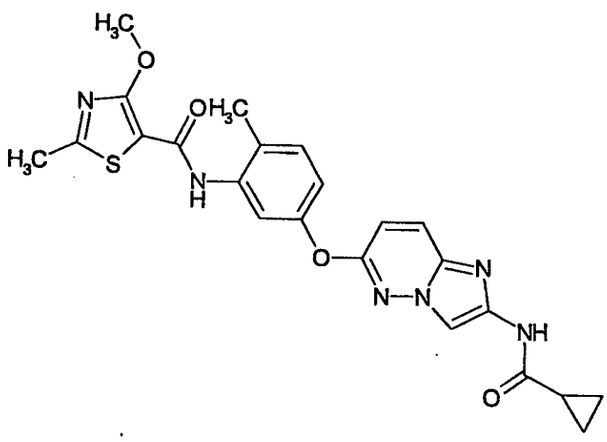


In the same manner as in Example 278 and using 2-methoxycyclopropanecarboxylic acid (86 mg, 0.74 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.49 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (280 mg, 0.74 mmol), N, N-diisopropylethylamine (190 mg, 1.5 mmol) and N,N-dimethylformamide (7 mL) as starting materials, the title compound (83 mg, 35%) was obtained as a pale-yellow solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.09 - 1.20 (2H, m), 2.03 - 2.13 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 3.30 (3H, s), 3.40 - 3.49 (1H, m), 3.97 (3H, s), 6.81 (1H, s), 7.04 (1H, d, J = 9.8 Hz), 7.09 (1H, dd, J = 8.3, 2.7 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.91 (1H, s), 8.03 (1H, d, J = 9.8 Hz), 9.79 (1H, s), 11.09 (1H, s).

Example 293

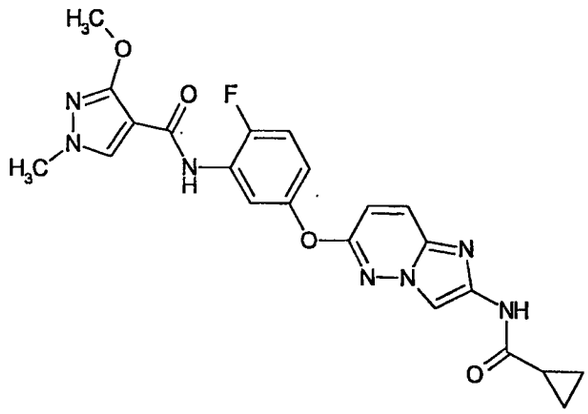
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methoxy-2-methyl-1,3-thiazole-5-carboxamide



In the same manner as in Example 259 and using 4-methoxy-2-methyl-1,3-thiazole-5-carboxylic acid (120 mg, 0.70 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (120 μL, 1.4 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (120 mg, 53%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.88 - 1.98 (1H, m), 2.32 (3H, s), 2.65 (3H, s), 4.18 (3H, s), 6.96 (1H, dd, J = 8.3, 2.7 Hz), 7.03 (1H, d, J = 9.8 Hz), 7.33 (1H, d, J = 8.3 Hz), 7.93 (1H, s), 7.97 (1H, d, J = 2.7 Hz), 8.02 (1H, d, J = 9.8 Hz), 9.05 (1H, s), 11.06 (1H, s).

Example 294

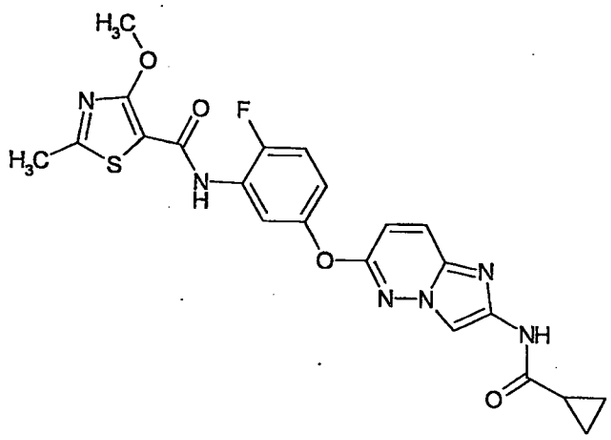
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-4-carboxamide



In the same manner as in Example 259 and using 3-methoxy-1-methyl-1H-pyrazole-4-carboxylic acid (93 mg, 0.60 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (61 μL, 0.72 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (59 mg, 28%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 3.75 (3H, s), 4.01 (3H, s), 6.97 - 7.09 (2H, m), 7.33 - 7.44 (1H, m), 7.94 (1H, s), 8.04 (1H, d, J = 9.8 Hz), 8.11 - 8.19 (2H, m), 8.94 (1H, d, J = 2.7 Hz), 11.07 (1H, s).

Example 295

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-4-methoxy-2-methyl-1,3-thiazole-5-carboxamide

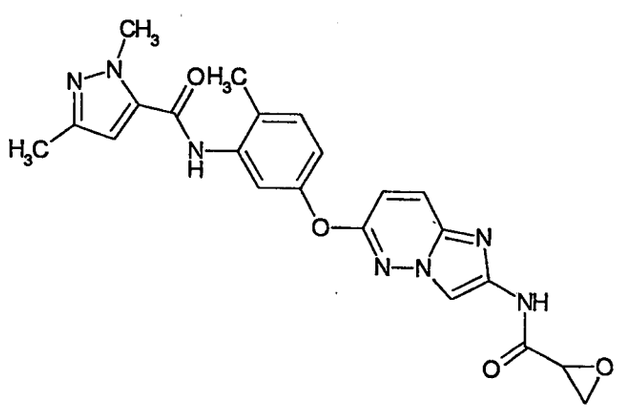


In the same manner as in Example 259 and using 4-methoxy-2-methyl-1,3-thiazole-5-carboxylic acid (100 mg, 0.60 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (61 μL, 0.72 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (89 mg, 40%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.88 - 1.96 (1H, m), 2.64 - 2.68 (3H, m), 4.18 (3H, s), 7.03 - 7.12 (2H, m), 7.42 (1H, dd, J = 10.6, 9.1 Hz), 7.93 (1H, s), 8.01 - 8.09 (2H, m), 9.27 (1H, s), 11.06 (1H, s).

Example 296

Production of 1,3-dimethyl-N-[2-methyl-5-({2-[(oxirane-2-ylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-pyrazole-5-carboxamide



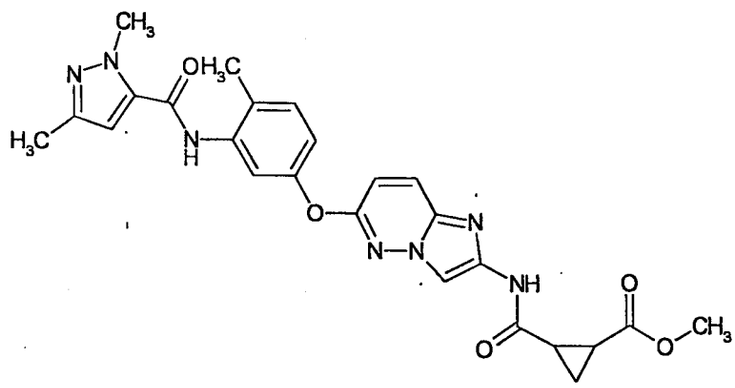
In the same manner as in Example 279 and using oxirane-2-

carboxylic acid (54 mg, 0.62 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (53 μL, 0.62 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (170 mg, 0.41 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (96 mg, 52%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.19 (3H, s), 2.25 (3H, s), 2.88 - 2.99 (2H, m), 3.64 - 3.70 (1H, m), 3.97 (3H, s), 6.81 (1H, s), 7.04 - 7.16 (2H, m), 7.29 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.99 (1H, s), 8.07 (1H, d, J = 9.8 Hz), 9.79 (1H, br. s), 11.30 (1H, br. s).

Example 297

Production of methyl 2-({[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}carbonyl)cyclopropanecarboxylate



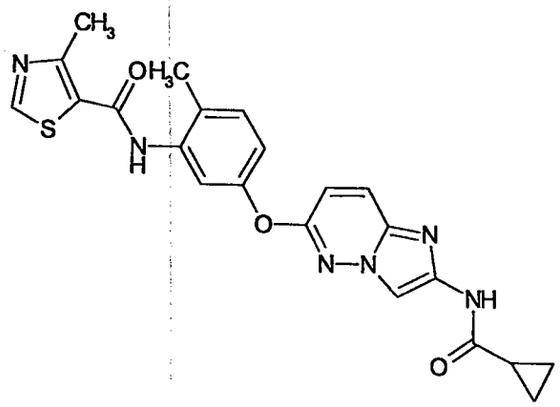
In the same manner as in Example 279 and using 2-(methoxycarbonyl)cyclopropanecarboxylic acid (140 mg, 0.78 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (69 μL, 0.8 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (250 mg, 0.6 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (75 mg, 25%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.19 - 1.29 (2H, m), 1.39 - 1.47 (1H, m), 2.19 (3H, s), 2.24 (3H, s), 2.25 - 2.33 (1H, m), 3.51 (3H,

s), 3.97 (3H, s), 6.80 (1H, s), 7.04 (1H, d, J = 9.8 Hz), 7.09 (1H, dd, J = 8.3, 2.7 Hz), 7.27 (1H, d, J = 2.7 Hz), 7.34 (1H, d, J = 8.3 Hz), 7.90 (1H, s), 8.03 (1H, d, J = 9.8 Hz), 9.79 (1H, s), 11.10 (1H, s).

Example 298

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide

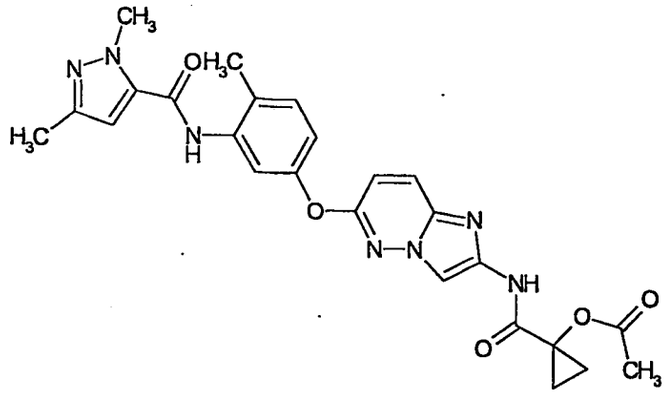


In the same manner as in Example 259 and using 4-methyl-1,3-thiazole-5-carboxylic acid (86 mg, 0.60 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (100 μL, 1.2 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (170 mg, 80%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.85 - 1.97 (1H, m), 2.26 (3H, s), 2.65 (3H, s), 7.04 (1H, d, J = 9.8 Hz), 7.09 (1H, dd, J = 8.3, 2.7 Hz), 7.30 - 7.39 (2H, m), 7.94 (1H, s), 8.03 (1H, d, J = 9.8 Hz), 9.12 (1H, s), 9.80 (1H, s), 11.06 (1H, s).

Example 299

Production of 1-({[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-

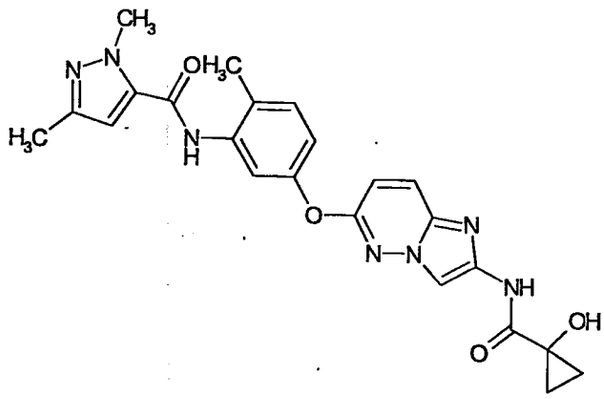
yl]amino}carbonyl)cyclopropyl acetate



In the same manner as in Example 279 and using 1-acetoxycyclopropanecarboxylic acid (90 mg, 0.63 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (54 μL, 0.63 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (200 mg, 0.48 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (180 mg, 74%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.11 - 1.19 (2H, m), 1.42 - 1.48 (2H, m), 2.10 (3H, s), 2.19 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.06 (1H, d, J = 9.8 Hz), 7.10 (1H, dd, J = 8.3, 2.7 Hz), 7.28 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.99 (1H, s), 8.03 (1H, d, J = 9.8 Hz), 9.79 (1H, br. s), 10.87 (1H, br. s).

Example 300

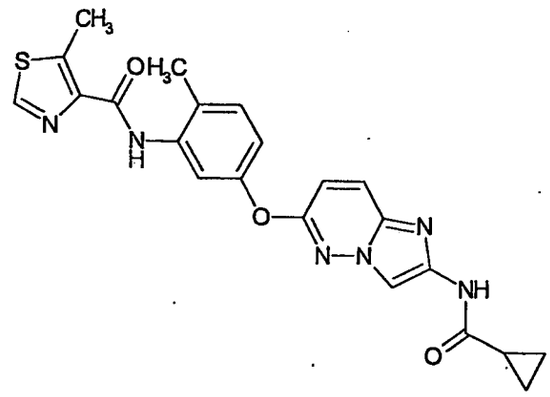
Production of N-{5-[(2-{[(1-hydroxycyclopropyl)carbonyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide



To a solution of 1-({[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}carbonyl)cyclopropyl acetate (130 mg, 0.25 mmol) in tetrahydrofuran (2 mL) was added 1N aqueous sodium hydroxide solution (2 mL), and the mixture was stirred at room temperature for 2 hr. 1N Hydrochloric acid (2.5 mL) and ethyl acetate were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (99 mg, 86%) as a pale-yellow solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.96 - 1.03 (2H, m), 1.13 - 1.22 (2H, m), 2.19 (3H, s), 2.26 (3H, s), 3.97 (3H, s), 6.63 (1H, br. s), 6.81 (1H, s), 7.03 - 7.14 (2H, m), 7.29 (1H, d, J = 2.7 Hz), 7.35 (1H, d, J = 8.3 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.8 Hz), 9.79 (2H, br. s).

Example 301

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-5-methyl-1,3-thiazole-4-carboxamide

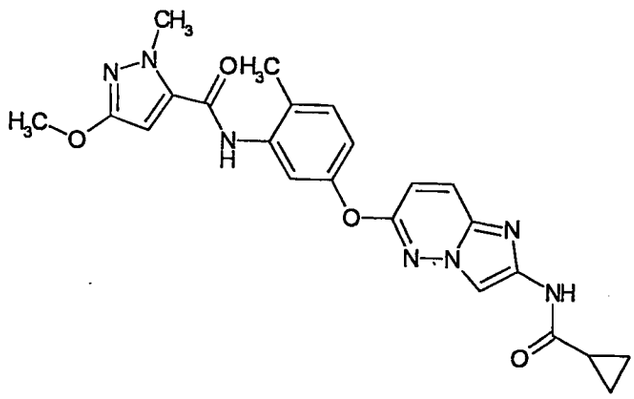


In the same manner as in Example 259 and using 5-methyl-1,3-thiazole-4-carboxylic acid (74 mg, 0.52 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (110 mg, 60%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.85 - 1.96 (1H, m), 2.31 (3H, s), 2.78 (3H, s), 6.96 - 7.09 (2H, m), 7.34 (1H, d, J = 8.7 Hz), 7.79 (1H, d, J = 2.4 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 10.2 Hz), 9.02 (1H, s), 9.79 (1H, s), 11.07 (1H, s).

Example 302

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide



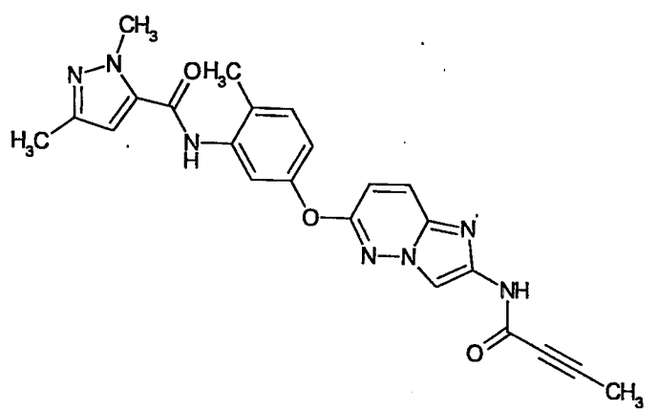
In the same manner as in Example 259 and using 3-methoxy-1-methyl-1H-pyrazole-5-carboxylic acid (80 mg, 0.52 mmol),

tetrahydrofuran (5 mL), N, N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (130 mg, 0.40 mmol) and N, N-dimethylacetamide (7 mL) as starting materials, the title compound (160 mg, 85%) was obtained as a white solid. melting point 224°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.86 - 1.97 (1H, m), 2.24 (3H, s), 3.80 (3H, s), 3.90 (3H, s), 6.46 (1H, s), 7.04 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.7, 2.6 Hz), 7.26 (1H, d, J = 2.6 Hz), 7.35 (1H, d, J = 8.7 Hz), 7.93 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.86 (1H, s), 11.07 (1H, s).

Example 303

Production of N-(5-{[2-(but-2-ynoylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



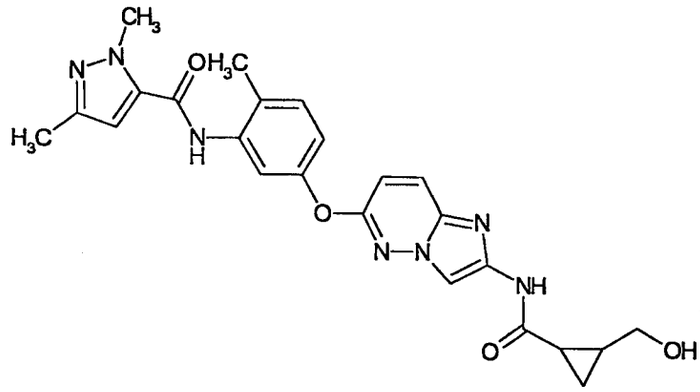
In the same manner as in Example 279 and using but-2-ynoic acid (46 mg, 0.54 mmol), tetrahydrofuran (1.5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (47 μL, 0.54 mmol), N-{5-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]-2-methylphenyl}-1,3-dimethyl-1H-pyrazole-5-carboxamide hydrochloride (150 mg, 0.36 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (60 mg, 37%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.03 (3H, s), 2.19 (3H, s), 2.25 (3H, s), 3.98 (3H, s), 6.81 (1H, s), 7.03 - 7.14 (2H, m), 7.28 (1H, d,

J = 2.4 Hz), 7.35 (1H, d, J = 8.5 Hz), 7.94 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 9.81 (1H, br. s), 11.48 (1H, br. s).

Example 304

Production of N-(5-{[2-({[2-(hydroxymethyl)cyclopropyl]carbonyl}amino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



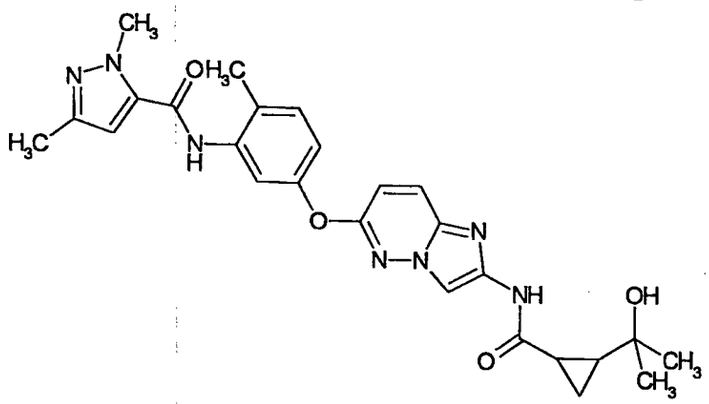
To a suspension of calcium chloride (135 mg, 1.1 mmol) in tetrahydrofuran/ethanol (2/1, 1 mL) was added a solution of sodium borohydride (92 mg, 2.2 mmol) and methyl 2-({[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}carbonyl)cyclopropanecarboxylate (180 mg, 0.37 mmol) in tetrahydrofuran/ethanol (2/1, 1 mL), and the mixture was stirred at room temperature for 18 hr. Saturated aqueous ammonium chloride solution and ethyl acetate were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→100/0, and then methanol/ethyl acetate=0/100→5/95) to give the title compound (35 mg, 20%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.83 - 1.04 (2H, m), 1.37 - 1.49 (1H, m), 1.94 - 2.05 (1H, m), 2.19 (3H, s), 2.25 (3H, s), 3.41 - 3.53

(1H, m), 3.56 - 3.66 (1H, m), 3.97 (3H, s), 4.44 (1H, t, J = 5.2 Hz), 6.81 (1H, s), 7.03 (1H, d, J = 9.6 Hz), 7.09 (1H, dd, J = 8.5, 2.6 Hz), 7.27 (1H, d, J = 2.6 Hz), 7.34 (1H, d, J = 8.5 Hz), 7.95 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 9.80 (1H, s), 10.99 (1H, s).

Example 305

Production of N-(5-{[2-({[2-(1-hydroxy-1-methylethyl)cyclopropyl]carbonyl}amino)imidazo[1,2-b]pyridazin-6-yl]oxy}-2-methylphenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide



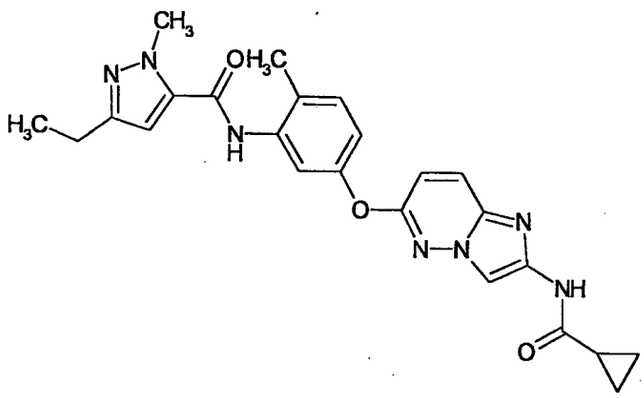
To a solution of methyl 2-({[6-(3-{[(1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]amino}-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}carbonyl)cyclopropanecarboxylate (250 mg, 0.49 mmol) in tetrahydrofuran (5 mL) was added a solution of iodo(methyl)magnesium in diethyl ether (2M, 540 μL, 1.1 mmol) at 0°C, and the mixture was stirred at room temperature for 1 hr. 0.5N Hydrochloric acid (3 mL) and ethyl acetate were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (×3). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was washed with ethyl acetate/hexane to give the title compound (190 mg, 78%) as a pale-green solid.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.35 - 1.46 (1H, m), 1.67 (3H, s), 1.69 - 1.78 (1H, m), 2.06 - 2.23 (2H, m), 2.30 (3H, s), 2.34 (3H, s), 3.70 (3H, s), 4.12 (3H, s), 6.43 (1H, s), 6.85 (1H, d, J = 9.6 Hz), 6.97 (1H, dd, J = 8.3, 2.4 Hz), 7.24 - 7.28 (1H, m), 7.58

(1H, s), 7.73 (1H, d, J = 9.6 Hz), 7.94 (1H, m), 8.13 (1H, s), 8.97 (1H, s).

Example 306

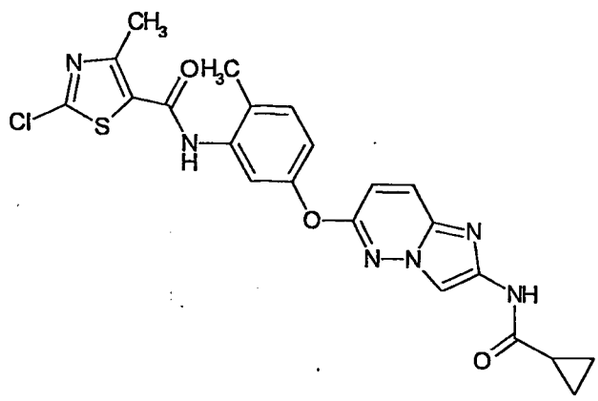
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide



In the same manner as in Example 259 and using 3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (120 mg, 0.80 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (190 mg, 68%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.19 (3H, t, J = 7.8 Hz), 1.87 - 1.97 (1H, m), 2.25 (3H, s), 2.57 (2H, q, J = 7.8 Hz), 3.99 (3H, s), 6.85 (1H, s), 7.04 (1H, d, J = 9.5 Hz), 7.10 (1H, d, J = 8.3 Hz), 7.27 (1H, s), 7.35 (1H, d, J = 8.3 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.81 (1H, s), 11.06 (1H, s).

Example 307

Production of 2-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-4-methyl-1,3-thiazole-5-carboxamide

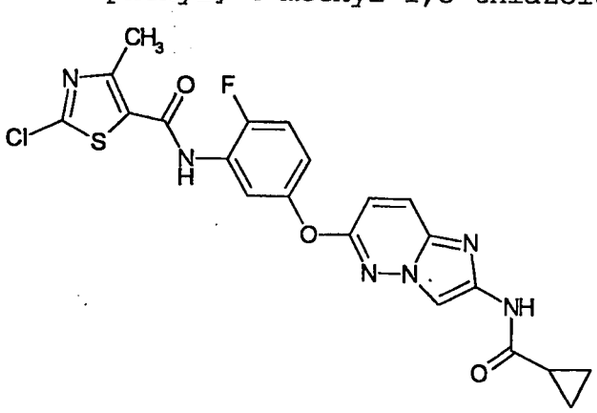


In the same manner as in Example 259 and using 2-chloro-4-methyl-1,3-thiazole-5-carboxylic acid (140 mg, 0.80 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (270 mg, 91%) was obtained as a pale-green solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.86 - 1.96 (1H, m), 2.25 (3H, s), 2.58 (3H, s), 7.04 (1H, d, J = 9.5 Hz), 7.10 (1H, dd, J = 8.3, 2.3 Hz), 7.31 - 7.38 (2H, m), 7.93 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.86 (1H, s), 11.06 (1H, s).

Example 308

Production of 2-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-4-methyl-1,3-thiazole-5-carboxamide

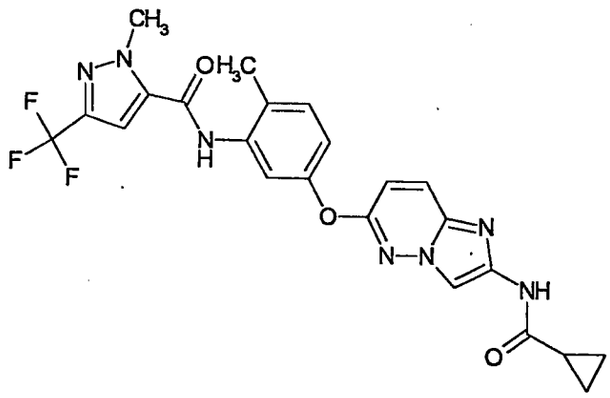


In the same manner as in Example 259 and using 2-chloro-4-methyl-1,3-thiazole-5-carboxylic acid (140 mg, 0.80 mmol),

tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (140 μL, 1.6 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (230 mg, 78%) was obtained as a pale-green solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.85 - 1.97 (1H, m), 2.58 (3H, s), 7.08 (1H, d, J = 9.4 Hz), 7.17 - 7.26 (1H, m), 7.41 (1H, dd, J = 10.0, 9.0 Hz), 7.59 (1H, dd, J = 6.3, 2.9 Hz), 7.94 (1H, s), 8.05 (1H, d, J = 9.4 Hz), 10.23 (1H, s), 11.08 (1H, s).

Example 309

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide

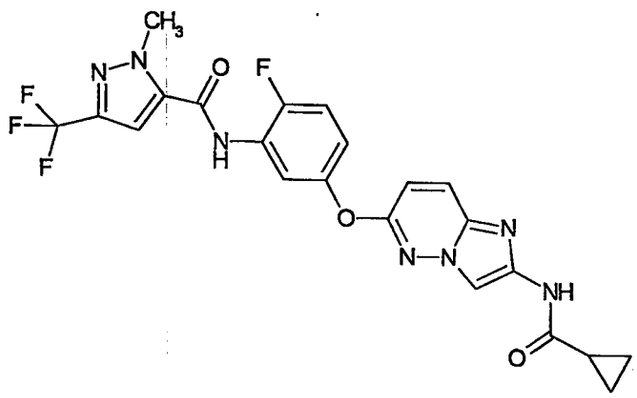


In the same manner as in Example 259 and using 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (160 mg, 0.80 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (240 mg, 76%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.86 - 1.97 (1H, m), 2.27 (3H, s), 4.15 (3H, s), 7.05 (1H, d, J = 9.6 Hz), 7.13 (1H, dd, J = 8.3, 2.6 Hz), 7.30 (1H, d, J = 2.6 Hz), 7.37 (1H, d,

J = 8.3 Hz), 7.49 (1H, s), 7.94 (1H, s), 8.04 (1H, d, J = 9.6 Hz), 10.13 (1H, s), 11.08 (1H, s).

Example 310

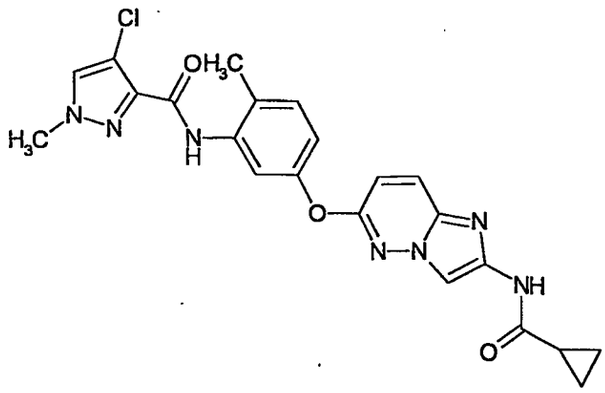
Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide



In the same manner as in Example 259 and using 1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (150 mg, 0.79 mmol), tetrahydrofuran (5mL), N,N-dimethylformamide (1 drop), oxalyl chloride (140 μL, 1.6 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (240 mg, 77%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.85 (4H, m), 1.85 - 1.97 (1H, m), 4.15 (3H, s), 7.09 (1H, d, J = 9.4 Hz), 7.21 - 7.28 (1H, m), 7.39 - 7.47 (1H, m), 7.54 (1H, s), 7.58 (1H, dd, J = 6.3, 2.9 Hz), 7.95 (1H, s), 8.05 (1H, d, J = 9.4 Hz), 10.45 (1H, s), 11.08 (1H, s).

Example 311

Production of 4-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-pyrazole-3-carboxamide

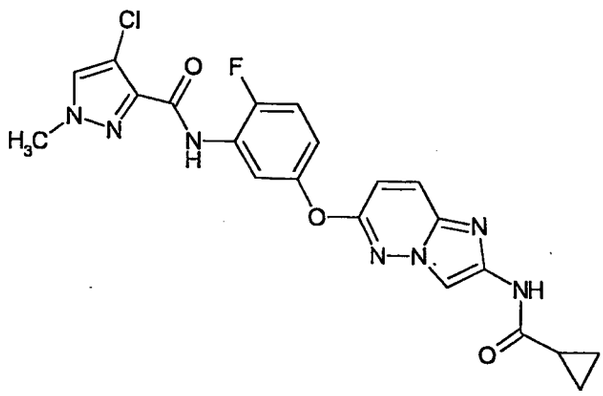


In the same manner as in Example 259 and using 4-chloro-1-methyl-1H-pyrazole-3-carboxylic acid (130 mg, 0.80 mmol), tetrahydrofuran (5mL), N, N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.62 mmol) and N, N-dimethylacetamide (7 mL) as starting materials, the title compound (235 mg, 82%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.84 (4H, m), 1.87 - 1.96 (1H, m), 2.27 (3H, s), 3.93 (3H, s), 6.99 - 7.08 (2H, m), 7.32 (1H, d, J = 8.7 Hz), 7.52 (1H, d, J = 2.6 Hz), 7.95 (1H, s), 8.03 (1H, d, J = 10.2 Hz), 8.12 (1H, s), 9.54 (1H, s), 11.07 (1H, s).

Example 312

Production of 4-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-3-carboxamide

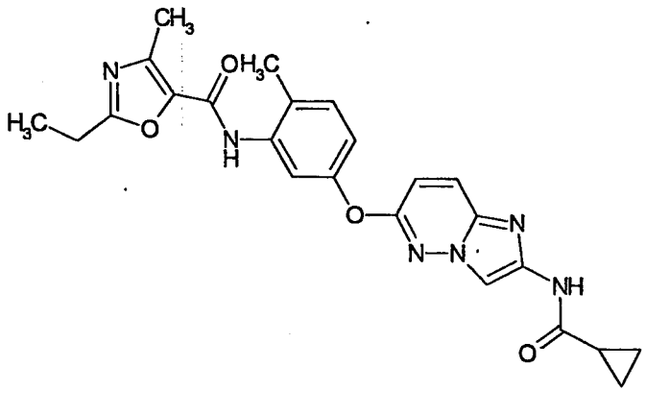


In the same manner as in Example 259 and using 4-chloro-1-methyl-1H-pyrazole-3-carboxylic acid (130 mg, 0.79 mmol),

tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (170 μL, 2.0 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.61 mmol) and N,N-dimethylacetamide (7 mL) as starting materials, the title compound (230 mg, 80%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 3.94 (3H, s), 7.08 (1H, d, J = 9.6 Hz), 7.10 - 7.18 (1H, m), 7.39 (1H, dd, J = 10.4, 9.0 Hz), 7.80 (1H, dd, J = 6.5, 2.9 Hz), 7.95 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 8.14 (1H, s), 9.68 (1H, s), 11.08 (1H, s).

Example 313

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide

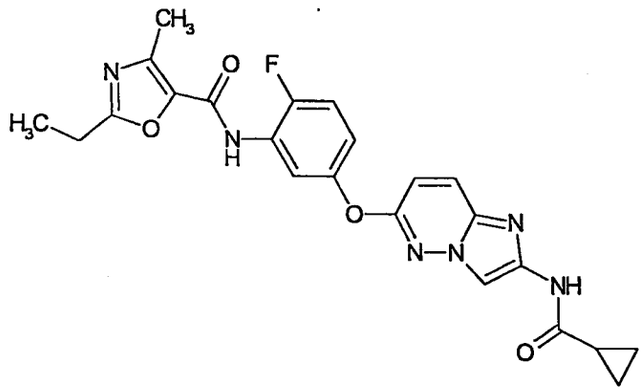


In the same manner as in Example 259 and using 2-ethyl-4-methyl-1,3-oxazole-5-carboxylic acid (230 mg, 1.5 mmol), tetrahydrofuran (6 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (520 μL, 6.0 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (400 mg, 1.2 mmol) and N,N-dimethylacetamide (10 mL) as starting materials, the title compound (390 mg, 69%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.29 (3H, t, J = 7.6 Hz), 1.92 (1H, m), 2.24 (3H, s), 2.36 (3H, s), 2.81 (2H, q, J = 7.6 Hz), 7.04 (1H, d, J = 9.5 Hz), 7.08 (1H, dd, J = 8.3,

2.7 Hz), 7.26 - 7.37 (2H, m), 7.94 (1H, s), 8.03 (1H, d, J = 9.5 Hz), 9.71 (1H, s), 11.07 (1H, s).

Example 314

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide

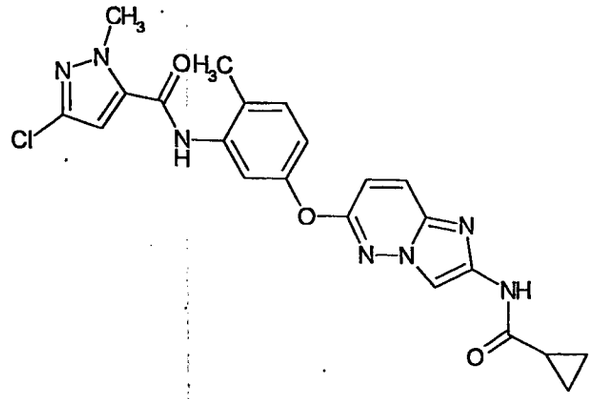


In the same manner as in Example 259 and using 2-ethyl-4-methyl-1,3-oxazole-5-carboxylic acid (230 mg, 1.5 mmol), tetrahydrofuran (6 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (520 μL, 6.0 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (400 mg, 1.2 mmol) and N,N-dimethylacetamide (10 mL) as starting materials, the title compound (400 mg, 70%) was obtained as a white solid. melting point 228°C.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.29 (3H, t, J = 7.6 Hz), 1.83 - 1.95 (1H, m), 2.36 (3H, s), 2.82 (2H, q, J = 7.6 Hz), 7.07 (1H, d, J = 9.8 Hz), 7.16 - 7.25 (1H, m), 7.33 - 7.44 (1H, m), 7.56 (1H, dd, J = 6.2, 2.8 Hz), 7.94 (1H, s), 8.04 (1H, d, J = 9.8 Hz), 9.95 (1H, s), 11.07 (1H, s).

Example 315

Production of 3-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1-methyl-1H-pyrazole-5-carboxamide

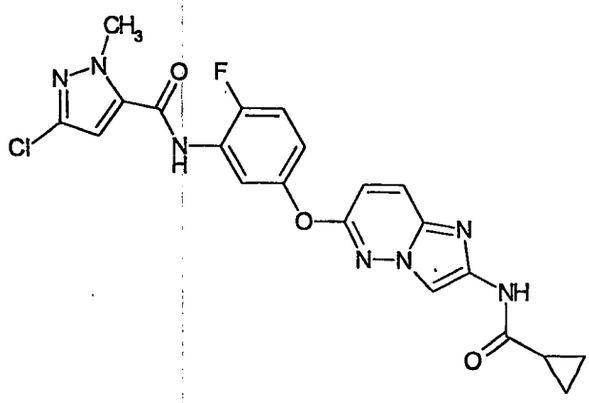


In the same manner as in Example 259 and using 3-chloro-1-methyl-1H-pyrazole-5-carboxylic acid (60 mg, 0.37 mmol), tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (130 μL, 1.5 mmol), N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.31 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (110 mg, 74%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.01 - 0.15 (4H, m), 1.14 - 1.27 (1H, m), 1.54 (3H, s), 1.80 (3H, s), 6.27 - 6.46 (3H, m), 6.58 (1H, d, J = 2.4 Hz), 6.65 (1H, d, J = 8.5 Hz), 7.22 (1H, s), 7.33 (1H, d, J = 9.6 Hz), 9.30 (1H, br. s), 10.37 (1H, s).

Example 316

Production of 3-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide

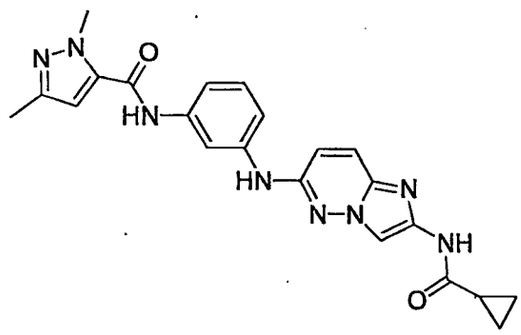


In the same manner as in Example 259 and using 3-chloro-1-methyl-1H-pyrazole-5-carboxylic acid (59 mg, 0.37 mmol),

tetrahydrofuran (5 mL), N,N-dimethylformamide (1 drop), oxalyl chloride (130 μL, 1.5 mmol), N-[6-(3-amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.31 mmol) and N,N-dimethylacetamide (5 mL) as starting materials, the title compound (100 mg, 71%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.85 (4H, m), 1.84 - 1.97 (1H, m), 4.03 (3H, s), 7.02 - 7.14 (2H, m), 7.19 - 7.28 (1H, m), 7.37 - 7.47 (1H, m), 7.56 (1H, dd, J = 6.3, 2.9 Hz), 7.94 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.33 (1H, br. s), 11.08 (1H, s).

Example 317

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}amino)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide



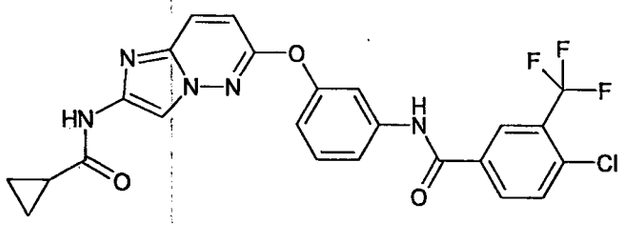
A mixture of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (330 mg, 1.0 mmol), N-(3-aminophenyl)-1,3-dimethyl-1H-pyrazole-5-carboxamide (280 mg, 1.2 mmol), tris(dibenzylideneacetone)dipalladium (0) (46 mg, 0.050 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl (48 mg, 0.10 mmol), potassium tert-butoxide (170 mg, 1.5 mmol) and tert-butanol was heated under reflux for 2 days. Ethyl acetate/tetrahydrofuran and saturated aqueous sodium hydrogencarbonate solution were added to the mixture, the aqueous layer was extracted with ethyl acetate/tetrahydrofuran (×4). Combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated under reduced pressure, and the residue was

purified by silica gel column chromatography (ethyl acetate/hexane=30/70→100/0) to give the title compound (37 mg, 9%) as a brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.88 (4H, m), 1.86 - 1.98 (1H, m), 2.22 (3H, s), 4.01 (3H, s), 6.85 (1H, s), 6.89 (1H, d, J = 9.6 Hz), 7.24 - 7.36 (2H, m), 7.45 - 7.53 (1H, m), 7.75 (1H, d, J = 9.6 Hz), 8.00 (1H, s), 8.21 (1H, s), 9.37 (1H, s), 10.15 (1H, s), 10.93 (1H, s).

Example 318

Production of 4-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



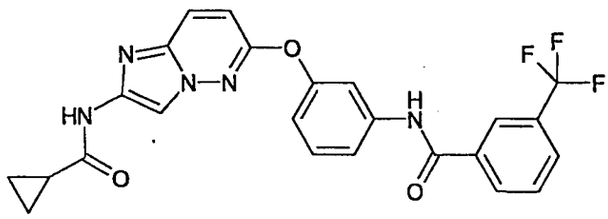
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol) in N,N-dimethylformamide (6.0 mL) were added 4-chloro-3-(trifluoromethyl)benzoic acid (73 mg, 0.32 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.34 mmol) and 1-hydroxybenzotriazole (46 mg, 0.34 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→80/20) and precipitated from ethyl acetate/diisopropyl ether to give the title compound (130 mg, 77%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.64 - 0.93 (4H, m), 1.79 - 2.04 (1H, m), 6.99 - 7.13 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.59 - 7.69

(1H, m), 7.71 (1H, t, J = 2.1 Hz), 7.93 (1H, d, J = 8.4 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.24 (1H, dd, J = 8.4, 2.1 Hz), 8.37 (1H, d, J = 2.1 Hz), 10.64 (1H, s), 11.09 (1H, s).

Example 319

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

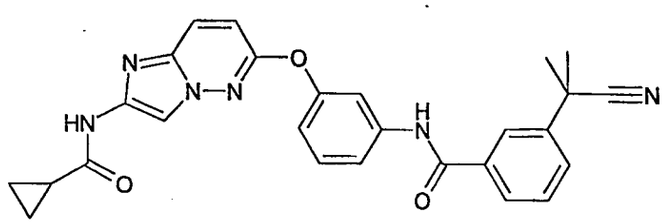


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.26 mmol), 3-(trifluoromethyl)benzoic acid (54 mg, 0.29 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (55 mg, 0.29 mmol), 1-hydroxybenzotriazole (39 mg, 0.29 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (86 mg, 69%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.89 (4 H, m), 1.84 - 2.03 (1 H, m), 6.98 - 7.15 (2 H, m), 7.46 (1 H, t, J = 8.1 Hz), 7.60 - 7.70 (1 H, m), 7.73 (1 H, t, J = 2.1 Hz), 7.79 (1 H, t, J = 7.8 Hz), 7.91 - 8.02 (2 H, m), 8.06 (1 H, d, J = 9.6 Hz), 8.19 - 8.34 (2 H, m), 10.59 (1 H, s), 11.09 (1 H, s).

Example 320

Production of 3-(1-cyano-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide

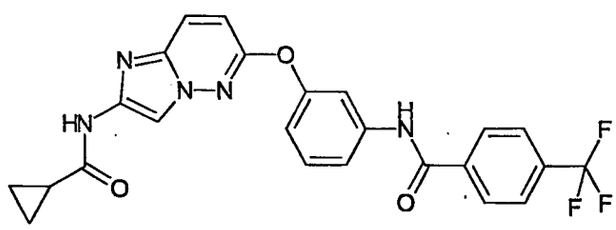


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol), 3-(1-cyano-1-methylethyl)benzoic acid (62 mg, 0.33 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.34 mmol), 1-hydroxybenzotriazole (46 mg, 0.34 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (120 mg, 77%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.74 (6H, s), 1.83 - 1.98 (1H, m), 6.99 - 7.04 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.54 - 7.69 (2H, m), 7.69 - 7.80 (2H, m), 7.92 (1H, dt, J = 7.8, 1.2 Hz), 7.98 (1H, s), 8.00 - 8.10 (2H, m), 10.45 (1H, s), 11.09 (1H, s).

Example 321

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-4-(trifluoromethyl)benzamide



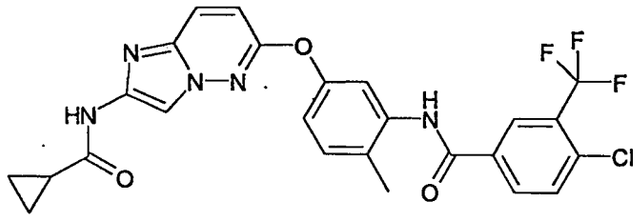
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol), 4-(trifluoromethyl)benzoic acid (63 mg, 0.33 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.34 mmol), 1-hydroxybenzotriazole (46 mg, 0.34 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (110 mg, 68%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.62 - 0.94 (4H, m), 1.76 - 2.06 (1H, m), 6.99 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.63 - 7.71 (1H, m), 7.74 (1H, t, J = 2.1 Hz), 7.92 (2H, d, J = 8.2 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.13 (2H, d, J = 8.2 Hz), 10.60 (1H, s), 11.09 (1H, s).

393
443

Example 322

Production of 4-chloro-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-(trifluoromethyl)benzamide

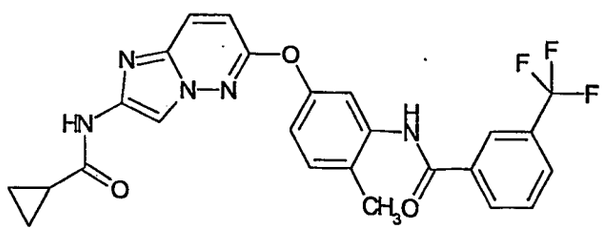


Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.25 mmol), 4-chloro-3-(trifluoromethyl)benzoic acid (57 mg, 0.25 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (50 mg, 0.26 mmol), 1-hydroxybenzotriazole (35 mg, 0.26 mmol) and N,N-dimethylformamide (4.0 mL) as starting materials and in the same manner as in Example 318, the title compound (83 mg, 63%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.84 - 1.97 (1H, m), 2.26 (3H, s), 7.05 (1H, d, J = 9.6 Hz), 7.12 (1H, dd, J = 8.4, 2.7 Hz), 7.30 (1H, d, J = 2.7 Hz), 7.36 (1H, d, J=8.4 Hz), 7.86 - 7.97 (2H, m), 8.03 (1H, d, J = 9.6 Hz), 8.25 (1H, dd, J = 8.4, 1.8 Hz), 8.39 (1H, d, J = 1.8 Hz), 10.26 (1H, s), 11.07 (1H, s).

Example 323

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-3-(trifluoromethyl)benzamide



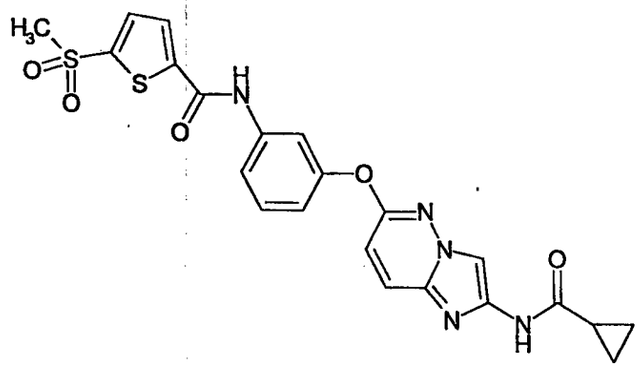
Using N-[6-(3-amino-4-methylphenoxy)imidazo[1,2-

b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.25 mmol), 3-(trifluoromethyl)benzoic acid (57 mg, 0.25 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (50 mg, 0.26 mmol), 1-hydroxybenzotriazole (35 mg, 0.26 mmol) and N,N-dimethylformamide (4.0 mL) as starting materials and in the same manner as in Example 318, the title compound (83 mg, 63%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.85 - 1.99 (1H, m), 2.27 (3H, s), 7.05 (1H, d, J = 9.6 Hz), 7.11 (1H, dd, J = 8.4, 2.4 Hz), 7.31 (1H, d, J = 2.4 Hz), 7.36 (1H, d, J = 8.6 Hz), 7.78 (1H, t, J = 7.8 Hz), 7.90 - 8.00 (2H, m), 8.03 (1H, d, J = 9.6 Hz), 8.20 - 8.36 (2H, m), 10.21 (1H, s), 11.07 (1H, s).

Example 324

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-(methylsulfonyl)thiophene-2-carboxamide



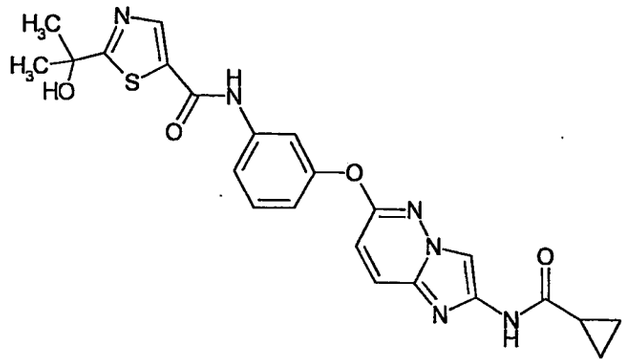
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol), 5-(methylsulfonyl)thiophene-2-carboxylic acid (47 mg, 0.33 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.34 mmol), 1-hydroxybenzotriazole (46 mg, 0.34 mmol) and N,N-dimethylformamide (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (41 mg, 26%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.82 - 1.98 (1H, m), 3.41 (3H, s), 6.99 - 7.14 (2H, m), 7.46 (1H, t, J = 8.1 Hz),

7.58 - 7.65 (1H, m), 7.66 (1H, t, J = 2.1 Hz), 7.88 (1H, d, J = 4.2 Hz), 7.97 (1H, s), 8.03 - 8.09 (2H, m), 10.66 (1H, s), 11.09 (1H, s).

Example 325

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carboxamide

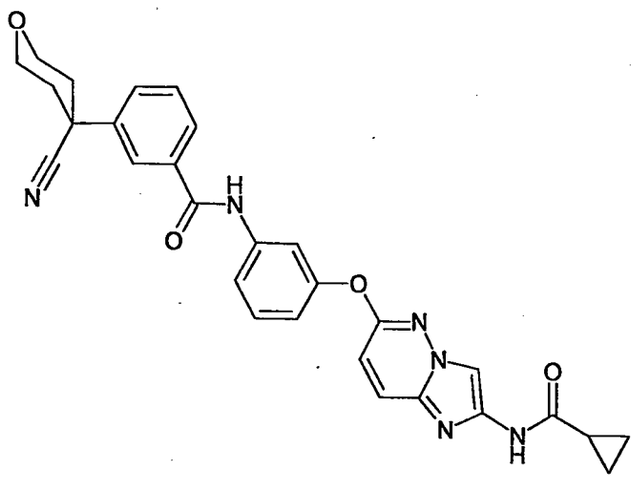


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol), 2-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carboxylic acid (96 mg, 0.51 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (95 mg, 0.50 mmol), 1-hydroxybenzotriazole (67 mg, 0.50 mmol) and N,N-dimethylformamide (8.0 mL) as starting materials and in the same manner as in Example 318, the title compound (99 mg, 43%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.85 (4H, m), 1.51 (6H, s), 1.85 - 1.98 (1H, m), 6.17 (1H, s), 6.98 - 7.04 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.54 - 7.68 (2H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.43 (1H, s), 10.42 (1H, s), 11.09 (1H, s).

Example 326

Production of 3-(4-cyanotetrahydro-2H-pyran-4-yl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide

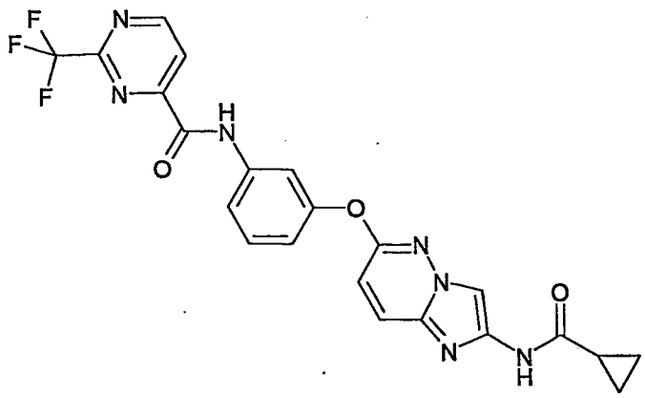


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol), 3-(4-cyanotetrahydro-2H-pyran-4-yl)benzoic acid (120 mg, 0.51 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (95 mg, 0.50 mmol), 1-hydroxybenzotriazole (67 mg, 0.50 mmol), triethylamine (130 μL, 0.97 mmol) and N,N-dimethylformamide (8.0 mL) as starting materials and in the same manner as in Example 318, the title compound (150 mg, 58%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.92 (4H, m), 1.85 - 1.98 (1H, m), 2.10 - 2.23 (4H, m), 3.58 - 3.79 (2H, m), 3.86 - 4.15 (2H, m), 6.95 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.52 - 7.70 (2H, m), 7.71 (1H, t, J = 2.1 Hz), 7.76 - 7.85 (1H, m), 7.92 - 8.00 (2H, m), 8.02 - 8.12 (2H, m), 10.44 (1H, s), 11.09 (1H, s).

Example 327

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-(trifluoromethyl)pyrimidine-4-carboxamide

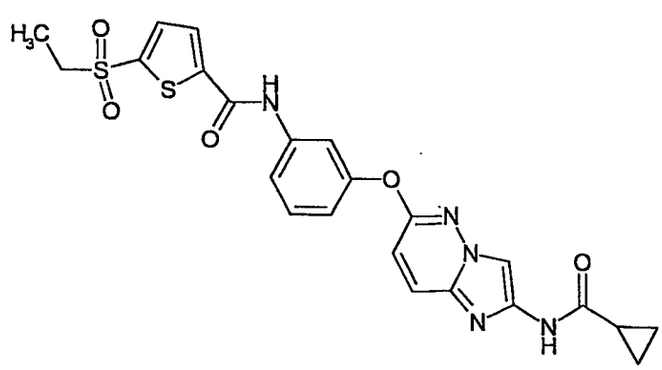


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol), 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (150 mg, 0.83 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (100 mg, 0.53 mmol), 1-hydroxybenzotriazole (72 mg, 0.53 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 318, the title compound (130 mg, 54%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.88 (4H, m), 1.84 - 1.98 (1H, m), 7.04 - 7.15 (2H, m), 7.49 (1H, t, J = 8.1 Hz), 7.72 - 7.86 (2H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.36 (1H, d, J = 4.8 Hz), 9.35 (1H, d, J = 4.8 Hz), 10.82 (1H, s), 11.09 (1H, s).

Example 328

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-(ethylsulfonyl)thiophene-2-carboxamide



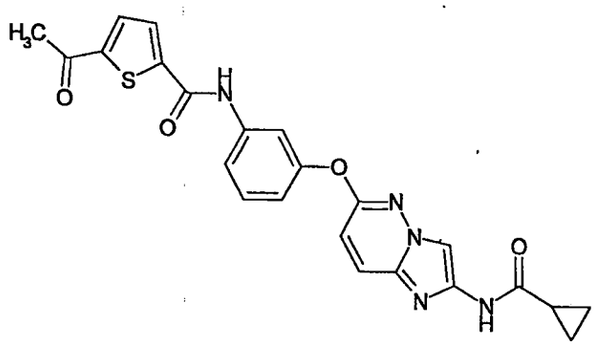
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (150 mg, 0.49 mmol), 5-(ethylsulfonyl)thiophene-2-carboxylic acid (110 mg, 0.50 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol), 1-hydroxybenzotriazole (69 mg, 0.51 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 318, the title compound (180 mg, 71%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.19 (3H, t, J = 7.2 Hz), 1.86 - 1.98 (1H, m), 3.47 (2H, q, J = 7.2 Hz), 7.01 - 7.12 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.58 - 7.64 (1H, m), 7.66 (1H, t, J = 2.1 Hz), 7.86 (1H, d, J = 3.9 Hz), 7.97 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.09 (1H, d, J = 3.9 Hz), 10.66 (1H, s), 11.09 (1H, s).

Example 329

Production of 5-acetyl-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]thiophene-2-carboxamide



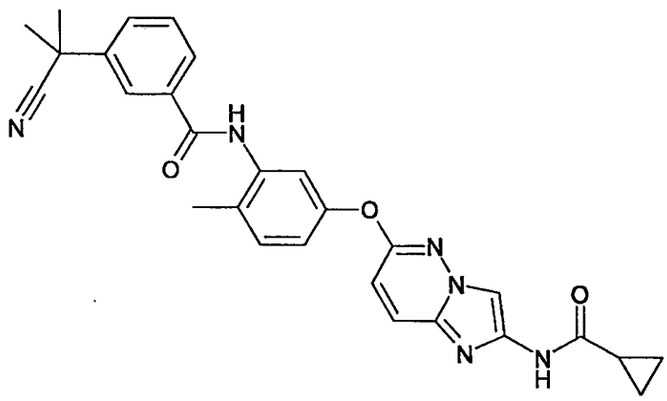
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol), 5-acetylthiophene-2-carboxylic acid (85 mg, 0.50 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol), 1-hydroxybenzotriazole (69 mg, 0.51 mmol) and N,N-dimethylformamide (6.0 mL) as starting materials and in the same manner as in Example 318, the title compound (110 mg, 48%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.86 - 1.98 (1H, m), 2.58 (3H, s), 7.00 - 7.13 (2H, m), 7.45 (1H, t, J = 8.1 Hz),

7.59 - 7.66 (1H, m), 7.67 (1H, t, J = 2.1 Hz), 7.96 - 8.01 (2H, m), 8.02 - 8.11 (2H, m), 10.55 (1H, s), 11.09 (1H, s).

Example 330

Production of 3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]benzamide

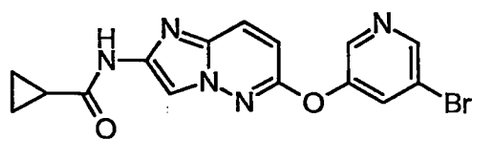


To a solution of 3-(1-cyano-1-methylethyl)benzoic acid (560 mg, 2.97 mmol) in tetrahydrofuran (15 mL) were added oxalyl chloride (320 μL, 3.71 mmol) and N,N-dimethylformamide (2 drops), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in N-methylpyrrolidone (15 mL). N-[6-(3-Amino-4-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (800 mg, 2.47 mmol) was added to the mixture, and the mixture was stirred at room temperature for 12 hr. The reaction mixture was diluted with 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give a colorless oil. The oil was dissolved ethyl acetate, and diisopropyl ether was added to allow precipitation to give the title compound (220 mg, 18%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.86 (4H, m), 1.74 (6H, s), 1.84 - 1.98 (1H, m), 2.27 (3H, s), 7.05 (1H, d, J = 9.6 Hz), 7.10 (1H, dd, J = 8.4, 2.7 Hz), 7.31 (1H, d, J = 2.7 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.70 - 7.80 (1H, m), 7.91 - 7.99 (2H, m), 8.00 - 8.11 (2H, m), 10.04 (1H, s), 11.07 (1H, s).

Example 331

Production of N-{6-[(5-bromopyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

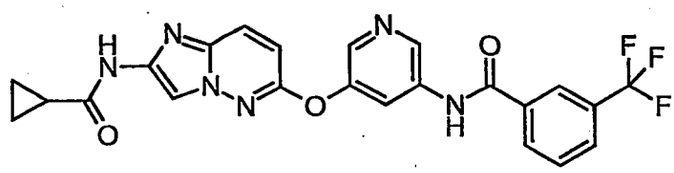


To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (1.7 g, 5.0 mmol) in N,N-dimethylformamide (20 mL) were added 5-bromopyridine-3-ol (1.7 g, 10 mmol) and potassium carbonate (1.7 g, 13 mmol), and the mixture was stirred at 140°C for 8 hr. After cooling the mixture to room temperature, the mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0), and precipitated from ethyl acetate/diisopropyl ether to give the title compound (1.6 g, 85%) as a yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.67 - 0.90 (4H, m), 1.85 - 1.98 (1H, m), 7.16 (1H, m), 7.98 (1H, s), 8.08 (1H, d, J = 9.6 Hz), 8.19 - 8.25 (1H, m), 8.61 - 8.67 (2H, m), 11.09 (1H, s).

Example 332

Production of N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)pyridin-3-yl]-3-(trifluoromethyl)benzamide

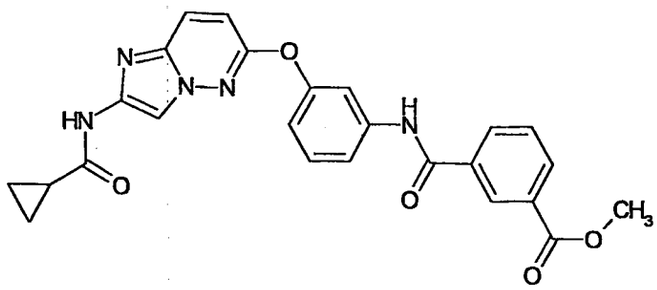


To a solution of N-{6-[(5-bromopyridin-3-yl)oxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (200 mg, 0.53 mmol), 3-(trifluoromethyl)benzamide (160 mg, 0.91 mmol), trans-1,2-diaminocyclohexane (15 mg, 0.13 mmol) and potassium carbonate (220 mg, 1.6 mmol) in 1,4-dioxane (3.0 mL) was added copper (I) iodide (25 mg, 0.13 mmol) under argon atmosphere, and the mixture was stirred at 110°C for 60 hr. The reaction mixture was cooled, and diluted with 20% tetrahydrofuran/ethyl acetate. The mixture was washed with water, 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=60/40→100/0) and precipitated from ethyl acetate/hexane to give the title compound (110 mg, 42%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.84 - 1.98 (1H, m), 7.17 (1H, d, J = 9.6 Hz), 7.81 (1H, t, J = 7.8 Hz), 7.96 - 8.04 (2H, m), 8.10 (1H, d, J = 9.6 Hz), 8.20 (1H, t, J = 2.4 Hz), 8.23 - 8.35 (2H, m), 8.38 (1H, d, J = 2.4 Hz), 8.85 (1H, d, J = 2.4 Hz), 10.83 (1H, s), 11.10 (1H, s).

Example 333

Production of methyl 3-({[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]amino}carbonyl)benzoate

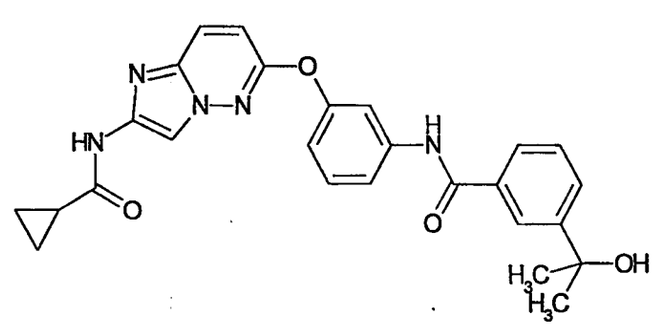


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (250 mg, 0.81 mmol), 3-(methoxycarbonyl)benzoic acid (150 mg, 0.83 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (160 mg, 0.84 mmol), 1-hydroxybenzotriazole (110 mg, 0.81 mmol) and N,N-dimethylformamide (8.0 mL) as starting materials and in the same manner as in Example 318, the title compound (270 mg, 72%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.84 - 1.98 (1H, m), 3.91 (3H, s), 6.97 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.63 - 7.79 (3H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.12 - 8.19 (1H, m), 8.19 - 8.26 (1H, m), 8.52 (1H, t, J = 1.5 Hz), 10.59 (1H, s), 11.09 (1H, s).

Example 334

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1-hydroxy-1-methylethyl)benzamide



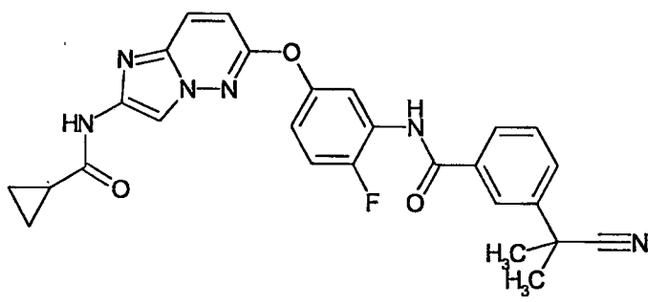
To a solution of methyl 3-({[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]amino}carbonyl)benzoate in tetrahydrofuran (5.0 mL) was added dropwise a solution of 1.4M methyl magnesium

bromide in tetrahydrofuran/toluene (0.76 mL, 1.1 mmol) under ice-cooling. After dropwise addition, the reaction mixture was stirred at room temperature for 12 hr, and water (10 mL) was added. 1N Hydrochloric acid (5.0 mL) was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=40/60→100/0) and precipitated from diisopropyl ether/hexane to give the title compound (19 mg, 19%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.46 (6H, s), 1.85 - 1.97 (1H, m), 5.14 (1H, s), 6.96 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.37 - 7.50 (2H, m), 7.67 (2H, m), 7.73 (1H, t, J = 2.1 Hz), 7.75 - 7.81 (1H, m), 7.98 (1H, s), 8.01 (1H, t, J = 1.5 Hz), 8.05 (1H, d, J = 9.6 Hz), 10.35 (1H, s), 11.09 (1H, s).

Example 335

Production of 3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]benzamide



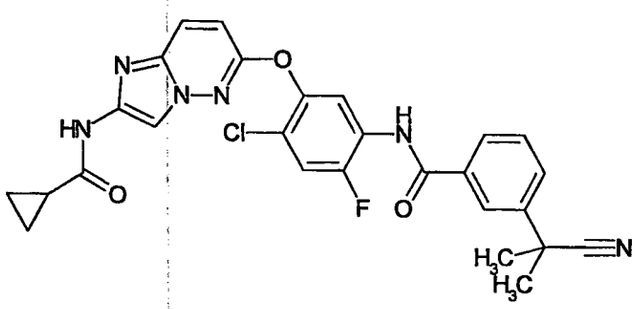
To a solution of 3-(1-cyano-1-methylethyl)benzoic acid (100 mg, 0.55 mmol) in tetrahydrofuran (2.0 mL) were added oxalyl chloride (59 μL, 0.69 mmol) and N,N-dimethylformamide (1 drop), and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated under reduced pressure, and the residue was dissolved in N-methylpyrrolidone (2 mL). N-[6-(3-Amino-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) was added to the mixture, and the mixture was stirred at room temperature for 10 hr. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=40/60→100/0), and precipitated from ethyl acetate/diisopropyl ether to give the title compound (140 mg, 62%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.74 (6H, s), 1.85 - 1.98 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.15 - 7.26 (1H, m), 7.34 - 7.48 (1H, m), 7.52 - 7.65 (2H, m), 7.71 - 7.82 (1H, m), 7.89 - 7.98 (2H, m), 8.01 - 8.12 (2H, m), 10.32 (1H, s), 11.07 (1H, s).

Example 336

Production of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(1-cyano-1-methylethyl)benzamide



Using 3-(1-cyano-1-methylethyl)benzoic acid (100 mg, 0.55 mmol), oxalyl chloride (59 μL, 0.69 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(5-amino-2-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (170 mg, 0.46 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same

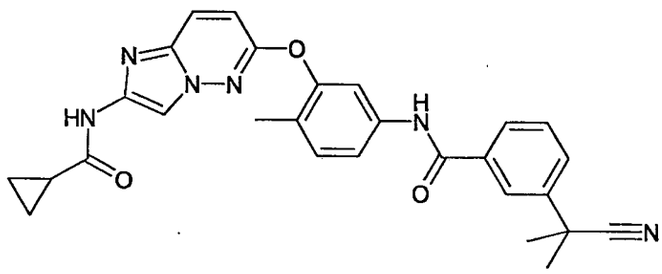
405
455

manner as in Example 335, the title compound (170 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.66 - 0.91 (4H, m), 1.74 (6H, s), 1.86 - 1.98 (1H, m), 7.18 (1H, d, J = 9.6 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.71 - 7.86 (3H, m), 7.89 - 7.99 (2H, m), 8.04 - 8.16 (2H, m), 10.42 (1H, s), 11.08 (1H, s).

Example 337

Production of 3-(1-cyano-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]benzamide

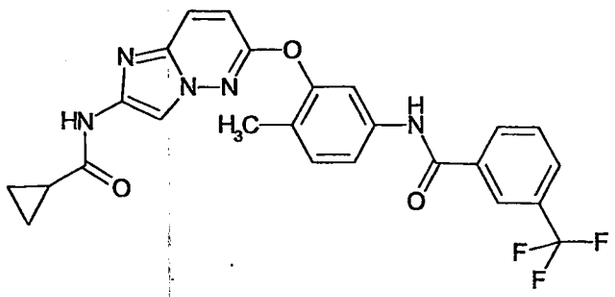


Using N-[6-(5-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 3-(1-cyano-1-methylethyl)benzoic acid (92 mg, 0.49 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (94 mg, 0.49 mmol), 1-hydroxybenzotriazole (66 mg, 0.49 mmol) and N,N-dimethylformamide (7.0 mL) as starting materials and in the same manner as in Example 318, the title compound (160 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.73 (6H, s), 1.85 - 1.98 (1H, m), 2.15 (3H, s), 7.08 (1H, d, J = 9.6 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.54 - 7.66 (3H, m), 7.70 - 7.78 (1H, m), 7.86 - 7.96 (2H, m), 8.01 (1H, t, J = 1.8 Hz), 8.05 (1H, d, J = 9.6 Hz), 10.37 (1H, s), 11.07 (1H, s).

Example 338

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]-3-(trifluoromethyl)benzamide

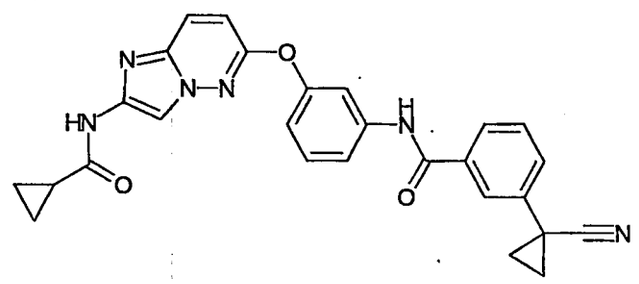


Using N-[6-(5-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 3-(trifluoromethyl)benzoic acid (93 mg, 0.49 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (94 mg, 0.49 mmol), 1-hydroxybenzotriazole (66 mg, 0.49 mmol) and N,N-dimethylformamide (7.0 mL) as starting materials and in the same manner as in Example 318, the title compound (166 mg, 72%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.89 (4H, m), 1.82 - 2.02 (1H, m), 2.16 (3H, s), 7.08 (1H, d, J = 9.6 Hz), 7.35 (1H, d, J = 8.4 Hz), 7.55 - 7.69 (2H, m), 7.77 (1H, t, J = 7.8 Hz), 7.91 - 8.00 (2H, m), 8.06 (1H, d, J = 9.6 Hz), 8.19 - 8.31 (2H, m), 10.51 (1H, s), 11.07 (1H, s).

Example 339

Production of 3-(1-cyanocyclopropyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide



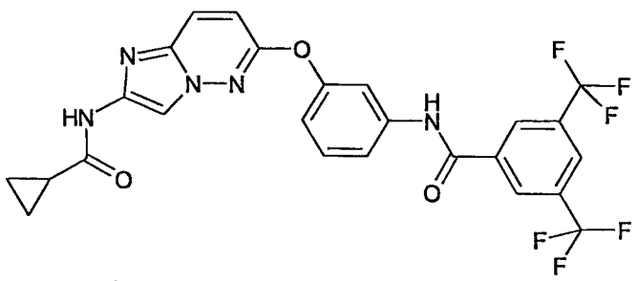
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (170 mg, 0.55 mmol), 3-(1-cyanocyclopropyl)benzoic acid (100 mg, 0.55 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (110

mg, 0.55 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol) and N,N-dimethylformamide (10 mL) as starting materials and in the same manner as in Example 318, the title compound (122 mg, 47%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.58 - 0.92 (4H, m), 1.55 - 1.68 (2H, m), 1.77 - 1.86 (2H, m), 1.86 - 1.99 (1H, m), 7.00 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.50 - 7.61 (2H, m), 7.61 - 7.68 (1H, m), 7.71 (1H, t, J = 2.1 Hz), 7.81 (1H, s), 7.84 - 7.91 (1H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.42 (1H, s), 11.09 (1H, s).

Example 340

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3,5-bis(trifluoromethyl)benzamide

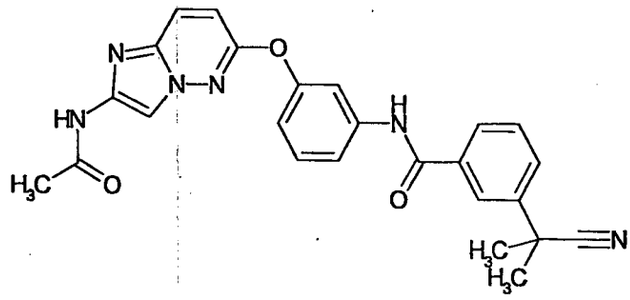


Using 3,5-bis(trifluoromethyl)benzoic acid (120 mg, 0.45 mmol), oxalyl chloride (48 μL, 0.56 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (120 mg, 0.37 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (63 mg, 31%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.86 (4H, m), 1.85 - 1.98 (1H, m), 7.01 - 7.15 (2H, m), 7.48 (1H, t, J = 8.1 Hz), 7.63 - 7.69 (1H, m), 7.71 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 8.38 (1H, s), 8.59 (2H, s), 10.77 (1H, s), 11.09 (1H, s).

Example 341

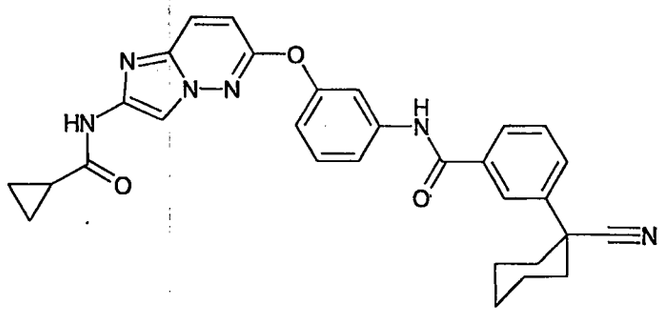
Production of N-(3-{[2-(acetylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(1-cyano-1-methylethyl)benzamide



Using 3-(1-cyano-1-methylethyl)benzoic acid (160 mg, 0.85 mmol), oxalyl chloride (90 μL, 1.1 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (4.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (200 mg, 0.71 mmol) and N-methylpyrrolidone (5.0 mL) as starting materials and in the same manner as in Example 335, the title compound (220 mg, 69%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.74 (6H, s), 2.07 (3H, s), 6.97 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.63 - 7.69 (1H, m), 7.70 - 7.80 (2H, m), 7.88 - 7.96 (1H, m), 8.00 (1H, s), 8.02 (1H, t, J = 1.8 Hz), 8.05 (1H, d, J = 9.6 Hz), 10.45 (1H, s), 10.80 (1H, s).

Example 342

Production of 3-(1-cyanocyclohexyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide



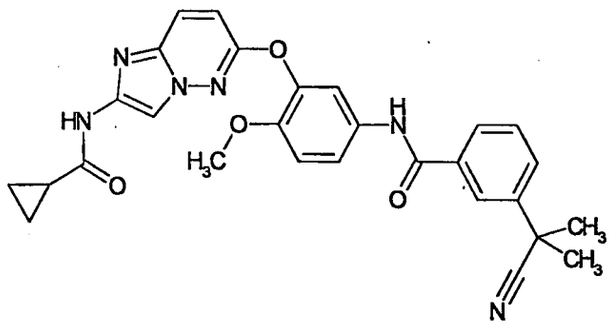
Using 3-(1-cyanocyclohexyl)benzoic acid (100 mg, 0.45 mmol), oxalyl chloride (48 μL, 0.56 mmol), N,N-dimethylformamide

(1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (120 mg, 0.37 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (150 mg, 78%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.85 (4H, m), 1.22 - 1.41 (1H, m), 1.54 - 1.98 (8H, m), 2.05 - 2.20 (2H, m), 6.97 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.63 - 7.69 (1H, m), 7.72 (1H, t, J = 2.1 Hz), 7.74 - 7.80 (1H, m), 7.89 - 7.96 (1H, m), 7.98 (1H, s), 8.01 - 8.10 (2H, m), 10.44 (1H, s), 11.09 (1H, s).

Example 343

Production of 3-(1-cyano-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]benzamide



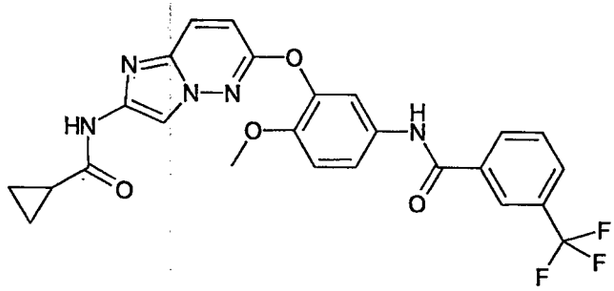
Using N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.44 mmol), 3-(1-cyano-1-methylethyl)benzoic acid (88 mg, 0.46 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (87 mg, 0.46 mmol), 1-hydroxybenzotriazole (62 mg, 0.46 mmol) and N,N-dimethylformamide (10 mL) as starting materials and in the same manner as in Example 318, the title compound (160 mg, 71%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.84 (4H, m), 1.74 (6H, s), 1.85 - 1.97 (1H, m), 3.72 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.65 (1H, dd,

J = 9.0, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.72 - 7.78 (1H, m), 7.89 (1H, s), 7.90 - 7.95 (1H, m), 7.97 - 8.07 (2H, m), 10.32 (1H, s), 11.05 (1H, s).

Example 344

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]-3-(trifluoromethyl)benzamide

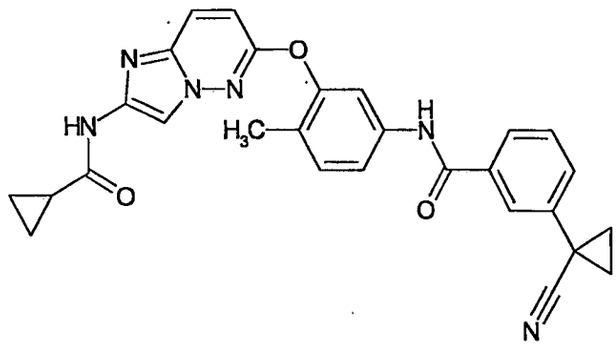


To a solution of N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.44 mmol) in N-methylpyrrolidone (6.0 mL) was added 3-(trifluoromethyl)benzoyl chloride (92 mg, 0.44 mmol) under ice-cooling, and the mixture was stirred at room temperature for 12 hr. The reaction mixture was diluted with 1N hydrochloric acid and extracted with ethyl acetate, and the organic layer was washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=50/50→100/0), and precipitated from ethyl acetate/diisopropyl ether to give the title compound (180 mg, 80%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.82 - 1.97 (1H, m), 3.73 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.66 (1H, dd, J = 9.0, 2.4 Hz), 7.73 (1H, d, J = 2.4 Hz), 7.78 (1H, t, J = 7.8 Hz), 7.89 (1H, s), 7.96 (1H, d, J = 7.8 Hz), 8.01 (1H, d, J = 10.2 Hz), 8.18 - 8.36 (2H, m), 10.48 (1H, s), 11.05 (1H, s).

Example 345

Production of 3-(1-cyanocyclopropyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]benzamide

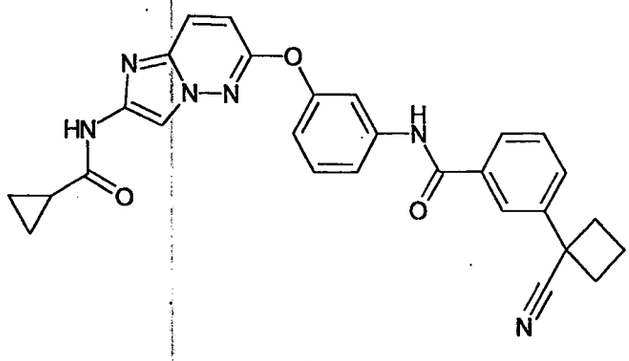


Using N-[6-(5-amino-2-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol), 3-(1-cyanocyclopropyl)benzoic acid (91 mg, 0.49 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (94 mg, 0.49 mmol), 1-hydroxybenzotriazole (66 mg, 0.49 mmol) and N,N-dimethylformamide (7.0 mL) as starting materials and in the same manner as in Example 318, the title compound (178 mg, 75%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.88 (4H, m), 1.55 - 1.65 (2H, m), 1.76 - 1.84 (2H, m), 1.85 - 2.00 (1H, m), 2.15 (3H, s), 7.08 (1H, d, J = 9.6 Hz), 7.34 (1H, d, J = 8.1 Hz), 7.48 - 7.69 (4H, m), 7.80 (1H, s), 7.82 - 7.89 (1H, m), 7.92 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.34 (1H, s), 11.06 (1H, s).

Example 346

Production of 3-(1-cyanocyclobutyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide

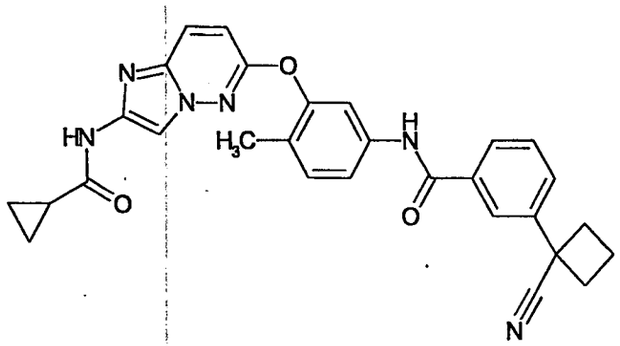


Using 3-(1-cyanocyclobutyl)benzoic acid (110 mg, 0.56 mmol), oxalyl chloride (60 μL, 0.70 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.47 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 335, the title compound (140 mg, 60%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.81 - 2.12 (2H, m), 2.20 - 2.41 (1H, m), 2.60 - 2.86 (4H, m), 6.97 - 7.05 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.64 - 7.76 (3H, m), 7.89 - 8.01 (3H, m), 8.06 (1H, d, J = 9.6 Hz), 10.46 (1H, s), 11.09 (1H, s).

Example 347

Production of 3-(1-cyanocyclobutyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]benzamide



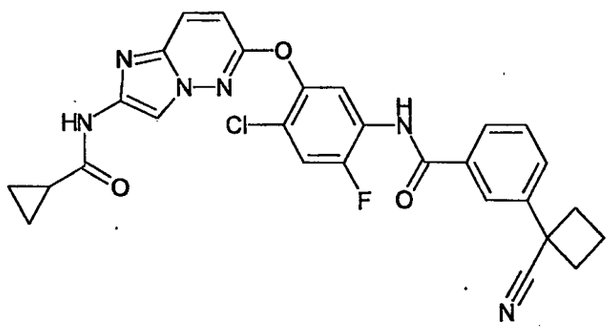
Using 3-(1-cyanocyclobutyl)benzoic acid (110 mg, 0.56 mmol), oxalyl chloride (60 μL, 0.70 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-

methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.46 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 335, the title compound (150 mg, 64%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.66 - 0.92 (4H, m), 1.72 - 2.11 (2H, m), 2.15 (3H, s), 2.20 - 2.42 (1H, m), 2.60 - 2.94 (4H, m), 7.08 (1H, d, J = 9.6 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.53 - 7.75 (4H, m), 7.81 - 7.99 (3H, m), 8.05 (1H, d, J = 9.6 Hz), 10.38 (1H, s), 11.07 (1H, s).

Example 348

Production of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(1-cyanocyclobutyl)benzamide



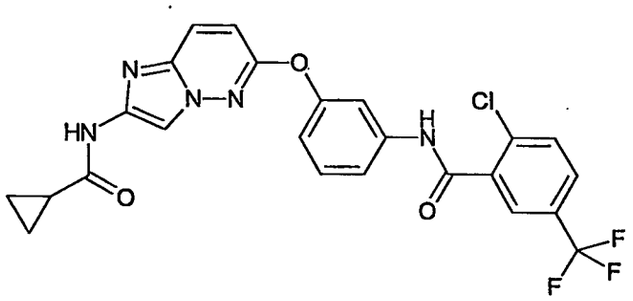
Using 3-(1-cyanocyclobutyl)benzoic acid (110 mg, 0.56 mmol), oxalyl chloride (60 μL, 0.70 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (170 mg, 0.46 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 335, the title compound (170 mg, 68%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.80 (4H, s), 1.85 - 1.96 (1H, m), 1.97 - 2.12 (1H, m), 2.20 - 2.41 (1H, m), 2.60 - 2.88 (4H, m), 7.18 (1H, d, J = 9.6 Hz), 7.61 (1H, t, J = 7.8 Hz), 7.67 - 7.75 (1H, m), 7.79 (1H, d, J = 2.7 Hz), 7.82 (1H, s), 7.88 - 7.97 (2H, m), 8.02 (1H, t, J = 1.5 Hz), 8.09 (1H, d, J = 9.6 Hz), 10.44

(1H, s), 11.08 (1H, s).

Example 349

Production of 2-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-5-(trifluoromethyl)benzamide

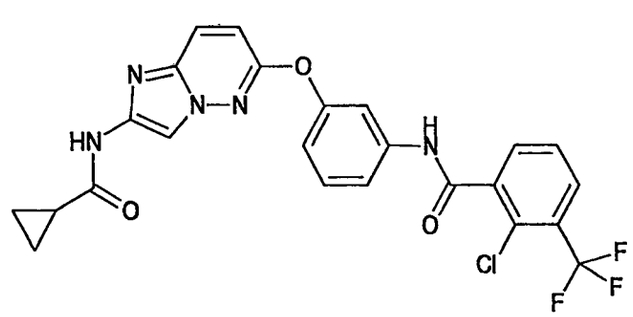


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol), 2-chloro-5-(trifluoromethyl)benzoyl acid chloride (87 mg, 0.36 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 344, the title compound (130 mg, 75%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.86 (4H, m), 1.86 - 1.98 (1H, m), 6.95 - 7.18 (2H, m), 7.45 (1H, t, J = 8.1 Hz), 7.50 - 7.58 (1H, m), 7.67 (1H, t, J = 2.1 Hz), 7.77 - 7.93 (2H, m), 7.97 (1H, s), 8.02 - 8.08 (2H, m), 10.80 (1H, s), 11.09 (1H, s).

Example 350

Production of 2-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



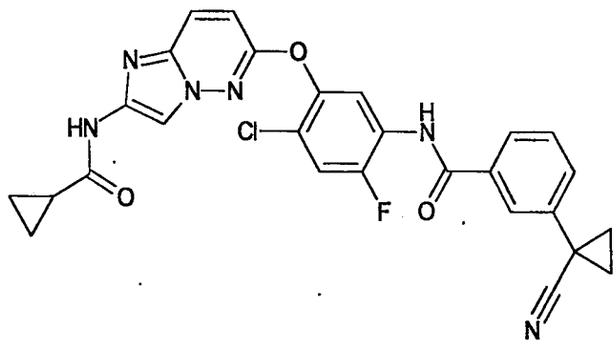
Using 2-chloro-3-(trifluoromethyl)benzoic acid (88 mg,

0.39 mmol), oxalyl chloride (42 μL, 0.49 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.32 mmol) and N-methylpyrrolidone (4.0 mL) as starting materials and in the same manner as in Example 335, the title compound (110 mg, 68%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.86 - 1.97 (1H, m), 6.99 - 7.15 (2H, m), 7.45 (1H, t, J=8.1 Hz), 7.49 - 7.58 (1H, m), 7.61 - 7.76 (2H, m), 7.88 - 7.95 (1H, m), 7.96 - 8.02 (2H, m), 8.05 (1H, d, J=9.6 Hz), 10.83 (1H, s), 11.09 (1H, s).

Example 351

Production of N-[4-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-(1-cyanocyclopropyl)benzamide



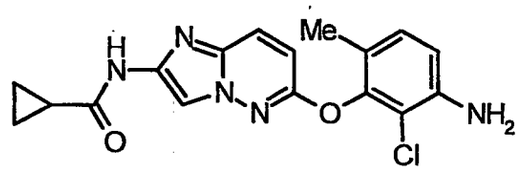
Using 3-(1-cyanocyclopropyl)benzoic acid (100 mg, 0.50 mmol), oxalyl chloride (55 μL, 0.62 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-chloro-4-fluorophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.42 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 335, the title compound (160 mg, 73%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.83 (4H, m), 1.55 - 1.66 (2H, m), 1.76 - 1.85 (2H, m), 1.86 - 1.97 (1H, m), 7.18 (1H, d, J = 9.6 Hz), 7.46 - 7.65 (2H, m), 7.79 (1H, d, J = 2.7 Hz), 7.82 (1H,

s), 7.83 - 7.91 (2H, m), 7.92 (1H, s), 8.09 (1H, d, J = 9.6 Hz), 10.40 (1H, s), 11.08 (1H, s).

Example 352

Production of N-[6-(3-amino-2-chloro-6-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

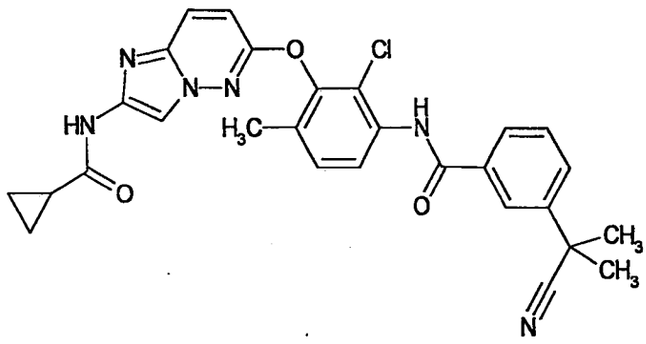


To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (2.0 g, 6.1 mmol) in N,N-dimethylformamide (20 mL) were added 3-amino-2-chloro-6-methylphenol (1.9 g, 12 mmol) and potassium carbonate (2.1 g, 15 mmol), and the mixture was stirred at 140°C for 12 hr. After cooling the mixture to room temperature, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=50/50→80/20) and precipitated from methanol/diisopropyl ether to give the title compound (1.4 g, 64%) as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.85 - 1.97 (1H, m), 2.00 (3H, s), 5.37 (2H, s), 6.69 (1H, d, J = 8.4 Hz), 6.99 (1H, d, J = 9.0 Hz), 7.07 (1H, d, J = 9.6 Hz), 7.87 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 11.04 (1H, s).

Example 353

Production of N-[2-chloro-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]-3-(1-cyano-1-methylethyl)benzamide

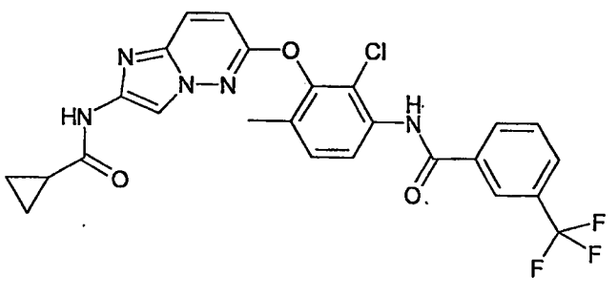


Using 3-(1-cyanocyclopropyl)benzoic acid (95 mg, 0.50 mmol), oxalyl chloride (55 μL, 0.63 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-amino-2-chloro-6-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.42 mmol) and N-methylpyrrolidone (3.0 mL) as starting materials and in the same manner as in Example 335, the title compound (110 mg, 51%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.63 - 0.95 (4H, m), 1.74 (6H, s), 1.82 - 1.97 (1H, m), 2.22 (3H, s), 7.20 (1H, d, J = 9.6 Hz), 7.34 - 7.53 (2H, m), 7.59 (1H, t, J = 7.8 Hz), 7.76 (1H, dq, J = 7.8, 1.2 Hz), 7.85 (1H, s), 7.97 (1H, dt, J = 7.8, 1.2 Hz), 8.06 - 8.15 (2H, m), 10.25 (1H, s), 11.06 (1H, s).

Example 354

Production of N-[2-chloro-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methylphenyl]-3-(trifluoromethyl)benzamide



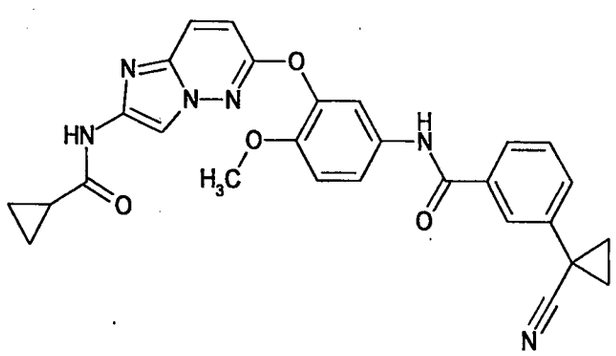
Using N-[6-(3-amino-2-chloro-6-methylphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.42 mmol), 3-(trifluoromethyl)benzoyl chloride (92 mg, 0.44 mmol) and N-

methylpyrrolidone (5.0 mL) as starting materials and in the same manner as in Example 344, the title compound (130 mg, 60%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.87 (4H, m), 1.81 - 1.98 (1H, m), 2.22 (3H, s), 7.20 (1H, d, J = 9.6 Hz), 7.33 - 7.58 (2H, m), 7.79 (1H, t, J = 7.8 Hz), 7.85 (1H, s), 7.98 (1H, d, J = 7.8 Hz), 8.09 (1H, d, J = 9.6 Hz), 8.29 (1H, d, J = 7.8 Hz), 8.34 (1H, s), 10.45 (1H, s), 11.06 (1H, s).

Example 355

Production of 3-(1-cyanocyclopropyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]benzamide

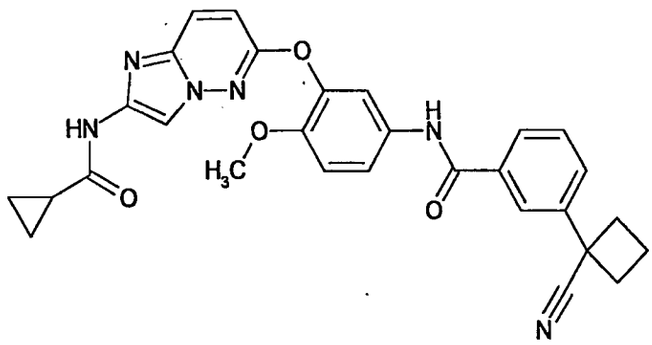


Using 3-(1-cyanocyclopropyl)benzoic acid (40 mg, 0.21 mmol), oxalyl chloride (23 μL, 0.27 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (60 mg, 0.18 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (67 mg, 74%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.83 (4H, m), 1.54 - 1.65 (2H, m), 1.75 - 1.86 (2H, m), 1.86 - 1.98 (1H, m), 3.72 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.48 - 7.60 (2H, m), 7.64 (1H, dd, J = 9.0, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.82 (1H, s), 7.84 - 7.92 (2H, m), 8.01 (1H, d, J = 9.6 Hz), 10.31 (1H, s), 11.06 (1H, s).

Example 356

Production of 3-(1-cyanocyclobutyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]benzamide

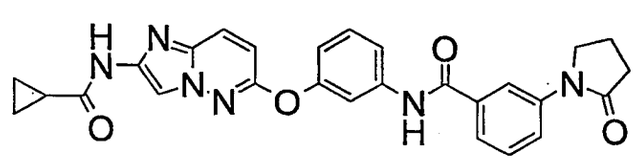


Using 3-(1-cyanocyclobutyl)benzoic acid (43 mg, 0.21 mmol), oxalyl chloride (23 μL, 0.27 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (60 mg, 0.18 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (68 mg, 74%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.86 - 1.96 (1H, m), 2.21 - 2.38 (2H, m), 2.64 - 2.87 (4H, m), 3.72 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.53 - 7.75 (4H, m), 7.89 (1H, s), 7.90 - 8.07 (3H, m), 10.35 (1H, s), 11.06 (1H, s).

Example 357

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(2-oxopyrrolidin-1-yl)benzamide

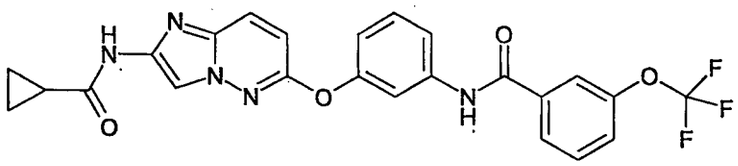


Using 3-(2-oxopyrrolidin-1-yl)benzoic acid (120 mg, 0.58 mmol), oxalyl chloride (60 μL, 0.68 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (170 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.85 - 1.97 (1H, m), 2.01 - 2.16 (2H, m), 2.52 - 2.56 (2H, m), 3.90 (2H, t, J = 6.6 Hz), 6.97 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.44 (1H, t, J = 8.1 Hz), 7.52 (1H, t, J = 8.1 Hz), 7.61 - 7.75 (3H, m), 7.89 - 7.95 (1H, m), 7.98 (1H, s), 8.02 - 8.11 (2H, m), 10.40 (1H, s), 11.09 (1H, s).

Example 358

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethoxy)benzamide

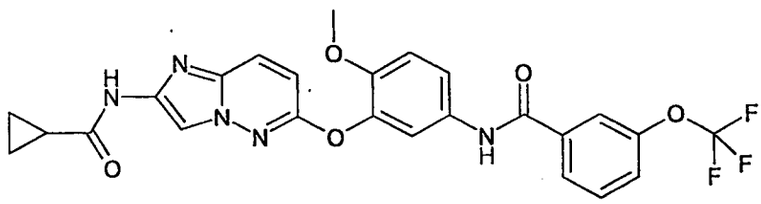


Using 3-(trifluoromethoxy)benzoic acid (120 mg, 0.58 mmol), oxalyl chloride (60 μL, 0.68 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (130 mg, 54%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.83 - 1.98 (1H, m), 6.99 - 7.05 (1H, m), 7.08 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.58 - 7.70 (3H, m), 7.72 (1H, t, J = 2.1 Hz), 7.89 (1H, s), 7.95 - 8.03 (2H, m), 8.06 (1H, d, J = 9.6 Hz), 10.51 (1H, s) 11.09 (1H, s).

Example 359

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]-3-(trifluoromethoxy)benzamide

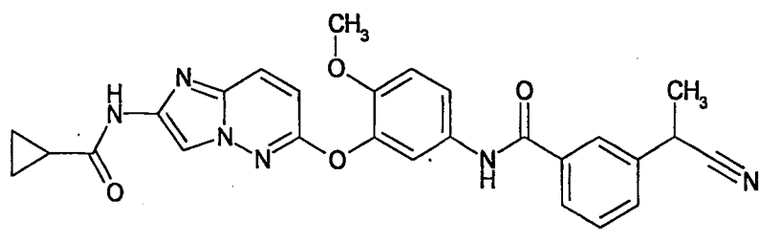


Using 3-(trifluoromethoxy)benzoic acid (120 mg, 0.58 mmol), oxalyl chloride (60 μL, 0.68 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (130 mg, 54%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.72 - 0.86 (4H, m), 1.83 - 1.98 (1H, m), 3.72 (3H, s), 7.06 (1H, d, J = 9.6 Hz), 7.22 (1H, d, J = 9.1 Hz), 7.54 - 7.78 (4H, m), 7.84 - 7.93 (2H, m), 7.96 - 8.08 (2H, m), 10.40 (1H, s), 11.05 (1H, s).

Example 360

Production of 3-(1-cyanoethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]benzamide



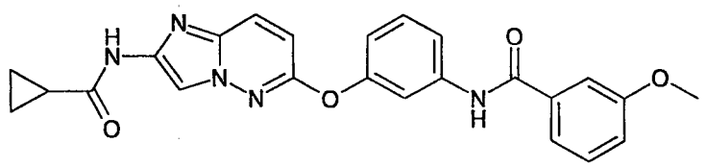
Using 3-(1-cyanoethyl)benzoic acid (62 mg, 0.35 mmol), oxalyl chloride (38 μL, 0.44 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-

methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.30 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (84 mg, 58%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.88 (4H, m), 1.60 (3H, d, J = 7.2 Hz), 1.81 - 1.99 (1H, m), 3.72 (3H, s), 4.42 (1H, q, J = 7.2 Hz), 7.06 (1H, d, J = 9.6 Hz), 7.22 (1H, d, J = 9.0 Hz), 7.47 - 7.70 (3H, m), 7.72 (1H, d, J = 2.4 Hz), 7.84 - 7.97 (3H, m), 8.01 (1H, d, J = 9.9 Hz), 10.32 (1H, s), 11.05 (1H, s).

Example 361

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-methoxybenzamide

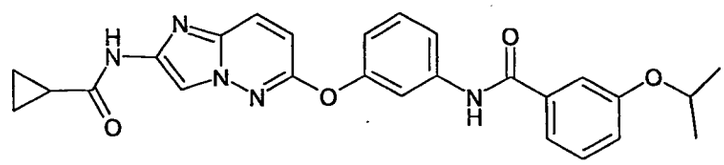


Using 3-methoxybenzoic acid (48 mg, 0.32 mmol), oxalyl chloride (32 μL, 0.37 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.26 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (49 mg, 43%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.85 (4H, m), 1.85 - 1.99 (1H, m), 3.83 (3H, s), 6.95 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.12 - 7.21 (1H, m), 7.37 - 7.49 (3H, m), 7.48 - 7.56 (1H, m), 7.61 - 7.70 (1H, m), 7.73 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.34 (1H, s), 11.09 (1H, s).

Example 362

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-isopropoxybenzamide

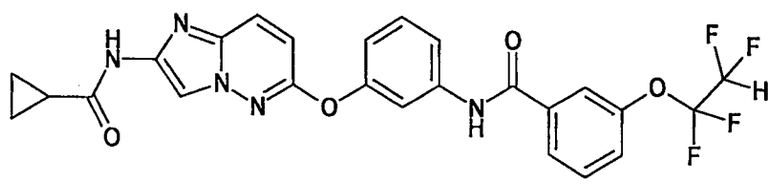


Using 3-(isopropoxy)benzoic acid (56 mg, 0.31 mmol), oxalyl chloride (33 μL, 0.39 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.26 mmol) and N,N-dimethylacetamide (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (82 mg, 67%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.85 (4H, m), 1.29 (6H, d, J = 6.0 Hz), 1.85 - 1.98 (1H, m), 4.60 - 4.78 (1H, m), 6.96 - 7.02 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.11 - 7.17 (1H, m), 7.33 - 7.55 (4H, m), 7.63 - 7.71 (1H, m), 7.74 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.31 (1H, s), 11.09 (1H, s).

Example 363

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1,1,2,2-tetrafluoroethoxy)benzamide

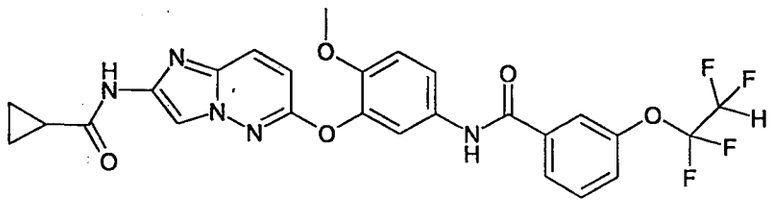


Using 3-(1,1,2,2-tetrafluoroethoxy)benzoic acid (74 mg, 0.31 mmol), oxalyl chloride (33 μL, 0.39 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (80 mg, 0.26 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (46 mg, 34%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.73 - 0.87 (4H, m), 1.85 - 1.99 (1H, m), 6.62 - 7.05 (2H, m), 7.07 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.1 Hz), 7.49 - 7.58 (1H, m), 7.61 - 7.69 (2H, m), 7.72 (1H, t, J = 2.1 Hz), 7.82 (1H, br. s.), 7.93 - 8.00 (2H, m), 8.06 (1H, d, J = 9.6 Hz), 10.50 (1H, s), 11.09 (1H, s).

Example 364

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]-3-(1,1,2,2-tetrafluoroethoxy)benzamide

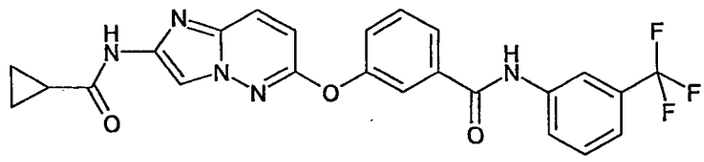


Using 3-(1,1,2,2-tetrafluoroethoxy)benzoic acid (85 mg, 0.35 mmol), oxalyl chloride (38 μL, 0.44 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.30 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (110 mg, 64%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.86 (4H, m), 1.84 - 1.98 (1H, m), 3.83 (3H, s), 6.96 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.12 - 7.20 (1H, m), 7.36 - 7.49 (3H, m), 7.49 - 7.55 (1H, m), 7.62 - 7.70 (1H, m), 7.73 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.34 (1H, s), 11.09 (1H, s).

Example 365

Production of 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-N-[3-(trifluoromethyl)phenyl]benzamide

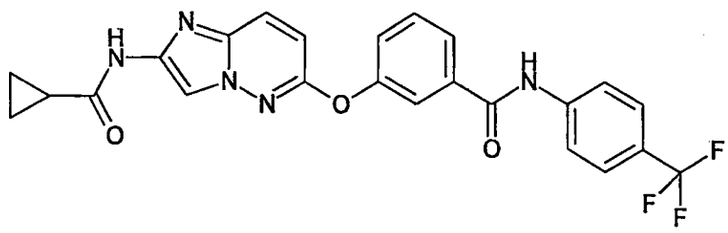


Using 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid (100 mg, 0.30 mmol), oxalyl chloride (100 μL, 1.2 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), 3-(trifluoromethyl)aniline (80 mg, 0.48 mmol) and N-methylpyrrolidone (1.0 mL) as starting materials and in the same manner as in Example 335, the title compound (13 mg, 8.9%) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.83 (4H, m), 1.86 - 1.97 (1H, m), 7.12 (1H, d, J = 9.6 Hz), 7.46 (1H, d, J = 7.8 Hz), 7.51 - 7.70 (3H, m), 7.83 - 7.99 (3H, m), 8.01 - 8.11 (2H, m), 8.23 (1H, s), 10.59 (1H, s), 11.08 (1H, s).

Example 366

Production of 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-N-[4-(trifluoromethyl)phenyl]benzamide



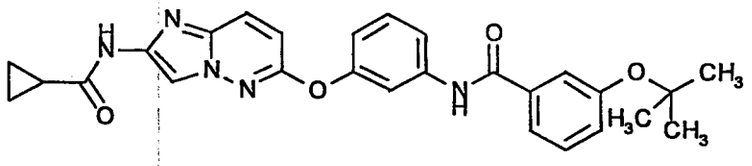
Using 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid (30 mg, 0.089 mmol), 4-(trifluoromethyl)aniline (44 mg, 0.27 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (26 mg, 0.14 mmol), 4-(dimethylamino)pyridine (17 mg, 0.14 mmol) and pyridine (1.0 mL) as starting materials and in the same manner as in Example 318, the title compound (18 mg, 42%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.86 (4H, m), 1.84 - 1.98 (1H, m), 7.11 (1H, d, J = 9.6 Hz), 7.50 - 7.59 (1H, m), 7.65 (1H, t, J = 7.9 Hz), 7.73 (2H, d, J = 8.7 Hz), 7.81 - 7.93 (2H, m), 7.95

(1H, s), 8.00 (2H, d, J = 8.7 Hz), 8.07 (1H, d, J = 9.6 Hz), 10.63 (1H, s), 11.08 (1H, s).

Example 367

Production of 3-tert-butoxy-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide

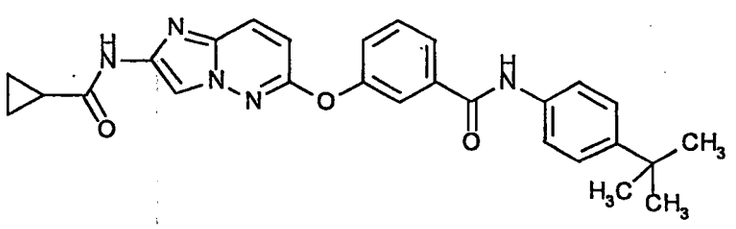


Using 3-tert-butoxybenzoic acid (110 mg, 0.58 mmol), oxalyl chloride (63 μL, 0.73 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (4.0 mL), N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.49 mmol) and N-methylpyrrolidone (4.0 mL) as starting materials and in the same manner as in Example 335, the title compound (160 mg, 57%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.87 (4H, m), 1.33 (9H, s), 1.85 - 1.98 (1H, m), 6.90 - 7.03 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.16 - 7.27 (1H, m), 7.36 - 7.48 (2H, m), 7.48 - 7.53 (1H, m), 7.61 - 7.70 (2H, m), 7.73 (1H, t, J = 2.1 Hz), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.34 (1H, s), 11.09 (1H, s).

Example 368

Production of N-(4-tert-butylphenyl)-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzamide

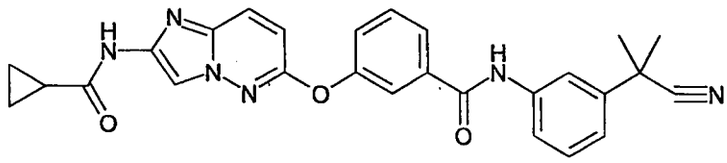


Using 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-

b]pyridazin-6-yl}oxy)benzoic acid (100 mg, 0.30 mmol), 4-tert-butylaniline (57 mg, 0.36 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (68 mg, 0.36 mmol), 4-(dimethylamino)pyridine (43 mg, 0.36 mmol) and pyridine (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (70 mg, 50%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.88 (4H, m), 1.28 (9H, s), 1.85 - 1.98 (1H, m), 7.11 (1H, d, J = 9.6 Hz), 7.37 (2H, d, J = 8.7 Hz), 7.47 - 7.55 (1H, m), 7.56 - 7.72 (3H, m), 7.77 - 7.92 (2H, m), 7.96 (1H, s), 8.07 (1H, d, J = 9.6 Hz), 10.23 (1H, s), 11.08 (1H, s).

Example 369

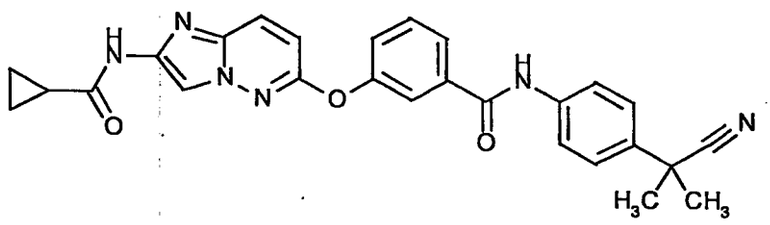
Production of N-[3-(1-cyano-1-methylethyl)phenyl]-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzamide



Using 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid (100 mg, 0.30 mmol), 2-(3-aminophenyl)-2-methylpropanenitrile (57 mg, 0.36 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (68 mg, 0.36 mmol), 4-(dimethylamino)pyridine (43 mg, 0.36 mmol) and pyridine (5.0 mL) as starting materials and in the same manner as in Example 318, the title compound (64 mg, 45%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.68 - 0.89 (4H, m), 1.69 (6H, s), 1.85 -1.98 (1H, m), 7.11 (1H, d, J=9.6 Hz), 7.20 - 7.30 (1H, m), 7.41 (1H, t, J=8.0 Hz), 7.48 - 7.57 (1H, m), 7.64 (1H, t, J=7.9 Hz), 7.74 - 8.00 (5H, m), 8.07 (1H, d, J=9.6 Hz), 10.42 (1H, s), 11.08 (1H, s).

Example 370

Production of N-[4-(1-cyano-1-methylethyl)phenyl]-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzamide

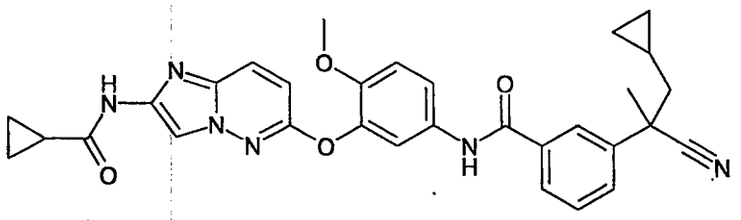


Using 3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)benzoic acid (100 mg, 0.30 mmol), 2-(4-aminophenyl)-2-methylpropanenitrile (57 mg, 0.36 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol), 4-(dimethylamino)pyridine (54 mg, 0.44 mmol) and pyridine (3.0 mL) as starting materials and in the same manner as in Example 318, the title compound (81 mg, 57%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.87 (4H, m), 1.68 (6H, s), 1.85 - 1.98 (1H, m), 7.11 (1H, d, J=9.6 Hz), 7.45 - 7.56 (3H, m), 7.63 (1H, t, J=7.9 Hz), 7.77 - 7.86 (3H, m), 7.86 - 7.92 (1H, m), 7.95 (1H, s), 8.07 (1H, d, J=9.4 Hz), 10.38 (1H, s), 11.08 (1H, s).

Example 371

Production of 3-(1-cyano-2-cyclopropyl-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]benzamide



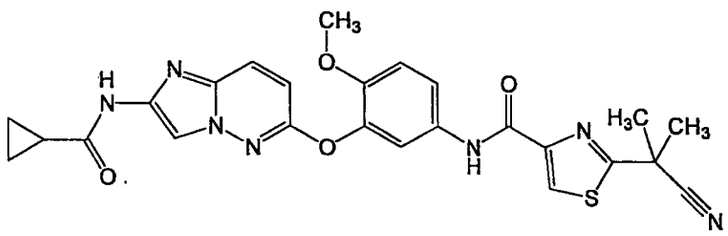
Using 3-(1-cyano-2-cyclopropyl-1-methylethyl)benzoic acid (70 mg, 0.31 mmol), oxalyl chloride (33 μL, 0.38 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (2.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-

yl]cyclopropanecarboxamide (86 mg, 0.25 mmol) and N-methylpyrrolidone (2.0 mL) as starting materials and in the same manner as in Example 335, the title compound (67 mg, 48%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ -0.03 - 0.08 (1H, m), 0.16 - 0.27 (1H, m), 0.30 - 0.52 (2H, m), 0.55 - 0.69 (1H, m), 0.73 - 0.86 (4H, m, J=4.5 Hz), 1.69 - 2.12 (6H, m), 3.72 (3H, s), 7.06 (1H, d, J=9.3 Hz), 7.22 (1H, d, J=9.3 Hz), 7.59 (1H, t, J=7.8 Hz), 7.65 (1H, dd, J=8.7, 2.4 Hz), 7.69 - 7.80 (2H, m), 7.86 - 7.97 (2H, m), 7.96 - 8.07 (2H, m), 10.31 (1H, s), 11.05 (1H, s).

Example 372

Production of 2-(1-cyano-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-4-methoxyphenyl]-1,3-thiazole-4-carboxamide

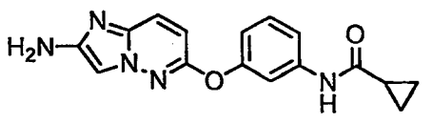


Using 2-(1-cyano-1-methylethyl)-1,3-thiazole-4-carboxylic acid (104 mg, 0.53 mmol), oxalyl chloride (57 μL, 0.66 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (5.0 mL), N-[6-(5-amino-2-methoxyphenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.44 mmol) and N,N-dimethylacetamide (4.0 mL) as starting materials and in the same manner as in Example 335, the title compound (179 mg, 78%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.70 - 0.89 (4H, m), 1.82 - 1.98 (7H, m), 3.73 (3H, s), 7.06 (1H, d, J=9.6 Hz), 7.22 (1H, d, J=9.4 Hz), 7.64 - 7.80 (2H, m), 7.89 (1H, s), 8.01 (1H, d, J=10.2 Hz), 8.47 (1H, s), 10.13 (1H, s), 11.05 (1H, s).

Example 373

N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}cyclopropanecarboxamide

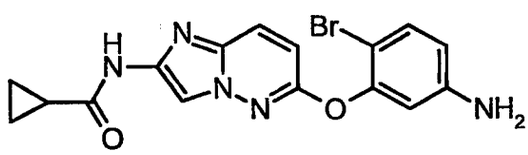


A mixture of N-{3-[(2-acetamidoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}cyclopropanecarboxamide (465 mg, 1.32 mmol), 4N hydrochloric acid-ethyl acetate solution (10 mL) and methanol (10 mL) was stirred at room temperature for 14 hr. The reaction mixture was neutralized by the addition of 8N aqueous sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether to give the title compound (376 mg, 92%) as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.81 (4H, m), 1.69 - 1.79 (1H, m), 5.33 (2H, s), 6.76 (1H, d, J = 9.3 Hz), 6.80 - 6.86 (1H, m), 7.14 (1H, s), 7.28 - 7.39 (2H, m), 7.47 (1H, t, J = 1.9 Hz), 7.71 (1H, d, J = 9.3 Hz), 10.30 (1H, s).

Example 374

Production of N-[6-(5-amino-2-bromophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide



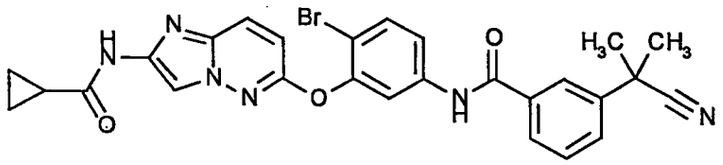
To a solution of N-(6-iodoimidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide (2.2 g, 6.7 mmol) in N,N-dimethylformamide (60 mL) were added 5-amino-2-bromophenol (1.9 g, 10 mmol) and potassium carbonate (1.8 g, 13 mmol), and the mixture was stirred at 140°C for 12 hr. After cooling the mixture to room temperature, the mixture was diluted with water, and extracted with ethyl acetate. The organic layer was washed

with 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=50/50→100/0). The solvent was evaporated under reduced pressure and the obtained solid was washed with diisopropyl ether to give the title compound (0.79 g, 31%) as a yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.69 - 0.88 (4H, m), 1.84 - 1.97 (1H, m), 5.52 (2H, s), 6.45 (1H, dd, J = 8.7, 2.7 Hz), 6.50 (1H, d, J = 2.7 Hz), 7.03 (1H, d, J = 9.0 Hz), 7.29 (1H, d, J = 8.7 Hz), 7.94 (1H, s), 8.03 (1H, d, J = 9.0 Hz), 11.07 (1H, s).

Example 375

Production of N-[4-bromo-3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1-cyano-1-methylethyl)benzamide

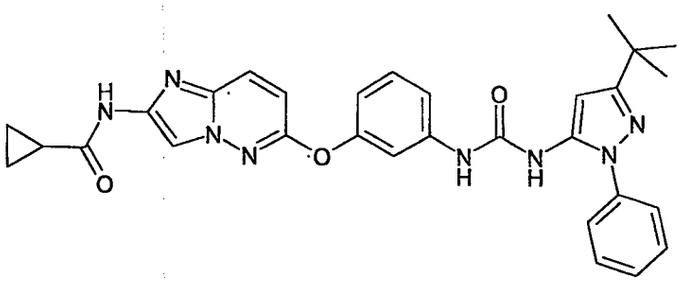


Using 3-(1-cyano-1-methylethyl)benzoic acid (330 mg, 1.8 mmol), oxalyl chloride (170 μL, 2.0 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (15 mL), N-[6-(5-amino-2-bromophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (650 mg, 1.7 mmol) and N,N-dimethylacetamide (5.0 mL) as starting materials and in the same manner as in Example 335, the title compound (800 mg, 85%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.71 - 0.88 (4H, m), 1.74 (6H, s), 1.85 - 1.96 (1H, m), 7.16 (1H, d, J = 9.6 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.64 - 7.71 (1H, m), 7.73 - 7.81 (2H, m), 7.83 - 7.97 (3H, m), 8.02 (1H, s), 8.10 (1H, d, J = 9.6 Hz), 10.56 (1H, s), 11.10 (1H, s).

Example 376

Production of N-{6-[3-({[(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)amino]carbonyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

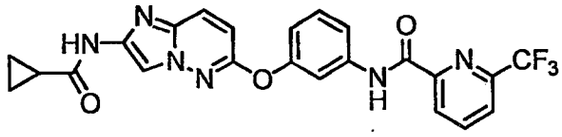


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (160 mg, 0.52 mmol) and 2,2,2-trichloroethyl (3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)carbamate (200 mg, 0.52 mmol) in dimethylsulfoxide/water (2.0 mL/1.5 mL) was added triethylamine (53 mg, 0.52 mmol), and the mixture was stirred at 85°C for 8 hr. The reaction mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, 5% aqueous sodium hydrogencarbonate solution and saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) and precipitated from ethyl acetate/diisopropyl ether/hexane to give the title compound (285 mg, 99%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.85 - 2.02 (1H, m), 3.32 (9H, s), 6.35 (1H, s), 6.84 (1H, dd, J = 7.8, 1.8 Hz), 7.03 (1H, d, J = 9.6 Hz), 7.16 (1H, dd, J = 8.1, 1.2 Hz), 7.28 - 7.46 (3H, m), 7.48 - 7.58 (4H, m), 7.96 (1H, s), 8.03 (1H, d, J = 9.6 Hz), 8.46 (1H, s), 9.22 (1H, s), 11.08 (1H, s).

Example 377

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-6-(trifluoromethyl)pyridine-2-carboxamide

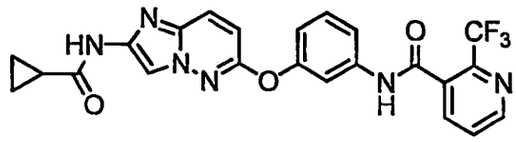


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (95 mg, 0.307 mmol) in N,N-dimethylformamide (5 mL) were added 6-(trifluoromethyl)pyridine-2-carboxylic acid (65 mg, 0.337 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.337 mmol) and 1-hydroxybenzotriazole (46 mg, 0.337 mmol), and the mixture was stirred at room temperature for 2 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate/diisopropyl ether to give the title compound (126 mg, 85%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.87 - 1.98 (1H, m), 7.03 - 7.11 (2H, m), 7.47 (1H, t, J = 8.2 Hz), 7.75 - 7.81 (1H, m), 7.83 (1H, t, J = 2.2 Hz), 7.98 (1H, s), 8.06 (1H, d, J = 9.2 Hz), 8.18 (1H, dd, J = 6.9, 2.0 Hz), 8.31 - 8.41 (2H, m), 10.56 (1H, s), 11.09 (1H, s).

Example 378

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-(trifluoromethyl)nicotinamide



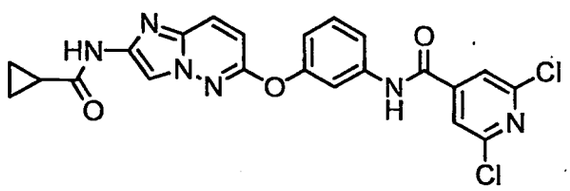
To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (95 mg, 0.307 mmol) in N,N-dimethylformamide (5 mL) were added 2-(trifluoromethyl)nicotinic acid (65 mg, 0.337 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.337 mmol) and 1-hydroxybenzotriazole (46 mg, 0.337 mmol), and

the mixture was stirred at room temperature for 2 hr, heated to 50°C and stirred for 2 hr. 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 solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→100/0), and precipitated from ethyl acetate/diisopropyl ether to give the title compound (79.6 mg, 54%) as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.87 - 1.98 (1H, m), 7.01 - 7.11 (2H, m), 7.41 - 7.53 (2H, m), 7.62 (1H, t, J = 2.0 Hz), 7.82 - 7.89 (1H, m), 7.94 - 7.99 (1H, m), 8.05 (1H, d, J = 9.6 Hz), 8.25 (1H, d, J = 7.5 Hz), 8.86 (1H, d, J = 4.7 Hz), 10.85 (1H, s), 11.09 (1H, s).

Example 379

Production of 2,6-dichloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]isonicotinamide



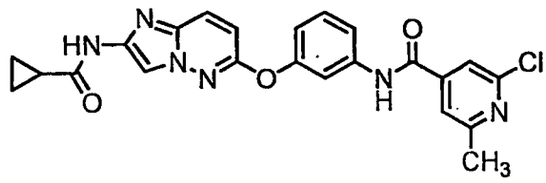
Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (95 mg, 0.307 mmol), 2,6-dichloropyridine-4-carboxylic acid (65 mg, 0.337 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.337 mmol), 1-hydroxybenzotriazole (46 mg, 0.337 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 377, the title compound (124 mg, 84%) was obtained as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.84 (4H, m), 1.87 - 1.98 (1H, m), 7.04 - 7.11 (2H, m), 7.47 (1H, t, J = 8.2 Hz), 7.60 - 7.65 (1H, m), 7.68 (1H, t, J = 2.1 Hz), 7.96 - 8.02 (3H, m), 8.06 (1H,

d, J = 9.2 Hz), 10.73 (1H, s), 11.09 (1H, s).

Example 380

Production of 2-chloro-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-6-methylisonicotinamide

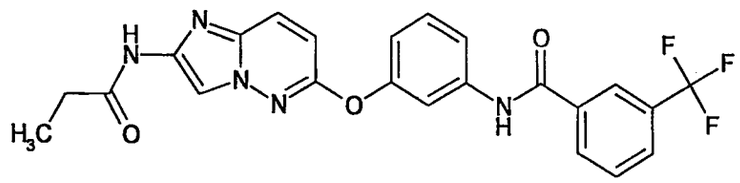


To a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (95 mg, 0.307 mmol) in N,N-dimethylformamide (5 mL) were added 2-chloro-6-methylpyridine-4-carboxylic acid (58 mg, 0.337 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (65 mg, 0.337 mmol) and 1-hydroxybenzotriazole (46 mg, 0.337 mmol), and the mixture was stirred at room temperature for 2 hr. 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 solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=3/97→100/0) and precipitated from ethyl acetate/hexane to give the title compound (115 mg, 82%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.83 (4H, m), 1.86 - 1.98 (1H, m), 2.55 (3H, s), 7.01 - 7.11 (2H, m), 7.46 (1H, t, J = 8.2 Hz), 7.60 - 7.79 (4H, m), 7.98 (1H, s), 8.06 (1H, d, J = 9.6 Hz), 10.64 (1H, s), 11.09 (1H, s).

Example 381

Production of N-(3-{[2-(propionylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(trifluoromethyl)benzamide

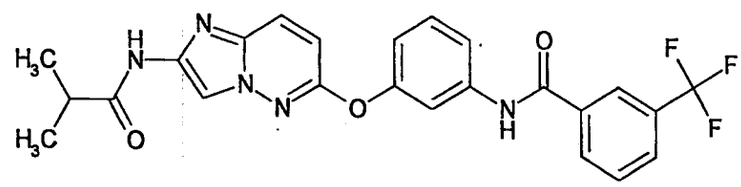


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.363 mmol), propionic acid (40 μL, 0.544 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (104 mg, 0.544 mmol), 1-hydroxybenzotriazole (73 mg, 0.544 mmol), triethylamine (76 μL, 0.544 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 380, the title compound (116 mg, 68%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.07 (3H, t, J = 7.5 Hz), 2.37 (2H, q, J = 7.5 Hz), 7.01 - 7.11 (2H, m), 7.46 (1H, t, J = 8.2 Hz), 7.65 - 7.83 (3H, m), 7.94 - 8.00 (1H, m), 8.02 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 8.22 - 8.30 (2H, m), 10.59 (1H, s), 10.75 (1H, s).

Example 382

Production of N-(3-{[2-(isobutyrylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(trifluoromethyl)benzamide



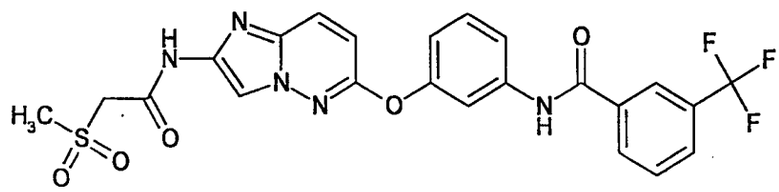
Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.363 mmol), 2-methylpropanoic acid (50 μL, 0.544 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (104 mg, 0.544 mmol), 1-hydroxybenzotriazole (73 mg, 0.544 mmol), triethylamine (76 μL, 0.544 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 380, the title compound (74 mg, 42%) was obtained as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.08 (6H, d, J = 7.0 Hz), 2.65 - 2.77 (1H, m), 7.00 - 7.11 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.63 -

7.83 (3H, m), 7.94 - 8.09 (3H, m), 8.22 - 8.30 (2H, m), 10.59 (1H, s), 10.75 (1H, s).

Example 383

Production of N-{3-[(2-{[(methylsulfonyl)acetyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide

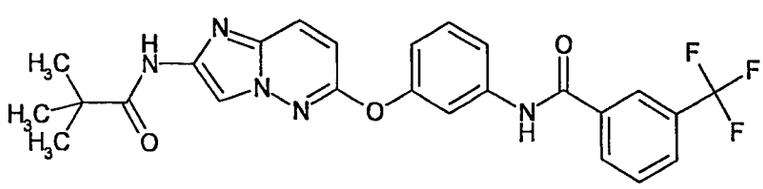


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.363 mmol), (methylsulfonyl)acetic acid (75 mg, 0.544 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (104 mg, 0.544 mmol), 1-hydroxybenzotriazole (73 mg, 0.544 mmol), triethylamine (76 μL, 0.544 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 377, the title compound (171 mg, 88%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.16 (3H, s), 4.37 (2H, m), 7.05 (1H, dd, J = 8.1, 2.0 Hz), 7.14 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.1 Hz), 7.65 - 7.83 (3H, m), 7.94 - 8.01 (1H, m), 8.06 (1H, s), 8.12 (1H, d, J = 9.6 Hz), 8.22 - 8.30 (2H, m), 10.60 (1H, s), 11.29 (1H, s).

Example 384

Production of N-[3-({2-[(2,2-dimethylpropanoyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

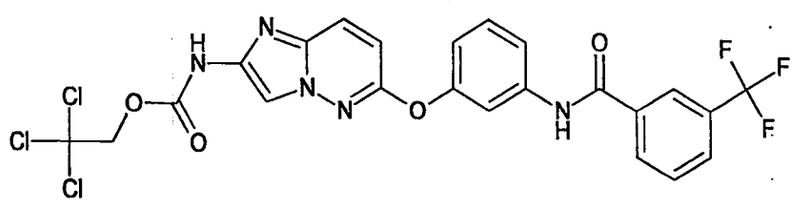


To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.363 mmol) in pyridine (5 mL) was added dropwise 2,2-dimethylpropanoyl chloride (49 μL, 0.399 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=0/100→50/50), and precipitated from ethyl acetate/hexane to give the title compound (90 mg, 50%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.22 (9 H, s), 6.99 - 7.12 (2 H, m), 7.46 (1 H, t, J=8.2 Hz), 7.63 - 7.84 (3 H, m), 7.98 (1 H, d, J=7.9 Hz), 8.05 (2 H, m), 8.22 - 8.30 (2 H, m), 10.36 (1 H, s), 10.60 (1 H, s)

Example 385

Production of 2,2,2-trichloroethyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate



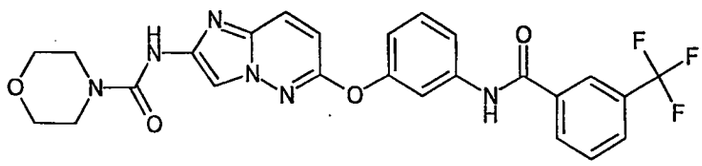
To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (400 mg, 0.967 mmol) in tetrahydrofuran (10 mL) were added dropwise 2,2,2-trichloroethyl chlorocarbonate (159 μL, 1.16 mmol) and triethylamine (202 μL, 1.45 mmol), and the mixture was stirred at room temperature for 16 hr. The solvent was evaporated under reduced pressure, and the residue was washed with diisopropyl ether and water to give the title compound (436 mg, 76%) as a

pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.97 (2H, s), 7.01 - 7.14 (2H, m), 7.46 (1H, t, J = 8.0 Hz), 7.64 - 7.88 (4H, m), 7.98 (1H, d, J = 8.0 Hz), 8.08 (1H, d, J = 9.6 Hz), 8.22 - 8.30 (2H, m), 10.59 (1H, s), 10.97 (1H, s).

Example 386

Production of N-[6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]morpholine-4-carboxamide

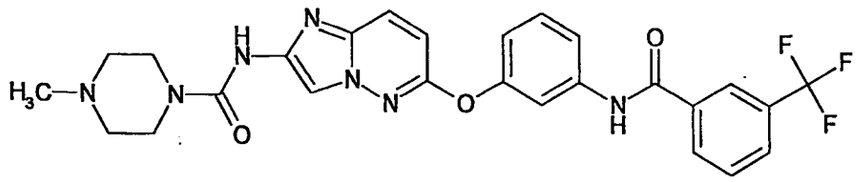


A mixture of 2,2,2-trichloroethyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate (140 mg, 0.237 mmol), morpholine (31 μL, 0.356 mmol), N,N-diisopropylpropan-2-amine (123 μL, 0.713 mmol) and dimethyl sulfoxide (10 mL) was heated to 80°C and the mixture was stirred for 24 hr. After the reaction mixture was allowed to cool to room temperature, saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) and precipitated from diisopropyl ether to give the title compound (92 mg, 73%) as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.41 - 3.49 (4H, m), 3.58 (4H, m), 6.98 - 7.06 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.64 - 7.83 (3H, m), 7.89 (1H, s), 7.93 - 8.03 (2H, m), 8.20 - 8.32 (2H, m), 9.56 (1H, s), 10.59 (1H, s).

Example 387

Production of 4-methyl-N-[6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]piperazine-1-carboxamide

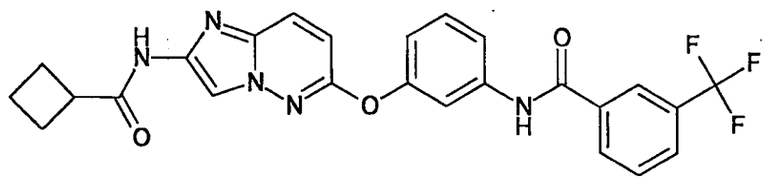


Using 2,2,2-trichloroethyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate (140 mg, 0.237 mmol), 1-methylpiperazine (40 μL, 0.356 mmol), N,N-diisopropylpropan-2-amine (123 μL, 0.713 mmol) and dimethyl sulfoxide (10 mL) as starting materials and in the same manner as in Example 386, the title compound (65 mg, 50%) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.18 (3H, s), 2.25 - 2.32 (4H, m), 3.41 - 3.49 (4H, m), 6.98 - 7.06 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.63 - 7.83 (3H, m), 7.88 (1H, s), 7.94 - 8.03 (2H, m), 8.22 - 8.30 (2H, m), 9.51 (1H, s), 10.59 (1H, s).

Example 388

Production of N-[3-({2-[(cyclobutylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



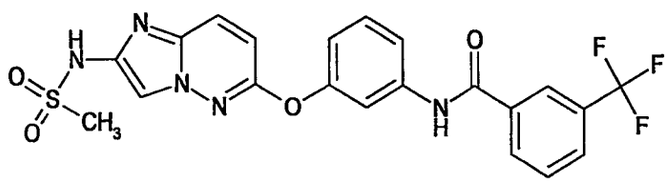
To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol) in tetrahydrofuran (5 mL) were added dropwise triethylamine (75 μL, 0.544 mmol) and cyclobutanecarbonyl chloride (50 μL, 0.435 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure,

and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give the title compound (98 mg, 54%) as a white powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.83 - 2.11 (2H, m), 2.15 - 2.46 (4H, m), 3.14 - 3.28 (1H, m), 6.88 (1H, d, J=9.4 Hz), 7.00 - 7.06 (1H, m), 7.42 - 7.48 (2H, m), 7.60 - 7.68 (1H, m), 7.69 - 7.85 (4H, m), 7.91 - 7.98 (1H, m), 8.04 - 8.09 (1H, m), 8.13 (1H, s), 8.19 (1H, s).

Example 389

Production of N-[3-({2-[(methylsulfonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

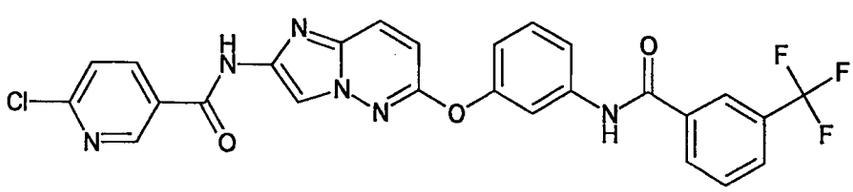


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), triethylamine (76 μL, 0.544 mmol), methanesulfonyl chloride (34 μL, 0.435 mmol) and tetrahydrofuran (5 mL) as starting materials and in the same manner as in Example 388, the title compound (108 mg, 61%) was obtained as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.13 (3H, s), 7.05 (1H, dd, J = 8.0, 1.6 Hz), 7.14 (1H, d, J = 9.6 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.63 - 7.84 (4H, m), 7.98 (1H, d, J = 8.0 Hz), 8.10 (1H, d, J = 9.6 Hz), 8.22 - 8.30 (2H, m), 10.29 (1H, s), 10.60 (1H, s).

Example 390

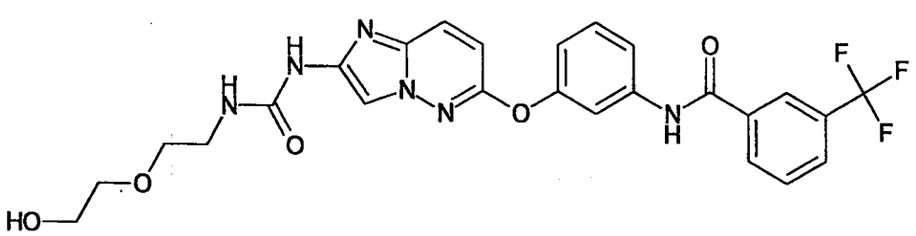
Production of 6-chloro-N-[6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]nicotinamide



Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), triethylamine (76 μL, 0.544 mmol), 6-chloronicotinoyl chloride (76 mg, 0.435 mmol) and tetrahydrofuran (5 mL) as starting materials and in the same manner as in Example 388, the title compound (155 mg, 77%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.07 (1H, dd, J = 8.2, 1.8 Hz), 7.15 (1H, d, J = 9.7 Hz), 7.48 (1H, t, J = 8.2 Hz), 7.69 (2H, d, J = 8.5 Hz), 7.74 - 7.84 (2H, m), 7.98 (1H, d, J = 7.7 Hz), 8.14 (1H, d, J = 9.7 Hz), 8.20 - 8.33 (3H, m), 8.43 (1H, dd, J = 8.5, 2.4 Hz), 9.03 (1H, d, J = 2.4 Hz), 10.61 (1H, s), 11.66 (1H, s).

Example 391

Production of N-(3-{[2-({[2-(2-hydroxyethoxy)ethyl]carbamoyl}amino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(trifluoromethyl)benzamide

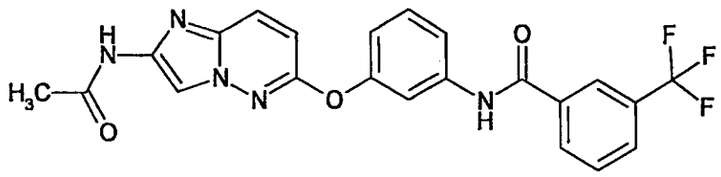


Using 2,2,2-trichloroethyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate (140 mg, 0.237 mmol), 2-(2-aminoethoxy)ethanol (43 μL, 0.435 mmol), N,N-diisopropylpropane-2-amine (76 μL, 0.435 mmol) and dimethyl sulfoxide (5 mL) as starting materials and in the same manner as in Example 386, the title compound (86 mg, 62%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.40 - 3.67 (8H, m), 4.58 (1H, t, J = 5.4 Hz), 6.67 (1H, brs), 7.01 (2H, d, J = 9.4 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.63 - 7.83 (4H, m), 7.93 - 8.02 (2H, m), 8.21 - 8.30 (2H, m), 9.11 (1H, s), 10.58 (1H, s).

Example 392

Production of N-{3-[(2-acetamidoimidazo[1,2-b]pyridazin-6-

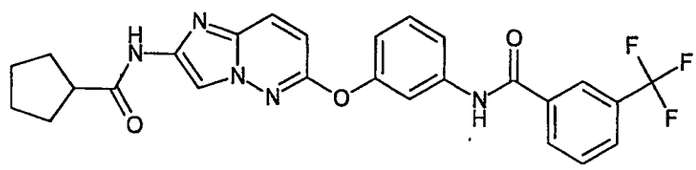
yl)oxy]phenyl}-3-(trifluoromethyl)benzamide



Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), acetyl chloride (31 μL, 0.435 mmol) and pyridine (3 mL) as starting materials and in the same manner as in Example 384, the title compound (99 mg, 60%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.07 (3H, s), 7.01 - 7.11 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.63 - 7.83 (3H, m), 7.95 - 8.01 (2H, m), 8.06 (1H, d, J = 9.6 Hz), 8.22 - 8.30 (2H, m), 10.59 (1H, s), 10.80 (1H, s).

Example 393

Production of N-[3-({2-[(cyclopentylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

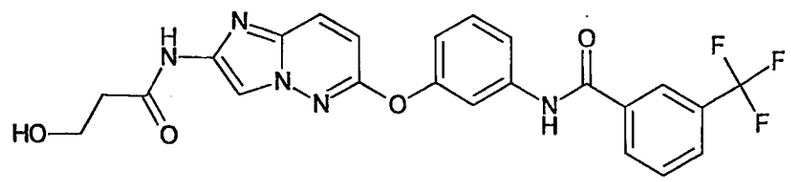


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), cyclopentanecarbonyl chloride (53 μL, 0.435 mmol), triethylamine (75 μL, 0.544 mmol) and tetrahydrofuran (5 mL) as starting materials and in the same manner as in Example 388, the title compound (105 mg, 57%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.47 - 1.90 (8H, m), 2.81 - 2.95 (1H, m), 7.00 - 7.10 (2H, m), 7.46 (1H, t, J = 8.2 Hz), 7.63 - 7.83 (3H, m), 7.94 - 8.09 (3H, m), 8.21 - 8.30 (2H, m), 10.59 (1H, s), 10.77 (1H, s).

Example 394

Production of N-[3-({2-[(3-hydroxypropanoyl)amino]imidazo[1,2-

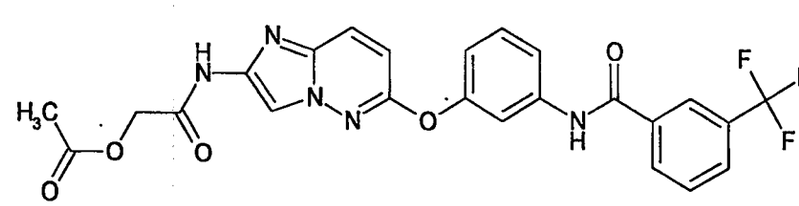
b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol) and 3-hydroxypropanoic acid (131 mg, 0.435 mmol) in N,N-dimethylformamide (5 mL) was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (160 mg, 0.544 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=30/70→100/0) and precipitated from ethanol to give the title compound (30 mg, 17%) as a pale-green powder. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.63 - 2.70 (2H, m), 3.73 (1H, brs), 3.96 - 4.03 (2H, m), 6.89 (1H, d, J = 9.4 Hz), 7.01 - 7.07 (1H, m), 7.42 - 7.48 (2H, m), 7.59 - 7.86 (4H, m), 7.95 (1H, s), 8.07 (1H, d, J = 7.9 Hz), 8.11 - 8.17 (2H, m), 8.54 (1H, s).

Example 395

Production of 2-oxo-2-{[6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}ethyl acetate



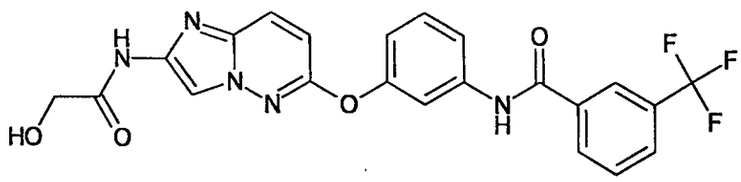
Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (300 mg, 0.725 mmol),

triethylamine (152 μL, 1.08 mmol), 2-chloro-2-oxoethyl acetate (94 μL, 0.870 mmol) and tetrahydrofuran (7 mL) as starting materials and in the same manner as in Example 388, the title compound (299 mg, 80%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 2.11 (3H, s), 4.70 (2H, s), 7.04 (1H, dd, J = 8.6, 2.0 Hz), 7.11 (1H, d, J = 9.8 Hz), 7.46 (1H, t, J = 8.0 Hz), 7.64 - 7.83 (3H, m), 7.94 - 8.02 (2H, m), 8.09 (1H, d, J = 9.8 Hz), 8.22 - 8.30 (2H, m), 10.59 (1H, s), 11.03 (1H, s).

Example 396

Production of N-(3-{[2-(glycoloylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)-3-(trifluoromethyl)benzamide



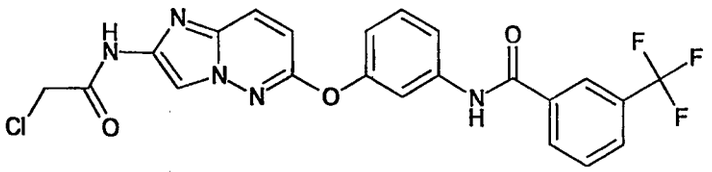
A mixture of 2-oxo-2-{[6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}ethyl acetate (250 mg, 0.486 mmol), 1N aqueous sodium hydroxide solution (3 mL) and methanol (5 mL) was stirred at room temperature for 3 hr. The reaction mixture was neutralized by the addition of 1N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethanol to give the title compound (185 mg, 81%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.02 - 4.08 (2H, m), 5.46 - 5.55 (1H, m), 7.05 (1H, dd, J = 7.6, 2.2 Hz), 7.11 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.64 - 7.83 (3H, m), 7.98 (1H, d, J = 8.0 Hz), 8.03 - 8.12 (2H, m), 8.22 - 8.30 (2H, m), 10.23 (1H, s), 10.60 (1H, s).

Example 397

Production of N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-

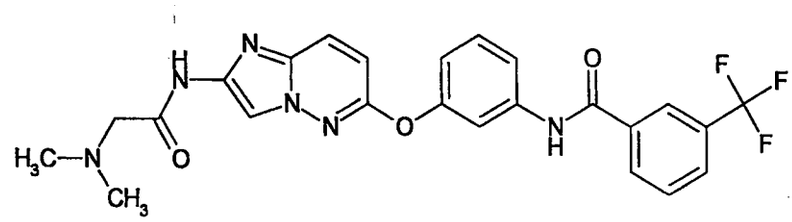
b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



To a solution of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (500 mg, 1.20 mmol) in tetrahydrofuran (10 mL) were added chloroacetyl chloride (168 μL, 1.45 mmol) and triethylamine (253 μL, 1.81 mmol), and the mixture was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethanol to give the title compound (418 mg, 71%) as a pale-yellow powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 4.31 (2H, s), 7.05 (1H, dd, J = 8.2, 2.4 Hz), 7.12 (1H, d, J = 9.4 Hz), 7.47 (1 H, t, J = 8.2 Hz), 7.64 - 7.84 (3H, m), 7.93 - 8.13 (3H, m), 8.21 - 8.30 (2H, m), 10.59 (1H, s), 11.20 (1H, s).

Example 398

Production of N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide



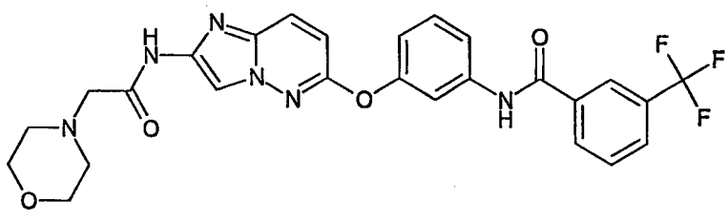
A mixture of N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (120 mg, 0.244 mmol), aqueous dimethylamine (3 mL) solution and acetonitrile (3 mL) was heated to 80°C and stirred for 3 hr. After the reaction mixture was allowed to cool to room temperature, saturated aqueous sodium hydrogencarbonate solution

was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethanol to give the title compound (85 mg, 70%) as a pale-yellow powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.37 (6H, s), 3.11 (2H, s), 6.88 (1H, d, J = 9.6 Hz), 6.99 - 7.06 (1H, m), 7.39 - 7.50 (2H, m), 7.63 (1H, t, J = 7.9 Hz), 7.69 - 7.72 (1H, m), 7.75 (1H, d, J = 9.6 Hz), 7.81 (1H, d, J = 7.9 Hz), 8.00 (1H, s), 8.06 (1H, d, J = 7.5 Hz), 8.13 (1H, s), 8.21 (1H, s), 9.65 (1H, brs).

Example 399

Production of N-[3-({2-[(morpholin-4-ylacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

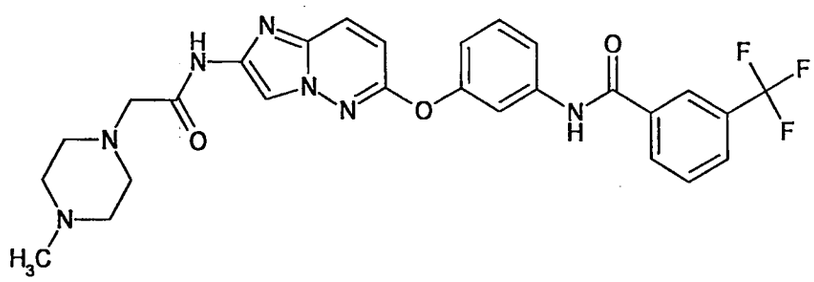


Using N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (120 mg, 0.244 mmol), morpholine (1 mL) and acetonitrile (3 mL) as starting materials and in the same manner as in Example 398, the title compound (116 mg, 87%) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.59 - 2.65 (4H, m), 3.18 (2H, s), 3.75 - 3.82 (4H, m), 6.90 (1H, d, J = 9.6 Hz), 7.01 - 7.07 (1H, m), 7.42 - 7.46 (2H, m), 7.59 - 7.68 (1H, m), 7.71 - 7.85 (3H, m), 7.92 - 7.98 (1H, m), 8.06 (1H, d, J = 7.9 Hz), 8.13 (1H, s), 8.21 (1H, s), 9.50 (1H, s).

Example 400

Production of N-{3-[(2-{[(4-methylpiperazin-1-yl)acetyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide

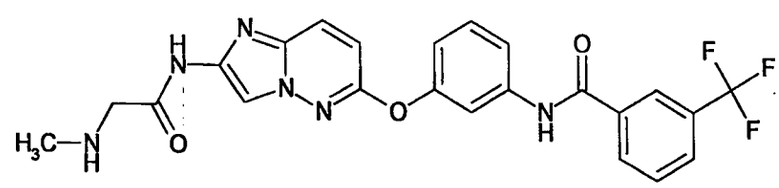


Using N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (120 mg, 0.244 mmol), 1-methylpiperazine (1 mL) and acetonitrile (2 mL) as starting materials and in the same manner as in Example 398, the title compound (67 mg, 50%) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.32 (3H, s), 2.43 - 2.74 (8H, m), 3.18 (2H, s), 6.89 (1H, d, J = 9.6 Hz), 7.00 - 7.07 (1H, m), 7.41 - 7.48 (2H, m), 7.64 (1H, t, J = 7.8 Hz), 7.71 - 7.85 (3H, m), 7.96 - 8.01 (1H, m), 8.06 (1H, d, J = 7.8 Hz), 8.13 (1H, s), 8.21 (1H, s), 9.55 (1H, s).

Example 401

Production of N-[3-({2-[(N-methylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

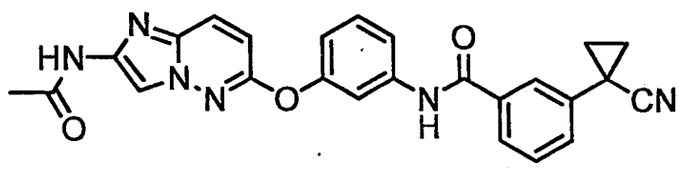


Using N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide (92 mg, 0.187 mmol), methylamine/methanol (2 mL) solution and acetonitrile (1 mL) as starting materials and in the same manner as in Example 398, the title compound (22 mg, 25%) was obtained as a white powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.50 (3H, s), 3.39 (2H, s), 6.88 (1H, d, J = 9.4 Hz), 7.03 (1H, dd, J = 6.7, 2.0 Hz), 7.39 - 7.51 (2H, m), 7.59 - 7.85 (4H, m), 7.93 - 8.10 (2H, m), 8.13 (1H, s), 8.20 - 8.25 (1H, m), 9.72 (1H, s).

Example 402

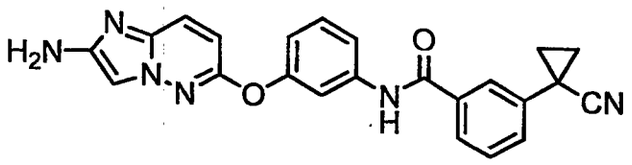
Production of N-{3-[(2-acetamidoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide



To a solution of 3-(1-cyanocyclopropyl)benzoic acid (1.50 g, 8.01 mmol) in tetrahydrofuran (30 mL) were added N,N-dimethylformamide (2 drops) and oxalyl chloride (1.16 mL, 13.3 mmol), and the mixture was stirred at room temperature for 1.5 hr. The solvent was evaporated under reduced pressure, and the residue and N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]acetamide (1.89 g, 6.67 mmol) were dissolved in N-methylpyrrolidone (30 mL), and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and filtrated, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=0/100→100/0) to give the title compound (2.25 g, 75%) as a pale-brown powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.77 - 1.84 (2H, m), 2.07 (3H, s), 6.99 - 7.11 (2H, m), 7.45 (1H, t, J = 8.2 Hz), 7.51 - 7.60 (2H, m), 7.62 - 7.68 (1H, m), 7.72 (1H, t, J = 2.1 Hz), 7.82 (1H, s), 7.84 - 7.90 (1H, m), 8.00 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.42 (1H, s), 10.80 (1H, s).

Example 403

Production of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide

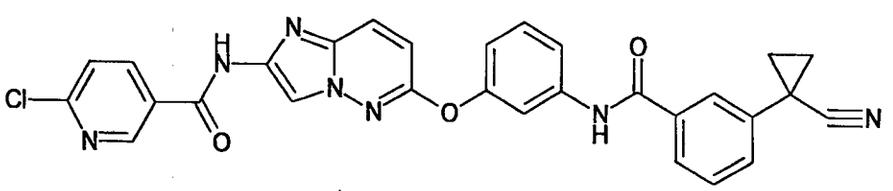


A mixture of N-{3-[(2-acetamidoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (2.20 g, 4.86 mmol), 4N hydrochloric acid-ethyl acetate solution (35 mL) and methanol (35 mL) was stirred at room temperature for 14 hr. The reaction mixture was neutralized by the addition of 8N aqueous sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with diisopropyl ether to give the title compound (1.63 g, 82%) as a yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.64 (2H, m), 1.77 - 1.84 (2H, m), 5.34 (2H, brs), 6.80 (1H, d, J = 9.3 Hz), 6.91 - 6.97 (1H, m), 7.15 (1H, s), 7.41 (1H, t, J = 8.3 Hz), 7.51 - 7.67 (4H, m), 7.73 (1H, d, J = 9.3 Hz), 7.81 (1H, s), 7.84 - 7.89 (1H, m), 10.38 (1H, s).

Example 404

Production of 6-chloro-N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]nicotinamide

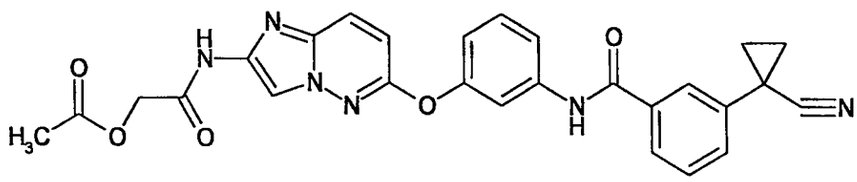


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (120 mg, 0.292 mmol), 6-chloronicotinoyl chloride (61 mg, 0.350 mmol), triethylamine (62 μL, 0.438 mmol) and tetrahydrofuran (5 mL) as starting materials and in the same manner as in Example 385, the title compound (121 mg, 75%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.78 - 1.84 (2H, m), 7.05 (1H, dd, J = 8.2, 1.8 Hz), 7.14 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.52 - 7.60 (2H, m), 7.64 - 7.72 (2H, m), 7.73 - 7.77 (1H, m), 7.82 (1H, s), 7.85 - 7.91 (1H, m), 8.13 (1H, d, J = 9.6 Hz), 8.22 (1H, s), 8.43 (1H, dd, J = 8.2, 2.4 Hz), 9.02 (1H, d, J = 2.4 Hz), 10.44 (1H, s), 11.65 (1H, s).

Example 405

Production of 2-{[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}-2-oxoethyl acetate

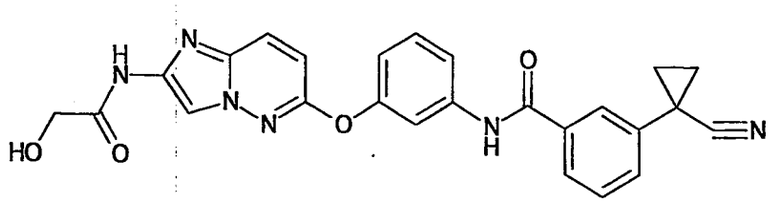


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (200 mg, 0.487 mmol), triethylamine (101 μL, 0.730 mmol), 2-chloro-2-oxoethyl acetate (63 μL, 0.584 mmol) and tetrahydrofuran (5 mL) as starting materials and in the same manner as in Example 385, the title compound (183 mg, 74%) was obtained as a gray powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.77 - 1.85 (2H, m), 2.11 (3H, s), 4.70 (2H, s), 7.02 (1H, dd, J = 7.9, 2.0 Hz), 7.10 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 7.9 Hz), 7.51 - 7.61 (2H, m), 7.66 (1H, d, J = 7.9 Hz), 7.72 (1H, t, J = 2.0 Hz), 7.82 (1H, s), 7.84 - 7.90 (1H, m), 8.00 (1H, s), 8.08 (1H, d, J = 9.6 Hz), 10.42 (1H, s), 11.03 (1H, s).

Example 406

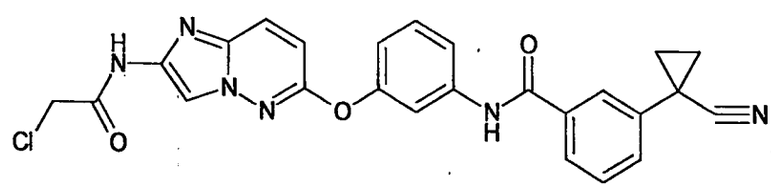
Production of 3-(1-cyanocyclopropyl)-N-(3-{[2-(glycoloylamino)imidazo[1,2-b]pyridazin-6-yl]oxy}phenyl)benzamide



Using 2-{[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]amino}-2-oxoethyl acetate (130 mg, 0.254 mmol), 1N aqueous sodium hydroxide solution (1.5 mL) and methanol (3 mL) as starting materials and in the same manner as in Example 396, the title compound (59 mg, 50%) was obtained as a pale-yellow powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.64 (2H, m), 1.78 - 1.84 (2H, m), 4.02 - 4.08 (2H, m), 5.47 - 5.54 (1H, m), 7.03 (1H, dd, J = 8.0, 2.0Hz), 7.10 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.0Hz), 7.53 - 7.59 (2H, m), 7.63 - 7.69 (1H, m), 7.73 (1H, t, J = 2.0), 7.81 (1H, d, J = 2.0), 7.84 - 7.90 (1H, m), 8.03 - 8.11 (2H, m), 10.22 (1H, s), 10.42 (1H, s).

Example 407

Production of N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1-cyanocyclopropyl)benzamide



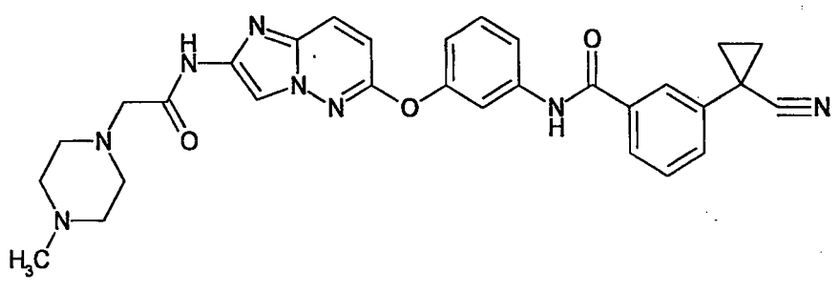
Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (600 mg, 1.46 mmol), triethylamine (305 μL, 2.19 mmol), chloroacetyl chloride (202 μL, 1.75 mmol) and tetrahydrofuran (10 mL) as starting materials and in the same manner as in Example 385, the title compound (636 mg, 89%) was obtained as a gray powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.57 - 1.65 (2H, m), 1.77 - 1.85 (2H, m), 4.31 (2H, s), 7.03 (1H, dd, J = 8.0, 2.2 Hz), 7.12 (1H, d, J = 9.6 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.52 - 7.60 (2H, m), 7.66 (1H, d, J = 8.0 Hz), 7.73 (1H, t, J = 2.2 Hz), 7.82 (1H, s), 7.85 - 7.91 (1H, m), 8.04 (1H, s), 8.09 (1H, d, J = 9.6 Hz),

903

10.43 (1H, s), 11.20 (1H, s).

Example 408

Production of 3-(1-cyanocyclopropyl)-N-{3-[(2-{[(4-methylpiperazin-1-yl)acetyl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}benzamide

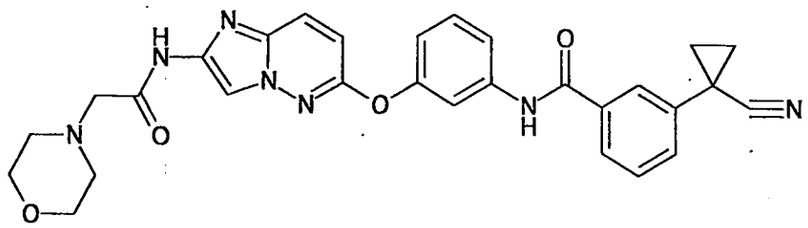


A mixture of N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1-cyanocyclopropyl)benzamide (140 mg, 0.287 mmol), 1-methylpiperazine (1 mL) and acetonitrile (2 mL) was stirred with heating at 80°C for 4 hr. After the reaction mixture was allowed to cool to room temperature, saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by NH silica gel column chromatography (ethyl acetate/hexane=0/100→100/0) to give the title compound (65 mg, 41%) as a white powder.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.43 - 1.53 (2H, m), 1.75 - 1.83 (2H, m), 2.32 (3H, s), 2.40 - 2.72 (8H, m), 3.18 (2H, s), 6.89 (1H, d, J = 9.6 Hz), 6.98 - 7.05 (1H, m), 7.38 - 7.59 (4H, m), 7.69 - 7.80 (4H, m), 8.01 (1H, s), 8.21 (1H, s), 9.55 (1H, s).

Example 409

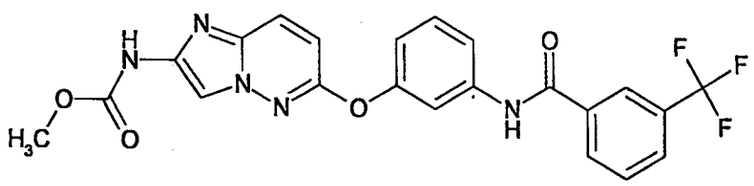
Production of 3-(1-cyanocyclopropyl)-N-[3-({2-[(morpholin-4-ylacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide



Using N-[3-({2-[(chloroacetyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(1-cyanocyclopropyl)benzamide (140 mg, 0.287 mmol), morpholine (1 mL) and acetonitrile (2 mL) as starting materials and in the same manner as in Example 408, the title compound (123 mg, 79%) was obtained as a white powder.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.45 - 1.52 (2H, m), 1.75 - 1.82 (2H, m), 2.59 - 2.66 (4H, m), 3.18 (2H, s), 3.75 - 3.82 (4H, m), 6.90 (1H, d, J = 9.4 Hz), 6.98 - 7.05 (1H, m), 7.37 - 7.59 (4H, m), 7.70 - 7.79 (4H, m), 8.02 (1H, s), 8.20 (1H, s), 9.50 (1H, s).

Example 410

Production of methyl [6-(3-{[3-(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate

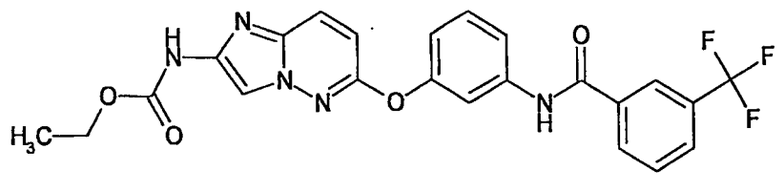


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), methyl chlorocarbonate (33 μL, 0.435 mmol), triethylamine (75 μL, 0.544 mmol) and tetrahydrofuran (3 mL) as starting materials and in the same manner as in Example 388, the title compound (104 mg, 61%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.68 (3H, s), 7.01 - 7.09 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.64 - 7.84 (4H, m), 7.94 - 8.06 (2H, m), 8.22 - 8.30 (2H, m), 10.40 (1H, brs), 10.58 (1H, s).

Example 411

Production of ethyl [6-(3-{[3-

(trifluoromethyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]carbamate

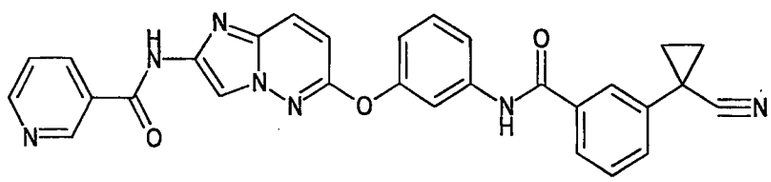


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (150 mg, 0.362 mmol), ethyl chlorocarbonate (41 μL, 0.435 mmol), triethylamine (75 μL, 0.544 mmol) and tetrahydrofuran (3 mL) as starting materials and in the same manner as in Example 388, the title compound (109 mg, 62%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.23 (3H, t, J = 7.1 Hz), 4.14 (2H, q, J = 7.1 Hz), 7.00 - 7.09 (2H, m), 7.46 (1H, t, J = 8.1 Hz), 7.63 - 7.84 (4H, m), 7.94 - 8.06 (2H, m), 8.22 - 8.30 (2H, m), 10.33 (1H, brs), 10.58 (1H, s).

Example 412

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]nicotinamide

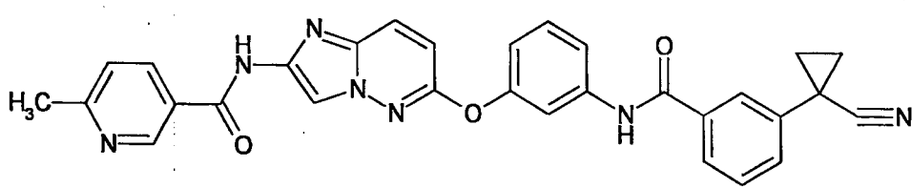


To a solution of nicotinic acid (54 mg, 0.438 mmol) in tetrahydrofuran (3 mL) were added N,N-dimethylformamide (1 drop) and oxalyl chloride (64 μL, 0.734 mmol), and the mixture was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure, and the residue and N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol) were dissolved in N-methylpyrrolidone (3 mL), and the mixture was stirred at room temperature for 14 hr. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture,

and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=20/80→100/0) to give the title compound (100 mg, 53%) as a pale-green powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.57 - 1.65 (2H, m), 1.76 - 1.85 (2H, m), 7.05 (1H, d, J = 8.5 Hz), 7.14 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.1 Hz), 7.51 - 7.61 (3H, m), 7.63 - 7.93 (4H, m), 8.13 (1H, d, J = 9.6 Hz), 8.24 (1H, s), 8.39 (1H, d, J = 7.7 Hz), 8.75 (1H, d, J = 4.9 Hz), 9.18 (1H, d, J = 1.1 Hz), 10.44 (1H, s), 11.57 (1H, s).

Example 413

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]-6-methylnicotinamide

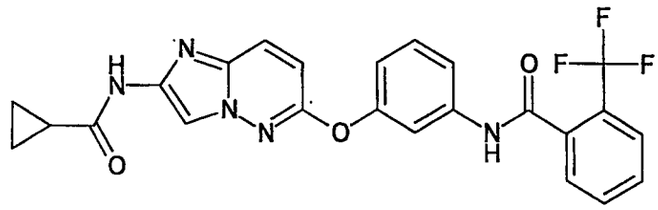


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol), 6-methylnicotinoyl chloride (75 mg, 0.548 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (105 mg, 0.548 mmol), 1-hydroxybenzotriazole (74 mg, 0.548 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 380, the title compound (44 mg, 23%) was obtained as a pale-green powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.59 - 1.65 (2H, m), 1.78 - 1.84 (2H, m), 2.55 (3H, s), 7.03 - 7.07 (1H, m), 7.14 (1H, d, J = 9.6 Hz), 7.40 (1H, d, J = 8.2 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.54 - 7.60 (2H, m), 7.65 - 7.69 (1H, m), 7.75 (1H, t, J = 2.2 Hz), 7.81 - 7.83 (1H, m), 7.86 - 7.90 (1H, m), 8.12 (1H, dd, J = 9.6, 0.5 Hz), 8.22 (1H, s), 8.29 (1H, dd, J = 8.2, 2.2 Hz), 9.08 (1H, d,

J = 2.2 Hz), 10.45 (1H, s), 11.50 (1H, s).

Example 414

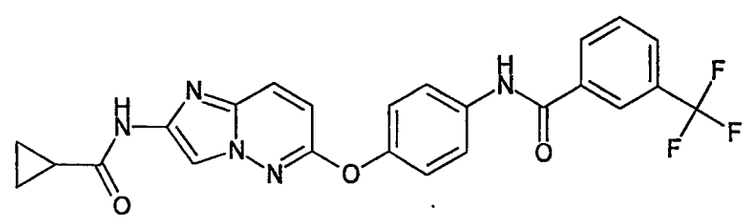
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2-(trifluoromethyl)benzamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol), 2-(trifluoromethyl)benzoic acid (110 mg, 0.581 mmol), oxalyl chloride (84 μL, 0.969 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (5 mL) and N-methylpyrrolidone (5 mL) as starting materials and in the same manner as in Example 412, the title compound (175 mg, 75%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.84 (4H, m), 1.86 - 1.98 (1H, m), 6.98 - 7.04 (1H, m), 7.07 (1H, d, J = 9.6 Hz), 7.43 (1H, t, J = 8.1 Hz), 7.51 - 7.57 (1H, m), 7.64 (1H, t, J = 2.1 Hz), 7.67 - 7.76 (2H, m), 7.76 - 7.88 (2H, m), 7.98 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 10.71 (1H, s), 11.07 (1H, s).

Example 415

Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide

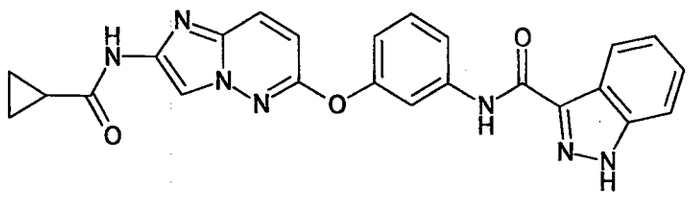


Using N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol), 3-(trifluoromethyl)benzoic acid (110 mg, 0.581 mmol), oxalyl chloride (84 μL, 0.969 mmol), N,N-dimethylformamide (1 drop),

tetrahydrofuran (5 mL) and N-methylpyrrolidone (5 mL) as starting materials and in the same manner as in Example 412, the title compound (57 mg, 24%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.86 - 1.97 (1H, m), 7.05 (1H, d, J = 9.6 Hz), 7.29 (2H, d, J = 8.9 Hz), 7.77 - 7.88 (3H, m), 7.94 (1H, s), 7.96 - 8.06 (2H, m), 8.25 - 8.32 (2H, m), 10.57 (1H, s), 11.06 (1H, s).

Example 416

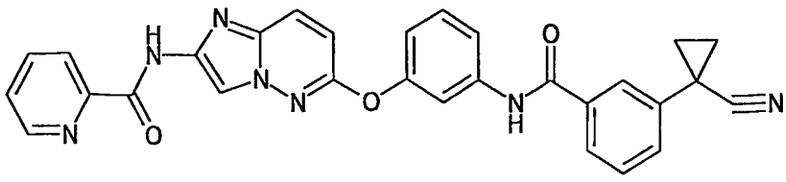
Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-indazole-3-carboxamide



Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol), 1H-indazole-3-carboxylic acid (94 mg, 0.581 mmol), oxalyl chloride (84 μL, 0.969 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (5 mL) and N-methylpyrrolidone (5 mL) as starting materials and in the same manner as in Example 412, the title compound (149 mg, 68%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.84 - 1.98 (1H, m), 6.98 (1H, dd, J = 7.6, 2.0 Hz), 7.07 (1H, d, J = 9.6 Hz), 7.28 (1H, t, J = 7.6 Hz), 7.38 - 7.49 (2H, m), 7.66 (1H, d, J = 8.3 Hz), 7.78 - 7.83 (1H, m), 7.88 (1H, t, J = 2.0 Hz), 7.99 (1H, s), 8.05 (1H, d, J = 9.6 Hz), 8.20 (1H, d, J = 8.3 Hz), 10.51 (1H, s), 11.08 (1H, s), 13.79 (1H, brs).

Example 417

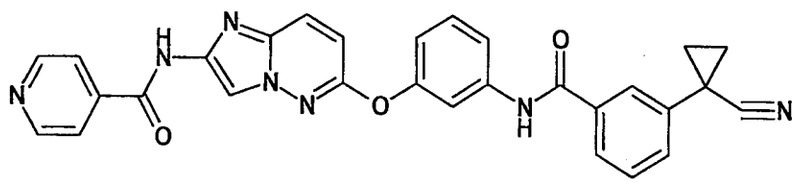
Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]pyridine-2-carboxamide



Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol), pyridine-2-carboxylic acid (54 mg, 0.438 mmol), oxalyl chloride (63 μL), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N-methylpyrrolidone (5 mL) as starting materials and in the same manner as in Example 412, the title compound (125 mg, 67%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.78 - 1.85 (2H, m), 7.05 (1H, dd, J = 8.0, 1.8 Hz), 7.16 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.52 - 7.61 (2H, m), 7.65 - 7.77 (3H, m), 7.83 (1H, s), 7.85 - 7.91 (1H, m), 8.05 - 8.20 (3H, m), 8.24 (1H, s), 8.73 - 8.78 (1H, m), 10.44 (1H, s), 10.69 (1H, s).

Example 418

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]isonicotinamide

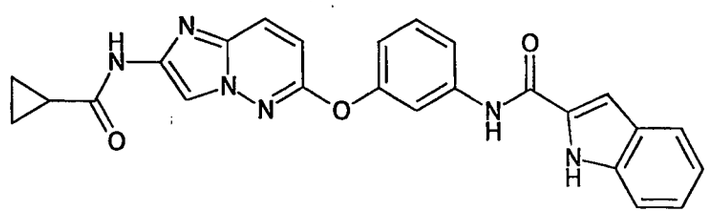


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol), pyridine-4-carboxylic acid (54 mg, 0.438 mmol), oxalyl chloride (63 μL, 0.734 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N-methylpyrrolidone (3 mL) as starting materials and in the same manner as in Example 412, the title compound (111 mg, 59%) was obtained as a pale-green powder.
1H-NMR (DMSO-d_6, 300 MHz) δ 1.57 - 1.65 (2H, m), 1.77 - 1.85 (2H, m), 7.01 - 7.09 (1H, m), 7.15 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.51 - 7.61 (2H, m), 7.64 - 7.70 (1H, m), 7.75 (1H,

t, J = 2.1 Hz), 7.79 - 7.84 (1H, m), 7.85 - 7.91 (1H, m), 7.93 - 7.98 (2H, m), 8.13 (1H, d, J = 9.6 Hz), 8.24 (1H, s), 8.73 - 8.81 (2H, m), 10.44 (1H, s), 11.67 (1H, s).

Example 419

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1H-indole-2-carboxamide

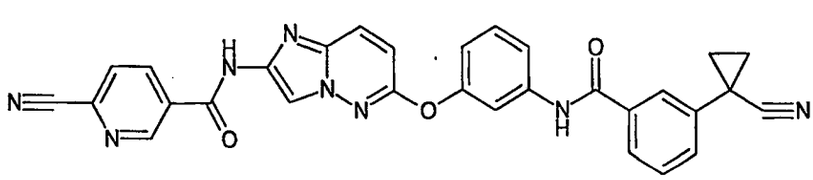


Using N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol), 1H-indole-2-carboxylic acid (93 mg, 0.581 mmol), oxalyl chloride (84 μL, 0.969 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (5 mL) and N-methylpyrrolidone (3 mL) as starting materials and in the same manner as in Example 412, the title compound (153 mg, 70%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.83 - 2.01 (1H, m), 6.96 - 7.12 (3H, m), 7.18 - 7.26 (1H, m), 7.39 - 7.49 (3H, m), 7.69 (2H, t, J = 8.1 Hz), 7.76 (1H, t, J = 2.1 Hz), 8.00 (1H, s), 8.06 (1H, d, J = 9.4 Hz), 10.33 (1H, s), 11.09 (1H, s), 11.75 (1H, s).

Example 420

Production of 6-cyano-N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]nicotinamide



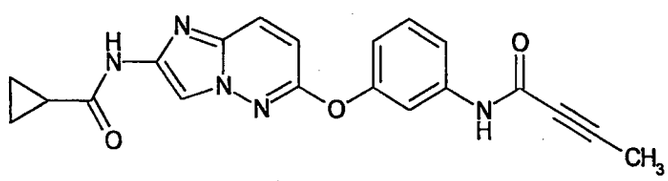
A mixture of 6-chloro-N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-

2-yl]nicotinamide (120 mg, 0.201 mmol), tetrakis(triphenylphosphine)palladium (0) (58 mg, 50.4 μmol), zinc cyanide (26 mg, 0.225 mmol) and N,N-dimethylformamide (2.5 mL) was stirred with heating under an argon atmosphere at 100°C for 6.5 hr. After the reaction mixture was allowed to cool to room temperature, saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=50/50→100/0) to give the title compound (51 mg, 47%) as a yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.78 - 1.85 (2H, m), 7.05 (1H, dd, J = 8.2, 1.4 Hz), 7.16 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.51 - 7.60 (2H, m), 7.67 (1H, d, J = 8.5 Hz), 7.74 - 7.91 (3H, m), 8.14 (1H, d, J = 9.6 Hz), 8.19 - 8.27 (2H, m), 8.60 (1H, dd, J = 8.0, 2.0 Hz), 9.29 (1H, s), 10.45 (1H, s), 11.84 (1H, s).

Example 421

Production of N-{6-[3-(but-2-ynoylamino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide



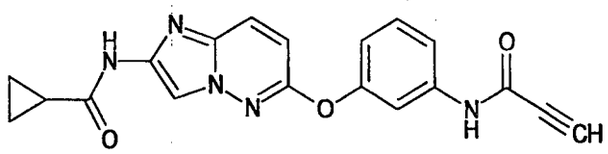
To a solution of but-2-ynoic acid (61 mg, 0.581 mmol) in tetrahydrofuran (3 mL) were added isobutyl chlorocarbonate (76 μL, 0.581 mmol) and 4-methylmorpholine (80 μL, 0.727 mmol), a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol) in pyridine (1.5 mL)/N,N-dimethylformamide (2 mL) was further added under ice-cooling, and the mixture was stirred at room temperature for 3 hr. Saturated aqueous sodium hydrogencarbonate solution was

added to the reaction mixture, and the mixture was extracted with ethyl acetate/tetrahydrofuran. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was washed with ethyl acetate to give the title compound (132 mg, 73%) as a pale-orange powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.85 (4H, m), 1.86 - 1.97 (1H, m), 2.04 (3H, s), 6.92 - 6.99 (1H, m), 7.04 (1H, d, J = 9.6 Hz), 7.32 - 7.47 (2H, m), 7.54 (1H, t, J = 1.9 Hz), 7.93 - 7.99 (1H, m), 8.04 (1H, d, J = 9.6 Hz), 10.75 (1H, s), 11.08 (1H, s).

Example 422

Production of N-{6-[3-(propioloylamino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

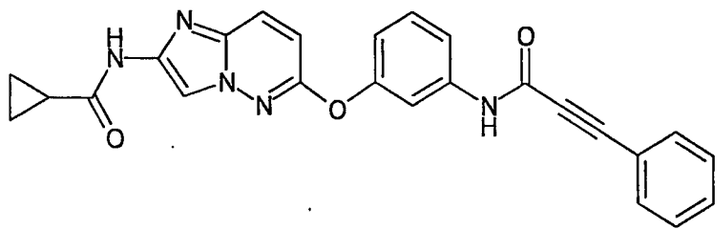


To a solution of propiolic acid (27 mg, 0.387 mmol) in tetrahydrofuran (2 mL) and N,N-dimethylformamide (2 mL) was added N,N'-dicyclohexylcarbodiimide (100 mg, 0.484 mmol) under ice-cooling, and the mixture was stirred for 30 min. To the reaction mixture was added N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (100 mg, 0.323 mmol), and the mixture was stirred under ice-cooling for 4 hr. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=0/100→100/0) to give the title compound (24 mg, 21%) as a pale-orange powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.85 (4H, m), 1.87 - 1.98 (1H, m), 4.45 (1H, s), 6.97 - 7.08 (2H, m), 7.35 - 7.48 (2H, m), 7.51 - 7.57 (1H, m), 7.96 (1H, s), 8.04 (1H, d, J = 9.8 Hz), 10.95 (1H, s), 11.08 (1H, s).

Example 423

Production of N-(6-{3-[(3-phenylprop-2-ynoyl)amino]phenoxy}imidazo[1,2-b]pyridazin-2-yl)cyclopropanecarboxamide

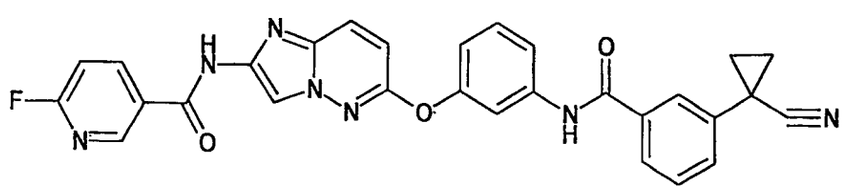


To a solution of 3-phenylprop-2-ynoic acid (85 mg, 0.581 mmol) in tetrahydrofuran (3 mL) were added isobutyl chlorocarbonate (76 μL, 0.581 mmol) and 4-methylmorpholine (80 μL, 0.727 mmol) under ice-cooling, a solution of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (150 mg, 0.484 mmol) in N,N-dimethylformamide (3 mL) was further added thereto, and the mixture was stirred at room temperature for 16 hr. Water was added to the reaction mixture, and the precipitated solid was filtrated and washed with water to give the title compound (188 mg, 89%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.84 (4H, m), 1.88 - 1.98 (1H, m), 6.98 - 7.04 (1H, m), 7.06 (1H, d, J = 9.5 Hz), 7.38 - 7.56 (5H, m), 7.59 (1H, t, J = 2.0 Hz), 7.62 - 7.68 (2H, m), 7.98 (1H, s), 8.05 (1H, d, J = 9.5 Hz), 11.01 (1H, s), 11.08 (1H, s).

Example 424

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]-6-fluoronicotinamide



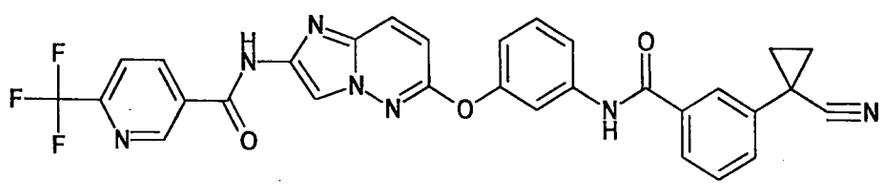
Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol), 6-fluoronicotinic acid (61 mg, 0.438 mmol), oxalyl

chloride (64 μL, 0.730 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) as starting materials and in the same manner as in Example 412, the title compound (38 mg, 20%) was obtained as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.57 - 1.65 (2H, m), 1.78 - 1.85 (2H, m), 7.05 (1H, dd, J = 8.2, 2.2 Hz), 7.15 (1H, d, J = 9.5 Hz), 7.35 (1H, dd, J = 8.2, 2.8 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.52 - 7.60 (2H, m), 7.64 - 7.69 (1H, m), 7.75 (1H, t, J = 2.2 Hz), 7.80 - 7.84 (1H, m), 7.85 - 7.91 (1H, m), 8.13 (1H, d, J = 9.5 Hz), 8.22 (1H, s), 8.55 - 8.63 (1H, m), 8.90 (1H, d, J = 2.2 Hz), 10.45 (1H, s), 11.61 (1H, s).

Example 425

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]-6-(trifluoromethyl)nicotinamide

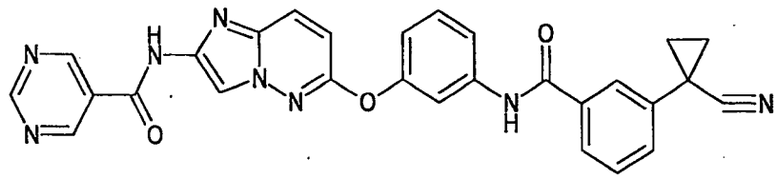


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (150 mg, 0.365 mmol), 6-(trifluoromethyl)nicotinic acid (83 mg, 0.438 mmol), oxalyl chloride (64 μL, 0.730 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) as starting materials and in the same manner as in Example 412, the title compound (57 mg, 27%) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.58 - 1.65 (2H, m), 1.78 - 1.85 (2H, m), 7.03 - 7.09 (1H, m), 7.16 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.1 Hz), 7.52 - 7.61 (2H, m), 7.64 - 7.70 (1H, m), 7.74 - 7.85 (2H, m), 7.86 - 7.91 (1H, m), 8.06 - 8.18 (2H, m), 8.25 (1H, s), 8.62 - 8.69 (1H, m), 9.31 - 9.35 (1H, m), 10.45 (1H, s), 11.83 (1H, s).

Example 426

Production of N-[6-(3-{[3-(1-cyanocyclopropyl)benzoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]pyrimidine-5-carboxamide

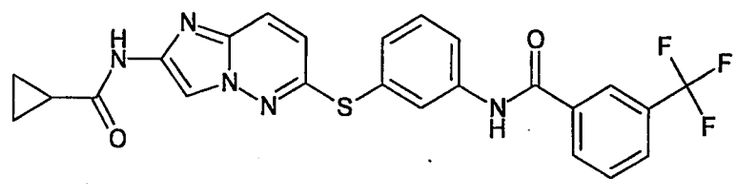


Using N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(1-cyanocyclopropyl)benzamide (140 mg, 0.313 mmol), pyrimidine-5-carboxylic acid (58 mg, 0.471 mmol), N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (90 mg, 0.471 mmol), 1-hydroxybenzotriazole (63 mg, 0.471 mmol), triethylamine (60 μL, 0.471 mmol) and N,N-dimethylformamide (5 mL) as starting materials and in the same manner as in Example 380, the title compound (42 mg, 26%) was obtained as a pale-yellow powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.59 - 1.65 (2H, m), 1.79 - 1.85 (2H, m), 7.03 - 7.08 (1H, m), 7.16 (1H, d, J = 9.6 Hz), 7.47 (1H, t, J = 8.2 Hz), 7.54 - 7.60 (2H, m), 7.65 - 7.70 (1H, m), 7.76 (1H, t, J = 2.1 Hz), 7.81 - 7.84 (1H, m), 7.86 - 7.91 (1H, m), 8.15 (1H, dd, J = 9.6, 0.7 Hz), 8.23 (1H, s), 9.32 - 9.37 (3H, m), 10.46 (1H, s), 11.79 (1H, s).

Example 427

Production of N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-(trifluoromethyl)benzamide

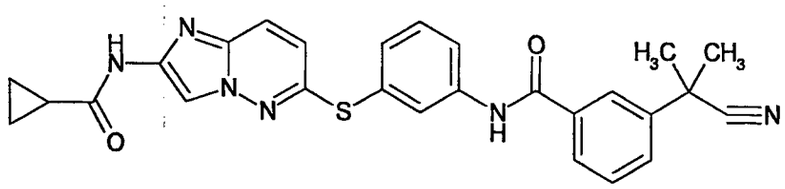


Using N-{6-[(3-aminophenyl)sulfanyl]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (140 mg, 0.430 mmol), 3-(trifluoromethyl)benzoic acid (98 mg, 0.516 mmol), oxalyl chloride (75 μL, 0.860 mmol), N,N-dimethylformamide (1 drop),

tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) as starting materials and in the same manner as in Example 412, the title compound (148 mg, 75%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 - 0.86 (4H, m), 1.89 - 2.00 (1H, m), 6.96 (1H, d, J = 9.4 Hz), 7.34 - 7.39 (1H, m), 7.50 (1H, t, J = 8.0 Hz), 7.79 (1H, t, J = 8.0 Hz), 7.88 - 7.94 (2H, m), 7.98 (1H, d, J = 8.0 Hz), 8.03 (1H, t, J = 1.8 Hz), 8.15 (1H, s), 8.25 (1H, d, J=8.0 Hz), 8.28 (1H, s), 10.60 (1H, s), 11.18 (1H, s).

Example 428

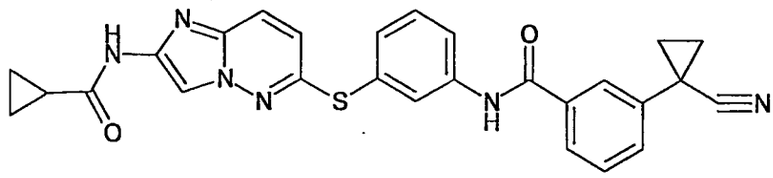
Production of 3-(1-cyano-1-methylethyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]benzamide



Using N-{6-[(3-aminophenyl)sulfanyl]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (140 mg, 0.430 mmol), 3-(1-cyano-1-methylethyl)benzoic acid (97 mg, 0.516 mmol), oxalyl chloride (75 μL, 0.860 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) as starting materials and in the same manner as in Example 412, the title compound (108 mg, 51%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.87 (4H, m), 1.74 (6H, s), 1.89 - 1.99 (1H, m), 6.95 (1H, d, J = 9.4 Hz), 7.32 - 7.38 (1H, m), 7.49 (1H, t, J = 8.0 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.72 - 7.79 (1H, m), 7.86 - 7.96 (3H, m), 8.00 - 8.05 (2H, m), 8.15 (1H, s), 10.45 (1H, s), 11.18 (1H, s).

Example 429

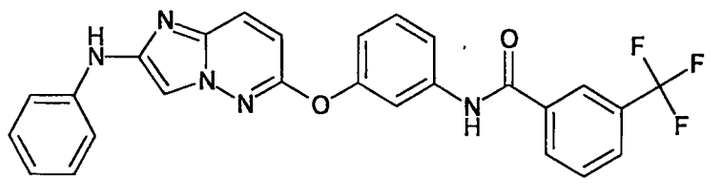
Production of 3-(1-cyanocyclopropyl)-N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]benzamide



Using N-{6-[(3-aminophenyl)sulfanyl]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (130 mg, 0.399 mmol), 3-(1-cyanocyclopropyl)benzoic acid (89 mg, 0.479 mmol), oxalyl chloride (70 μL, 0.799 mmol), N,N-dimethylformamide (1 drop), tetrahydrofuran (3 mL) and N,N-dimethylacetamide (3 mL) as starting materials and in the same manner as in Example 412, the title compound (158 mg, 80%) was obtained as a pale-brown powder. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.88 (4H, m), 1.58 - 1.65 (2H, m), 1.77 - 1.85 (2H, m), 1.89 - 2.00 (1H, m), 6.95 (1H, d, J = 9.4 Hz), 7.32 - 7.38 (1H, m), 7.45 - 7.53 (1H, m), 7.54 - 7.61 (2H, m), 7.82 (1H, s), 7.84 - 7.94 (3H, m), 8.02 (1H, t, J = 1.7 Hz), 8.15 (1H, s), 10.44 (1H, s), 11.18 (1H, s).

Example 430

Production of N-{3-[(2-anilinoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide



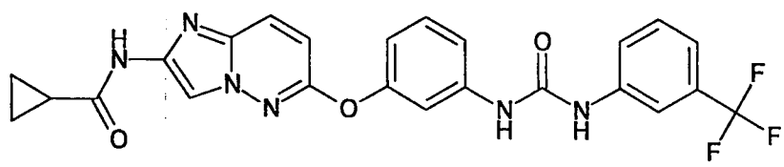
A mixture of N-{3-[(2-aminoimidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide (100 mg, 0.242 mmol), iodobenzene (32 μl, 0.290 mmol), tris(dibenzylideneacetone)dipalladium (0) (11 mg, 24.2 μmol), dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (23 mg, 48.4 μmol), sodium tert-butoxide (34 mg, 0.362 mmol) and toluene (2 mL) was stirred under an argon atmosphere with heating at 80°C for 5 hr. After the reaction mixture was allowed to cool to room temperature, saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine,

dried over anhydrous magnesium sulfate, and filtrated. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane=0/100→50/50) to give the title compound (19 mg, 16%) as a pale-green powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.78 (1H, t, J = 7.3 Hz), 6.96 - 7.07 (2H, m), 7.18 - 7.25 (2H, m), 7.36 - 7.50 (3H, m), 7.65 - 7.72 (3H, m), 7.79 (1H, t, J = 7.6 Hz), 7.98 (2H, d, J = 9.2 Hz), 8.18 - 8.32 (2H, m), 8.91 (1H, s), 10.58 (1H, s).

Example 431

Production of N-{6-[3-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

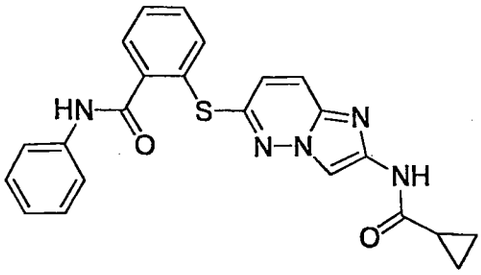


A mixture of N-[6-(3-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (300 mg, 0.969 mmol), 3-(trifluoromethyl)phenyl isocyanate (667 μL, 4.84 mmol), toluene (4 mL) and tetrahydrofuran (1 mL) was stirred with heating under reflux for 3 hr. After the reaction mixture was allowed to cool to room temperature, the precipitate was collected by filtration and washed with ethyl acetate/diisopropyl ether to give the title compound (268 mg, 56%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.84 (4H, m), 1.87 - 1.98 (1H, m), 6.83 - 6.89 (1H, m), 7.04 (1H, d, J = 9.5 Hz), 7.23 - 7.40 (3H, m), 7.46 - 7.53 (2H, m), 7.56 - 7.64 (1H, m), 7.95 - 8.00 (2H, m), 8.03 (1H, d, J = 9.5 Hz), 9.12 - 9.35 (2H, m), 11.08 (1H, s).

Example 432

Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)-N-phenylbenzamide

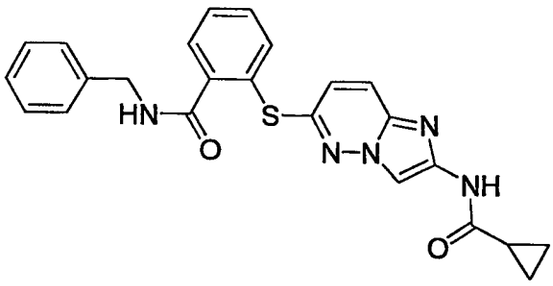


In the same manner as in Example 278 and using 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (250 mg, 0.71 mmol), aniline (184 mg, 2.0 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (380 mg, 1.0 mmol), N,N-diisopropylethylamine (270 mg, 2.0 mmol) and N,N-dimethylformamide (7 mL) as starting materials, the title compound (280 mg, 93%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.76 - 0.88 (4H, m), 1.88 - 1.97 (1H, m), 6.98 (1H, d, J = 9.5 Hz), 7.08 (1H, t, J = 7.4 Hz), 7.31 (2H, t, J = 8.0 Hz), 7.49 - 7.60 (3H, m), 7.61 - 7.76 (3H, m), 7.88 (1H, d, J = 9.1 Hz), 8.14 (1H, s), 10.51 (1H, s), 11.16 (1H, s).

Example 433

Production of N-benzyl-2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzamide

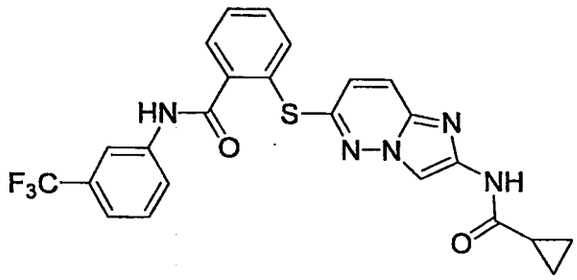


In the same manner as in Example 278 and using 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (250 mg, 0.71 mmol), benzylamine (212 mg, 2.0 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (380 mg, 1.0 mmol), N,N-diisopropylethylamine (270 mg, 2.0 mmol) and N,N-

dimethylformamide (7 mL) as starting materials, the title compound (280 mg, 89%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.90 (4H, m), 1.90 - 2.01 (1H, m), 4.42 (2H, d, J = 6.1 Hz), 6.96 (1H, d, J = 9.5 Hz), 7.17 - 7.35 (4H, m), 7.43 - 7.52 (4H, m), 7.61 (1H, dd, J = 7.0, 2.5 Hz), 7.88 (1H, d, J = 9.5 Hz), 8.16 (1H, s), 9.04 (1H, t, J = 5.9 Hz), 11.17 (1H, s).

Example 434

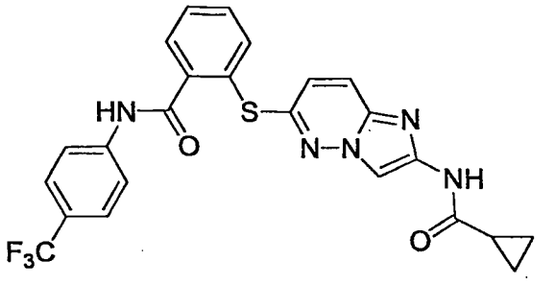
Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)-N-[3-(trifluoromethyl)phenyl]benzamide



In the same manner as in Example 278 and using 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (150 mg, 0.42 mmol), 3-(trifluoromethyl)aniline (191 mg, 1.2 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (230 mg, 0.6 mmol), N,N-diisopropylethylamine (160 mg, 1.3 mmol) and N,N-dimethylformamide (5 mL) as starting materials, the title compound (208 mg, 99%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.88 (4H, m), 1.87 - 1.97 (1H, m), 6.99 (1H, d, J = 9.4 Hz), 7.40 - 7.46 (1H, m), 7.49 - 7.63 (4H, m), 7.72 - 7.78 (1H, m), 7.83 - 7.90 (2H, m), 8.09 - 8.16 (2H, m), 10.85 (1H, s), 11.14 (1H, s).

Example 435

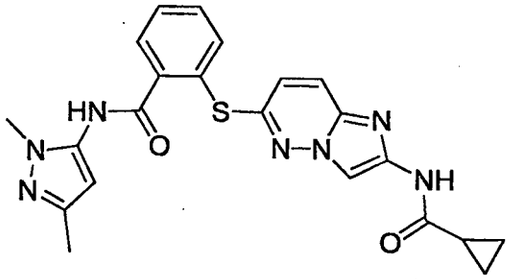
Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)-N-[4-(trifluoromethyl)phenyl]benzamide



In the same manner as in Example 278 and using 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (150 mg, 0.42 mmol), 4-(trifluoromethyl)aniline (191 mg, 1.2 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (230 mg, 0.6 mmol), N,N-diisopropylethylamine (160 mg, 1.3 mmol) and N,N-dimethylformamide (5 mL) as starting materials, the title compound (155 mg, 74%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.74 - 0.89 (4H, m), 1.86 - 1.98 (1H, m), 6.99 (1H, d, J = 9.3 Hz), 7.49 - 7.62 (3H, m), 7.67 (2H, d, J = 8.7 Hz), 7.72 - 7.77 (1H, m), 7.83 - 7.90 (3H, m), 8.13 (1H, s), 10.87 (1H, s), 11.14 (1H, s).

Example 436

Production of 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)-N-(1,3-dimethyl-1H-pyrazol-5-yl)benzamide

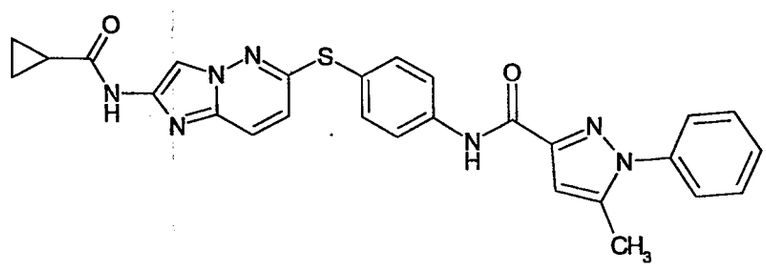


In the same manner as in Example 278 and using 2-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)benzoic acid (150 mg, 0.42 mmol), 1,3-dimethyl-1H-pyrazol-5-amine (130 mg, 1.2 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (230 mg, 0.6 mmol), N,N-diisopropylethylamine (160 mg, 1.3 mmol) and N, N-

dimethylformamide (5 mL) as starting materials, the title compound (130 mg, 70%) was obtained as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.75 - 0.86 (4H, m), 1.89 - 1.99 (1H, m), 2.08 (3H, s), 3.59 (3H, s), 5.97 (1H, s), 7.00 (1H, d, J = 9.8 Hz), 7.46 - 7.63 (3H, m), 7.71 - 7.79 (1H, m), 7.90 (1H, d, J = 9.8 Hz), 8.15 (1H, s), 10.49 (1H, s), 11.17 (1H, s).

Example 437

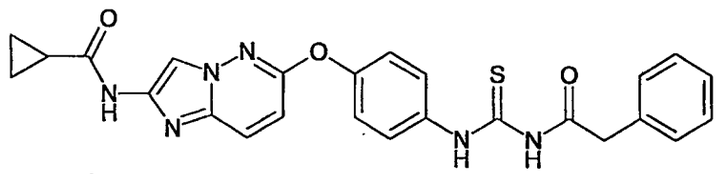
Production of N-[4-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-5-methyl-1-phenyl-1H-pyrazole-3-carboxamide



Using 5-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid (186 mg, 0.92 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (80 μL, 0.92 mmol), N-{6-[(4-aminophenyl)thio]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide (200 mg, 0.62 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 249, the title compound (201 mg, 64%) was obtained as a white powder.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.79 -0.85 (4H, m), 1.89 - 1.97 (1H, m), 2.31 (3H, s), 6.81 (1H, d, J = 9.3 Hz), 6.89 (1H, s), 7.35 - 7.49 (5H, m), 7.57 - 7.61 (2H, m), 7.76 - 7.86 (3H, m), 8.09 (1H, s), 10.74 (1H, s), 11.14 (1H, s).

Example 438

Production of N-{6-[4-({[(phenylacetyl)amino]thiocarbonyl}amino)phenoxy]imidazo[1,2-b]pyridazin-2-yl}cyclopropanecarboxamide

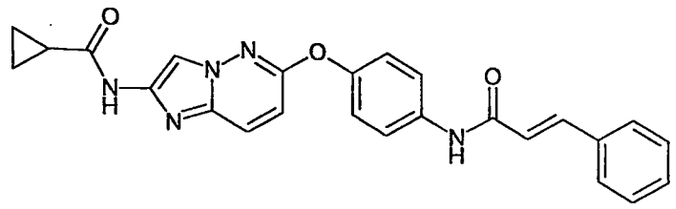


To a solution of phenylacetyl chloride (342 μL, 2.59 mmol) in acetonitrile (8.0 mL) was added potassium thiocyanate (0.31 g, 3.23 mmol), and the mixture was stirred at 50°C for 1 hr. After cooling the mixture to room temperature, the solvent was evaporated under reduced pressure. Saturated brine was added to the residue, and the mixture was extracted with ethyl acetate, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Toluene/ethanol (2.0 mL/2.0 mL) was added to the residue, N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.65 mmol) was added to the mixture, and the mixture was stirred at room temperature for 1 hr. Saturated brine was added to the reaction mixture, and the mixture was extracted with ethyl acetate, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=1/3) to give the title compound (164 mg, 51%) as white crystals.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.78 - 0.82 (4H, m), 1.87 - 1.95 (1H, m), 3.82 (2H, s), 7.05 (1H, d, J = 9.6 Hz), 7.24 - 7.36 (7H, m), 7.66 (2H, d, J = 9.0 Hz), 7.93 (1H, s), 8.02 (1H, d, J = 9.6 Hz), 11.06 (1H, s), 11.71 (1H, s), 12.36 (1H, s).

Example 439

Production of N-[6-(4-{[(2E)-3-phenylprop-2-enoyl]amino}phenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide

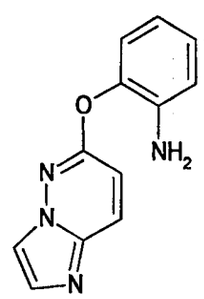


Using (2E)-3-phenylacrylic acid (135 mg, 0.91 mmol), tetrahydrofuran (3.0 mL), N,N-dimethylformamide (20 μL, 0.26 mmol), oxalyl chloride (80 μL, 0.91 mmol), N-[6-(4-aminophenoxy)imidazo[1,2-b]pyridazin-2-yl]cyclopropanecarboxamide (200 mg, 0.65 mmol) and N,N-dimethylacetamide (4.0 mL), and in the same manner as in Example 255, the title compound (133 mg, 47%) was obtained as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.77 - 0.82 (4H, m), 1.86 - 1.96 (1H, m), 6.84 (1H, d, J =15.9 Hz), 7.04 (1H, d, J = 9.8 Hz), 7.25 (2H, d, J = 9.0 Hz), 7.38 - 7.50 (3H, m), 7.58 - 7.66 (3H, m), 7.77 (2H, d, J = 9.0 Hz), 7.93 (1H, s), 8.02 (1H, d, J = 9.8 Hz), 10.33 (1H, s), 11.07 (1H, s).

Example 440

Production of 2-(imidazo[1,2-b]pyridazin-6-yloxy)aniline



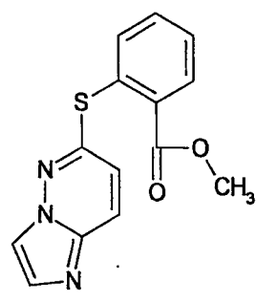
A mixture of 6-chloroimidazo[1,2-b]pyridazine (1536 mg, 10.0 mmol), 2-aminophenol (1419 mg, 13.0 mmol), potassium carbonate (4146 mg, 30.0 mmol) and N-methylpyrrolidone (10 mL) was stirred at 120°C for 3 days. The reaction mixture was diluted with 1N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by NH silica gel

column chromatography (hexane/ethyl acetate=70/30→0/100). The objective fraction was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→75/25), and precipitated from diisopropyl ether to give the title compound (307 mg, 1.4 mmol, yield 14%) as a pale-brown solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.08 (2H, s), 6.57 (1H, td, J=7.6, 1.6Hz), 6.81 (1H, dd, J=7.9, 1.7Hz), 6.95-7.04 (2H, m), 7.04 (1H, d, J=9.9Hz), 7.61 (1H, d, J=0.9Hz), 8.02 (1H, s), 8.11 (1H, d, J=9.9Hz).

Example 441

Production of methyl 2-(imidazo[1,2-b]pyridazin-6-ylthio)benzoate



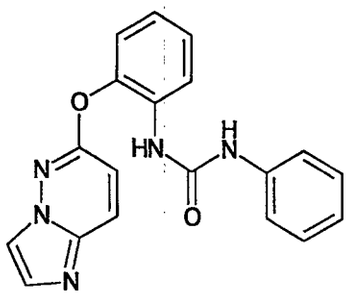
A mixture of 6-chloroimidazo[1,2-b]pyridazine (1536 mg, 10.0 mmol), methyl 2-mercaptobenzoate (1.788 mL, 13.0 mmol), potassium carbonate (4146 mg, 30.0 mmol) and N,N-dimethylformamide (20 mL) was stirred at 70°C for 18 hr. To the reaction mixture was added methyl 2-mercaptobenzoate (0.963 mL, 7.0 mmol), and the mixture was stirred at 70°C for 6 hr. The reaction mixture was concentrated under reduced pressure, the residue was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (hexane/ethyl acetate=90/10→20/80) and precipitated from diisopropyl ether to give the title compound (663 mg, 2.3 mmol, yield 23%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.83 (3H, s), 7.14 (1H, d, J=9.5Hz),

7.37 (1H, dd, J=7.7, 1.0Hz), 7.47 (1H, td, J=7.4, 1.4Hz), 7.55 (1H, td, J=7.7, 1.5Hz), 7.80 (1H, d, J=1.2Hz), 7.95 (1H, dd, J=7.7, 1.4Hz), 8.10 (1H, dd, J=9.5, 0.6Hz), 8.29 (1H, t, J=0.9Hz).

Example 442

Production of N-[2-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]-N'-phenylurea

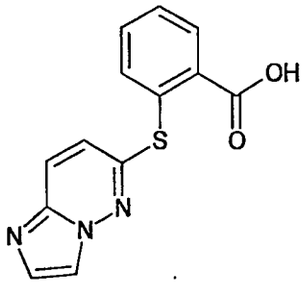


To a solution of 2-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (90 mg, 0.40 mmol) and triethylamine (0.011 mL, 0.08 mmol) in tetrahydrofuran (20 mL) was added phenyl isocyanate (0.061 mL, 0.56 mmol), and the mixture was stirred at room temperature for 18 hr. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from methanol to give the title compound (99 mg, 0.29 mmol, yield 72%) as a white powder.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.92-7.00 (1H, m), 7.02-7.09 (1H, m), 7.17-7.30 (5H, m), 7.38-7.44 (2H, m), 7.66 (1H, d, J=6.9Hz), 8.09 (1H, s), 8.20-8.28 (2H, m), 8.33 (1H, s), 9.04 (1H, s).

Example 443

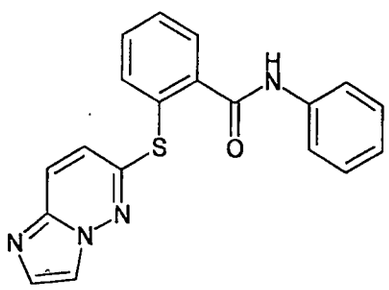
Production of 2-(imidazo[1,2-b]pyridazin-6-ylthio)benzoic acid



To a solution of methyl 2-(imidazo[1,2-b]pyridazin-6-ylthio)benzoate (619 mg, 2.17 mmol) in methanol (20 mL) was added 8N aqueous sodium hydroxide solution (1.00 mL), and the mixture was stirred at 70°C for 18 hr. After the reaction mixture was allowed to cool to room temperature, 6N hydrochloric acid (1.33 mL) was added to the reaction mixture, and the precipitated precipitate was collected by filtration, and washed with water. The precipitate was suspended in methanol (10 mL), and the suspension was stirred with heating under reflux for 10 min. After the suspension was allowed to cool to room temperature, the precipitate was collected by filtration, washed with methanol, and dried under reduced pressure to give the title compound (496 mg, 1.83 mmol, yield 84%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.15 (1H, d, J=9.5Hz), 7.29 (1H, dd, J=7.9, 1.1Hz), 7.42 (1H, td, J=7.5, 1.2Hz), 7.50 (1H, td, J=7.6, 1.6Hz), 7.80 (1H, d, J=1.2Hz), 7.95 (1H, dd, J=7.5, 1.5Hz), 8.10 (1H, d, J=9.5Hz), 8.30 (1H, t, J=0.9Hz), 13.39 (1H, br s).

Example 444

Production of 2-(imidazo[1,2-b]pyridazin-6-ylthio)-N-phenylbenzamide

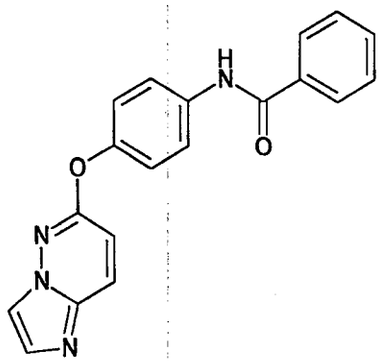


To a mixture of 2-(imidazo[1,2-b]pyridazin-6-ylthio)benzoic acid (109 mg, 0.40 mmol), aniline (75 mg, 0.81 mmol), 1-hydroxybenzotriazole hydrate (61 mg, 0.40 mmol) and N,N-dimethylformamide (5 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol) and triethylamine (0.167 mL, 1.20 mmol), and the mixture was stirred at room temperature for 18 hr. A 1N aqueous sodium hydroxide solution was added to the mixture and the mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→80/20) and precipitated from ethyl acetate/diisopropyl ether to give the title compound (110 mg, 0.32 mmol, yield 79%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 6.97 (1H, d, J = 9.5Hz), 7.08 (1H, t, J = 7.4Hz), 7.31 (2H, t, J = 7.8Hz), 7.51 - 7.76 (7H, m), 8.02 (1H, dd, J = 9.5, 0.5Hz), 8.18 (1H, s), 10.51 (1H, s).

Example 445

Production of N-[4-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl]benzamide



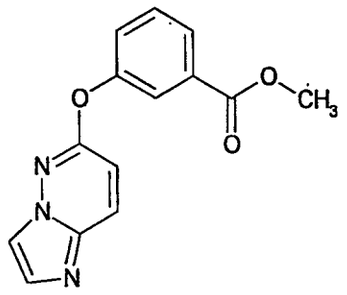
Using 4-(imidazo[1,2-b]pyridazin-6-yloxy)aniline (113 mg, 0.50 mmol), N-methylpyrrolidone (1 mL) and benzoyl chloride (0.116 mL, 1.00 mmol), and in the same manner as in Example 145, the title compound (144 mg, 0.44 mmol, yield 87%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.12 (1H, d, J = 9.6Hz), 7.29 (2H, d, J = 8.9Hz), 7.51 - 7.66 (3H, m), 7.65 (1H, d, J = 1.2Hz), 7.85

(2H, d, J = 8.9Hz), 7.94 - 8.01 (2H, m), 8.06 (1H, s), 8.17 (1H, dd, J = 9.6, 0.3Hz), 10.35 (1H, s).

Example 446

Production of methyl 3-(imidazo[1,2-b]pyridazin-6-yloxy)benzoate

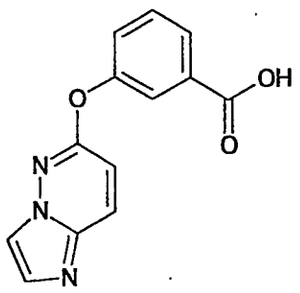


A mixture of 6-chloroimidazo[1,2-b]pyridazine (1536 mg, 10.0 mmol), methyl 3-hydroxybenzoate (1978 mg, 13.0 mmol), potassium carbonate (4146 mg, 30.0 mmol) and N-methylpyrrolidone (10 mL) was stirred at 120°C for 18 hr. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. The residue was purified by NH silica gel column chromatography (hexane/ethyl acetate=90/10→20/80). The objective fraction was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate=60/40→0/100) and precipitated from diisopropyl ether to give the title compound (1722mg, 6.4 mmol, yield 64%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 3.87 (3H, s), 7.16 (1H, d, J = 9.5Hz), 7.60 - 7.68 (3H, m), 7.79 - 7.83 (1H, m), 7.84 - 7.93 (1H, m), 8.05 (1H, s), 8.19 (1H, d, J=9.5Hz).

Example 447

Production of 3-(imidazo[1,2-b]pyridazin-6-yloxy)benzoic acid

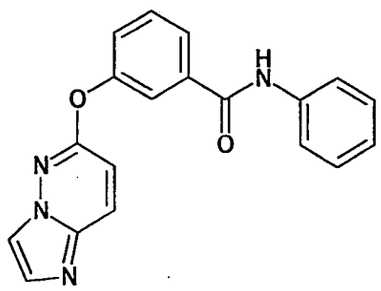


To a solution of methyl 3-(imidazo[1,2-b]pyridazin-6-yloxy)benzoate (1665 mg, 6.18 mmol) in methanol (30 mL) was added 8N aqueous sodium hydroxide solution (3.00 mL), and the mixture was stirred at room temperature for 18 hr and at 80°C for 8 hr. After the reaction mixture was allowed to cool to room temperature, 6N hydrochloric acid (4.00 mL) was added to the mixture, and the mixture was concentrated under reduced pressure. Water (30 mL) was added to the residue, and the precipitate was collected by filtration and washed with water. The precipitate was suspended in methanol (10 mL) and the suspension was stirred with heating under reflux for 10 min. After the suspension was allowed to cool to room temperature, the precipitate was collected by filtration washed with methanol and dried under reduced pressure to give the title compound (1045 mg, 4.09 mmol, yield 66%) as a white solid.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.15 (1H, d, J = 9.9Hz), 7.54 - 7.68 (3H, m), 7.74 - 7.80 (1H, m), 7.82 - 7.91 (1H, m), 8.06 (1H, s), 8.19 (1H, d, J = 9.9Hz), 13.17 (1H, br s).

Example 448

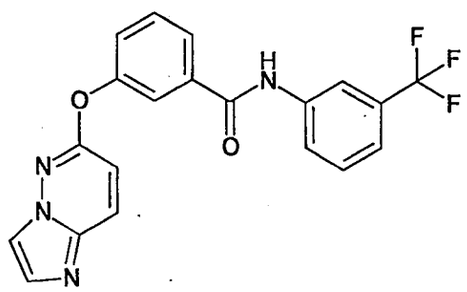
Production of 3-(imidazo[1,2-b]pyridazin-6-yloxy)-N-phenylbenzamide



To a mixture of 3-(imidazo[1,2-b]pyridazin-6-yloxy)benzoic acid (128 mg, 0.50 mmol), aniline (56 mg, 0.60 mmol), 1-hydroxybenzotriazole hydrate (92mg, 0.60 mmol) and N,N-dimethylformamide (5 mL) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192 mg, 1.00 mmol) and triethylamine (0.209 mL, 1.50 mmol), and the mixture was stirred at room temperature for 18 hr. 1N Aqueous sodium hydroxide solution was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol=100/0→75/25) and precipitated from ethyl acetate to give the title compound (122mg, 0.37 mmol, yield 74%) as a white solid.
^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.11 (1H, t, J = 7.4Hz), 7.18 (1H, d, J = 9.6Hz), 7.35 (2H, t, J = 7.9Hz), 7.52 - 7.58 (1H, m), 7.63 (1H, d, J = 8.1Hz), 7.66 (1H, d, J = 0.9Hz), 7.73 - 7.80 (2H, m), 7.86 - 7.93 (2H, m), 8.07 (1H, s), 8.21 (1H, d, J = 9.6Hz), 10.28 (1H, s).

Example 449

Production of 3-(imidazo[1,2-b]pyridazin-6-yloxy)-N-[3-(trifluoromethyl)phenyl]benzamide



Using 3-(imidazo[1,2-b]pyridazin-6-yloxy)benzoic acid (128 mg, 0.50 mmol), 3-(trifluoromethyl)aniline (97 mg, 0.60 mmol), 1-hydroxybenzotriazole hydrate (92mg, 0.60 mmol), N,N-dimethylformamide (5 mL), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (192mg, 1.00 mmol) and triethylamine (0.209 mL, 1.50 mmol), and in the same manner as in Example 448, the title compound (114 mg, 0.29 mmol, yield 57%) was obtained.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.18 (1H, d, J = 9.9Hz), 7.47 (1H, d, J = 7.8Hz), 7.55 - 7.71 (4H, m), 7.89 - 7.95 (2H, m), 8.02 - 8.08 (2H, m), 8.19 - 8.25 (2H, m), 10.59 (1H, s).

Formulation Example 1

A pharmaceutical agent containing the compound of the present invention as an active ingredient can be produced, for example, according to the following formulation.

1. capsule

(1) compound obtained in Example 1	40 mg
(2) lactose	70 mg
(3) microcrystalline cellulose	9 mg
(4) magnesium stearate	1 mg
1 capsule	120 mg

(1), (2), (3) and 1/2 of (4) are blended, granulated and the rest of (4) is added thereto. The whole mixture is sealed in a gelatin capsule.

2. tablet

(1) compound obtained in Example 1	40 mg
(2) lactose	58 mg
(3) cornstarch	18 mg

(4) microcrystalline cellulose 3.5 mg
(5) magnesium stearate 0.5 mg
1 tablet 120 mg

(1), (2), (3), 2/3 of (4), and 1/2 of (5) are blended and granulated. The rest of (4) and (5) are added to the granules. The mixture is compression-formed into a tablet.

Formulation Example 2

The compound (50 mg) obtained Example 1 is dissolved in Japanese Pharmacopoeia distilled water for injection(50 mL), and the Japanese Pharmacopoeia distilled water for injection is added to 100 mL. This solution is filtrated under sterile conditions. The solution (1 mL) is taken, filled in a vial for injection under sterile conditions, freeze-dried and sealed.

Experimental Example 1 Cloning of human vascular endothelial growth factor receptor 2 (VEGFR2) gene and preparation of recombinant baculovirus

Human vascular endothelial growth factor receptor 2 (hereinafter to be referred to as VEGFR2) gene was cloned by PCR using cDNA Libraries Human Placenta (Clontech) as a template. The primer used for PCR was prepared from base sequence (Genbank Accession AF035121) information of VEGFR2 gene by adding a base sequence encoding flag peptide and a recognition sequence of the restriction enzyme to a base sequence (2671-4374 of Genbank Accession AF035121) encoding the VEGFR2 intracellular domain region, so that the protein contains an N-terminal Flag tag. The primer base sequence is shown below.

VEGFR2-U:

5'-

AATTAAGTCGACATGGACTACAAGGATGACGATGACAAGAAGCGGGCCAATGGAGGGGAACTGA AGACA-3' (SEQ ID NO: 1)

and

VEGFR2-L:

5'-AATTAAGCATGCTTAAACAGGAGGAGAGCTCAGTGTGGTCCC-3' (SEQ ID NO: 2)

The base sequence of primer VEGFR2-U is shown in SEQUENCE LISTING SEQ ID NO: 1, and the base sequence of primer VEGFR2-L

is shown in SEQUENCE LISTING SEQ ID NO: 2.

The PCR reaction was conducted using a KOD-plus kit (TOYOBO). The obtained PCR product was electrophoresed on agarose gel (1%), the DNA fragment amplified by PCR was recovered from the gel, and then digested with restriction enzymes Sal I and Sph I. The DNA treated with the restriction enzymes was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes Sal I and Sph I to give expression plasmid pFB-VEGFR2. The base sequence of the insert fragment was confirmed and found to be identical with the base sequence (2671-4374 of Genbank Accession AF035121) of VEGFR2 intracellular domain. Furthermore, using BAC-TO-BAC Baculovirus Expression System (Invitrogen), virus stock BAC-VEGFR2 of recombinant baculovirus was prepared.

Experimental Example 2 Preparation of vascular endothelial growth factor receptor 2 (VEGFR2) intracellular domain protein

SF-21 cells were sown at 1×10^6 cells/mL to Sf-900II SFM medium (1 L, Invitrogen) containing 10% fetal bovine serum (trace), 50 mg/L Gentamicin (Invitrogen) and 0.1% Pluronic F-68 (Invitrogen), and shaking culture was performed using a 2 L volume Erlenmeyer flask at 27°C, 100 rpm. After culturing for 24 hrs, recombinant baculovirus BAC-VEGFR2 (13.4 mL) was added to the mixture, and the mixture was further cultured for 3 days. The culture medium was centrifuged at 2,000 rpm for 5 min to give virus-infected cells. The infected cells were washed with a phosphate buffered saline (Invitrogen), centrifuged under the same conditions, and the cells were preserved at -80°C. The cryopreserved cells were thawed in ice, suspended in buffer A (50 mM Tris buffer (30 mL, pH 7.4) containing 20% glycerol, 0.15 M NaCl) supplemented with Complete Protease Inhibitor (Boehringer), and ruptured 3 times with a Polytron homogenizer (Kinematica) at 20,000 rpm for 30 sec. The ruptured medium was clarified by centrifugation at 40,000 rpm for 30 min and filtered with a 0.45 μm filter. The filtrate was passed through

a column packed with Anti-FLAG M2 Affinity Gel (4 mL, Sigma) at a flow rate of about 0.5 mL/min. The column was washed with buffer A, and eluted with buffer A containing 100 μg/mL of FLAG peptide. The eluate was concentrated with Vivaspin 20 (Vivascience) having a molecular weight cut off of 30K. The buffer of this concentrate was exchanged using NAP™ 25 column (Amersham Bioscience) equilibrated with buffer A. The fractions containing intracellular domain protein of VEGFR2 were collected, glycerol was added to the final concentration of 50% and cryopreserved at -80°C.

Experimental Example 3 Cloning of human BRAF (B-Raf) gene and preparation of recombinant baculovirus

Human BRAF gene was cloned by PCR using human Testis cDNA library (Clontech) as a template. The primer used for PCR was prepared from base sequence (Genbank Accession NM_004333) information of BRAF gene by adding a base sequence encoding flag peptide and a recognition sequence of the restriction enzyme to area encoding the BRAF kinase domain region, so that the protein contains an N-terminal Flag. The primer base sequence is shown below.

BRAF-U:

5′-

AAAGAATTCACCATGGACTACAAGGACGACGATGACAAGACCCCCCCTGCCTCATTACCTGGCT -3′ (SEQ ID NO: 3)

and

BRAF-L:

5′- AAAAGTCGACTCAGTGGACAGGAAACGCACCATAT- 3′ (SEQ ID NO: 4)

The PCR reaction was conducted using Pyrobest (Takara Shuzo Co., Ltd). The obtained PCR product was electrophoresed on agarose gel (1%), the DNA fragment amplified by PCR was recovered from the gel, and then digested with restriction enzymes EcoRI and SalI. The DNA treated with the restriction enzymes was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid

pFASTBAC1 (Invitrogen) digested with restriction enzymes EcoRI and SalI to give expression plasmid pFB-BRAF, and the base sequence of the insert fragment was confirmed. In addition, mutation was introduced into V600E using a Quick change Site Directed Mutagenesis kit (Stratagene). The nucleotide sequences of the primers used are shown in the following.

V600E-U:

5′- GGTCTAGCTACAGAGAAATCTCGATGGAG -3′ (SEQ ID NO: 5)

and

V600E-L:

5′- CTCCATCGAGATTTCTCTGTAGCTAGACC - 3′ (SEQ ID NO: 6)

The obtained plasmid was sequenced to confirm the introduction of mutation into V600E. The plasmid was digested with restriction enzymes EcoRI and SalI, DNA was electrophoresed on agarose gel (1%), and the obtained DNA fragment was recovered and ligated to plasmid pFASTBAC1 (Invitrogen) digested with restriction enzymes EcoRI and SalI to give expression plasmid pFB-V600E.

Using BAC-TO-BAC Baculovirus Expression System (Invitrogen), virus stock BAC-V600E of recombinant baculovirus was prepared.

Experimental Example 4 Preparation of BRAF (V600E) protein

SF-21 cells were sown at 1×10^6 cells/mL to Sf-900II SFM medium (1 L, Invitrogen) containing 10% fetal bovine serum (Trace), 50 mg/L Gentamicin (Invitrogen) and 0.1% Pluronic F-68 (Invitrogen), and shaking culture was performed using a 2 L volume Erlenmeyer flask at 27°C, 100 rpm. After culturing for 24 hrs, recombinant baculovirus BAC-V600E (13.4 mL) was added to the mixture, and the mixture was further cultured for 3 days. The culture medium was centrifuged at 2,000 rpm for 5 min to give virus-infected cells. The infected cells were washed with a phosphate buffered saline (Invitrogen), centrifuged under the same conditions, and the cells were preserved at -80°C. The cryopreserved cells were thawed in ice, suspended in buffer A

(50 mM Tris buffer (30 mL, pH 7.4) containing 20% glycerol, 0.15 M NaCl) supplemented with Complete Protease Inhibitor (Boehringer), and ruptured 3 times with a Polytron homogenizer (Kinematica) at 20,000 rpm for 30 sec. The ruptured medium was clarified by centrifugation at 40,000 rpm for 30 min and filtered with a 0.45 μm filter. The filtrate was passed through a column packed with Anti-FLAG M2 Affinity Gel (4 mL, Sigma) at a flow rate of about 0.5 mL/min. The column was washed with buffer A, and eluted with buffer A containing 100 μg/mL of FLAG peptide. The buffer of this concentrate was exchanged using NAP25 column (Amersham Bioscience) equilibrated with buffer A and the fractions were cryopreserved at -80°C.

Test Example 1 Determination of vascular endothelial growth factor receptor 2 (VEGFR2) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 50 ng/mL of VEGFR2 intracellular domain protein and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). To the obtained mixture was added a buffer (10 μL) containing ATP (25 μM), the mixture was allowed to react at 25°C for 5 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PY-100 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-100) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader Fusion™ (PerkinElmer). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank". The inhibitory rate of the compounds of Examples 95, 97, 103, 108, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 and 317 at 1 μM was not less than 90%.

Test Example 2 Vascular endothelial cell growth inhibitory test

Human umbilical vein-derived vascular endothelial cells (HUVEC purchased from KURABO INDUSTRIES LTD.) were cultured in an incubator at 37°C, 5% carbon dioxide in a vascular endothelial cell medium (Invitrogen) containing 5% bovine fetal serum and 2.5 ng/mL basic fibroblast growth factor. To be specific, HUVEC was suspended in a vascular endothelial cell medium containing the aforementioned 5% bovine fetal serum and plated on a 96 well flat bottom plate by 50 μL (3000 cells) each well. After culture overnight, various concentrations of the test substance and 120 ng/mL of vascular endothelial growth factor (VEGF) were dissolved in a vascular endothelial cell medium containing 5% bovine fetal serum and added to each well by 50 μL. After 5 days of culture, a XTT reagent (Wako Pure Chemical Industries, Ltd.) was added to each well by 10 μL, and the mixture was reacted in an incubator at 37°C, 5% carbon dioxide for 2-3 hr. The absorbance at 450 nm was measured by a microtiter plate reader and the cell growth inhibitory activity was determined. Using the absorbance with addition of a test substance at each concentration and based on the nonlinear least-squares analysis using a logistic curve of SAS system NLIN procedure, the concentration of the test substance (IC_{50} value) necessary for showing 50% of the value obtained without addition of the test substance was calculated.

As a result, IC_{50} value of the compounds of Examples 95, 97, 103, 108, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 and 317 was not more than 500 nM.

Test Example 3 Antitumor test

Cancer cells are cultivated in an incubator at 37°C, 5% carbon dioxide in a culture medium containing 10% bovine fetal serum. The cells are isolated by a trypsin treatment, washed with HBSS (HANK's Balanced Saline Solution) and adjusted to cell density of $5x10^7$ cells/mL with HBSS. The cell suspension (0.1 mL, $5x10^6$ cells) is transplanted by subcutaneously injecting into the abdomen of 6-week-old female nude mice (BALB/c nu/nu, CLEA Japan, Inc.). When the tumor volume reached 100-200 mm^3, the mice are grouped, and orally administered with various doses of test substance for 14 consecutive days starting from the next day. The major axis length and minor axis length of the tumor are measured over time and the tumor volume is calculated from tumor volume = major axis length × minor axis length × minor axis length × 0.5.

Test Example 4 Determination of platelet-derived growth factor receptor α (PDGFRα) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 125 ng/ml of PDGFRα intracellular domain protein (UPSTATE) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (25 μM), the mixture was allowed to react at 25°C for 30 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed

to stand at 25°C for 16 hrs, and the wells were counted using a plate reader Fusion™ (PerkinElmer). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

The IC_{50} value of the compounds of Examples 95, 97, 111, 148, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 267, 287, 289, 298, 302, 314 and 317 was not more than 500 nM.

Test Example 5 Determination of platelet-derived growth factor receptor β (PDGFRβ) kinase inhibitory activity

A test compound dissolved in dimethyl sulfoxide (DMSO) was diluted with a buffer (50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM dithiothreitol, 0.01% Tween-20). To this compound solution (5 μL) was added a buffer (10 μL) containing 125 ng/ml of PDGFRβ intracellular domain protein (UPSTATE) and 250 ng/mL of biotin labeled polypeptide biotinyl-poly-Glu:Tyr (4:1) (CIS bio International). At 5 min after mixing kinase enzyme and the compound and biotin labeled polypeptide, to the obtained mixture was added a buffer (10 μL) containing ATP (25 μM), the mixture was allowed to react at 25°C for 30 min and the reaction was quenched with 25 μL of a stop solution (100 mM EDTA disodium salt, 62.5 mM HEPES buffer (pH 7.4), 250 mM NaCl, 0.1% bovine serum albumin, 10 μg/mL AlphaScreen assay streptavidin donor beads (Streptavidin Donor Beads: PerkinElmer), 10 μg/mL AlphaScreen assay anti-phosphotyrosine recognition antibody PT-66 binding acceptor beads (Anti-phosphotyrosine (P-Tyr-66) Acceptor beads: PerkinElmer)). The reaction solution was allowed to stand at 25°C for 16 hrs, and the wells were counted using a plate reader Fusion™ (PerkinElmer). The kinase inhibitory rate (%) of the test compound was calculated by the following

formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and ATP was used as a "blank".

The IC_{50} value of the compounds of Examples 97, 103, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 and 317 was not more than 500 nM.

Test Example 6 Determination of BRAF (V600E) kinase inhibitory activity

A test compound (2.5 μl) dissolved in dimethyl sulfoxide (DMSO) was added to 37.5 μl of a reaction solution (25 mM HEPES (pH 7.5), 10 mM magnesium acetate, 1 mM dithiothreitol) containing BRAF (V600E) enzyme (30 ng) and recombinant type protein GST-MEK1 (K96R) 250 ng, and the mixture was incubated at room temperature for 10 min. ATP solution (10 μl) (2.5 μM ATP, 0.1 μCi [γ-^{32}P]ATP) was added to the obtained mixture, and the mixture was reacted at room temperature for 20 min. The reaction was quenched by adding 50 μL of ice-cooled 20% trichloroacetic acid (Wako Pure Chemical Industries, Ltd.). The reaction solution was allowed to stand at 4°C for 30 min, and the acid-precipitable fraction was transferred to GF/C filter plate (Millipore Corporation) using cell harvester (PerkinElmer). The plate was dried at 45°C for 60 min, and 40 μL of MicroScinti 0 (PerkinElmer) was added thereto. The radioactivity was measured using TopCount (PerkinElmer). The kinase inhibitory rate (%) of the test compound was calculated by the following formula:

Inhibitory rate (%)=(1-(count of test compound - blank)÷(control - blank))×100

The count of the solution reacted without addition of the compound was used as a "control", and the count of the solution without the compound and enzyme was used as a "blank".

The inhibitory rate of the compounds of Examples 70, 319, 330, 398, 427 and 431 at 1 μM was not less than 90%.

SEQUENCE LISTING free text

[SEQ ID NO: 1]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

[SEQ ID NO: 2]

Designed oligonucleotide primer to amplify DNA encoding human VEGFR2

[SEQ ID NO: 3]

Designed oligonucleotide primer to amplify DNA encoding human BRAF

[SEQ ID NO: 4]

Designed oligonucleotide primer to amplify DNA encoding human BRAF

[SEQ ID NO: 5]

Designed oligonucleotide primer to introduce V600E mutation

[SEQ ID NO: 6]

Designed oligonucleotide primer to introduce V600E mutation

Industrial Applicability

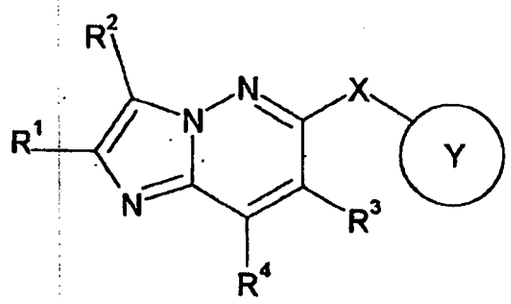
The compounds (I) - (IV), a salt thereof and a prodrug thereof of the present invention show superior inhibitory activity on kinases such as vascular endothelial growth factor receptor and the like. Therefore, a clinically useful agent for the prophylaxis or treatment of diseases related to the action of vascular endothelial growth factor in the living body (e.g., cancer etc.) can be provided. Moreover, since compounds (I) - (IV), a salt thereof and a prodrug thereof of the present invention are also superior in efficacy expression, pharmacokinetics, solubility, interaction with other pharmaceutical products, safety and stability, they are useful as pharmaceutical agents.

This application is based on patent application Nos.

2006-213981, 2006-331230 and 2007-144072 filed in Japan, the contents of which are incorporated in full herein by this reference.

Claims

1. A compound represented by the formula (I):



(I)

wherein

ring Y is an optionally substituted cyclic group;

X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;

R^4 is a hydrogen atom or a substituent;

provided that

when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that

methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate,

methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate,

ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,

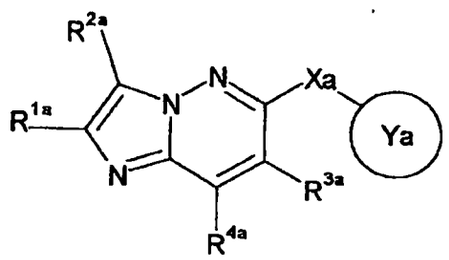
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline, and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof.

2. The compound of claim 1, wherein a compound represented by the formula (II):



(II)

wherein
ring Ya is an optionally substituted cyclic group;
Xa is -O-, -S-, -S(O)-, $-S(O)_2-$ or $-NR^a-$ (wherein R^a is a hydrogen atom or a substituent);
R^{1a} is an optionally substituted amino;
R^{2a} is a hydrogen atom or a substituent;
R^{3a} is a hydrogen atom or a substituent;
R^{4a} is a hydrogen atom or a substituent;

provided that
methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate and
methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate
are excluded,
or a salt thereof.

3. The compound of claim 2, wherein R^{1a} is
(1) amino,
(2) optionally substituted alkylcarbonylamino,
(3) optionally substituted alkenylcarbonylamino,
(4) optionally substituted alkynylcarbonylamino,
(5) optionally substituted cycloalkylcarbonylamino,
(6) optionally substituted cycloalkyl-alkylcarbonylamino,
(7) optionally substituted 6-membered heterocyclyl-carbonylamino,
(8) optionally substituted aminocarbonylamino,
(9) optionally substituted alkoxycarbonylamino,
(10) optionally substituted alkylsulfonylamino,
(11) optionally substituted cycloalkylsulfonylamino,
(12) optionally substituted arylamino, or
(13) optionally substituted heterocyclylamino.

4. The compound of claim 2, wherein R^{1a} is
(1) amino,
(2) C_{1-4} alkyl-carbonylamino optionally substituted by 1 to 3 substituents selected from
(a) a halogen atom,
(b) hydroxy,
(c) C_{1-4} alkoxy,
(d) C_{1-4} alkyl-carbonyloxy,
(e) C_{1-4} alkylamino,
(f) di-C_{1-4} alkylamino,
(g) C_{1-4} alkylsulfonyl, and
(h) a 6-membered heterocyclic group optionally having 1 to 3 C_{1-4} alkyl,
(3) C_{2-4} alkenyl-carbonylamino optionally having C_{1-4} alkoxy,

(4) C_{2-4} alkynyl-carbonylamino,

(5) C_{3-6} cycloalkyl-carbonylamino optionally substituted by 1 to 4 substituents selected from

(a) a halogen atom,

(b) hydroxy,

(c) C_{1-4} alkyl optionally having hydroxy,

(d) C_{1-4} alkoxy,

(e) C_{1-4} alkoxy-carbonyl, and

(f) C_{1-4} alkyl-carbonyloxy,

(6) C_{3-6} cycloalkyl-C_{1-4} alkyl-carbonylamino,

(7) 6-membered heterocyclyl-carbonylamino optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) cyano, and

(c) C_{1-4} alkyl optionally having 1 to 3 halogen atoms,

(8) aminocarbonylamino optionally substituted by 1 or 2 substituents selected from

(a) C_{1-4} alkyl optionally having 1 to 3 C_{1-4} alkoxy optionally having 1 to 3 hydroxy, and

(b) C_{1-4} alkoxy,

(9) C_{1-4} alkoxy-carbonylamino optionally substituted by 1 to 3 halogen atoms,

(10) C_{1-4} alkylsulfonylamino,

(11) C_{3-6} cycloalkylsulfonylamino,

(12) C_{6-10} arylamino, or

(13) heterocyclylamino optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom, and

(b) C_{1-4} alkylamino.

5. The compound of claim 2, wherein R^{2a} is a hydrogen atom.

6. The compound of claim 2, wherein R^{3a} is a hydrogen atom.

7. The compound of claim 2, wherein R^{4a} is a hydrogen atom.

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S48

8. The compound of claim 2, wherein Xa is -O-, -S- or -NH-.

9. The compound of claim 2, wherein ring Ya is an optionally substituted aromatic hydrocarbon group or an optionally substituted aromatic heterocyclic group.

10. The compound of claim 2, wherein ring Ya is

(1) C_{6-10} aryl optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom,

(b) C_{1-4} alkyl,

(c) C_{1-4} alkoxy,

(d) amino optionally substituted by the substituents selected from

(i) C_{1-4} alkyl optionally substituted by a 5-membered aromatic heterocyclic group optionally substituted by 1 to 3 C_{1-4} alkyl,

(ii) C_{1-4} alkyl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') hydroxy,

(ii') C_{1-4} alkylsulfonyl, and

(iii') a 6-membered aromatic heterocyclic group,

(iii) C_{2-4} alkenyl-carbonyl optionally substituted by C_{6-10} aryl,

(iv) C_{2-4} alkynyl-carbonyl optionally substituted by C_{6-10} aryl,

(v) C_{3-6} cycloalkyl-carbonyl,

(vi) C_{3-6} cycloalkenyl-carbonyl,

(vii) C_{6-10} aryl-carbonyl optionally substituted by 1 to 3 substituents selected from

(i') a halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom, cyano, hydroxy and C_{3-6} cycloalkyl,

(iii') C_{3-6} cycloalkyl optionally substituted by cyano,

(iv') C_{1-4} alkoxy optionally substituted by 1 to 5 halogen

atoms,

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

(vi') a 5- or 6-membered heterocyclic group optionally substituted by cyano or oxo,

(viii) 5- or 6-membered heterocyclyl-carbonyl containing, as ring-constituting atom, 1 to 3 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom besides carbon atoms, which is optionally substituted by 1 to 3 substituents selected from

(i') a halogen atom,

(ii') C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom, cyano, hydroxy and C_{1-4} alkoxy,

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

(iv') C_{6-10} aryl-C_{1-4} alkyl,

(v') C_{1-4} alkoxy optionally substituted by C_{1-4} alkoxy,

(vi') C_{1-4} alkylsulfonyl,

(vii') C_{1-4} alkyl-carbonyl, and

(viii') oxo,

(ix) aromatic fused heterocyclyl-carbonyl,

(x) C_{1-4} alkyl-aminocarbonyl,

(xi) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms,

(xii) C_{1-4} alkoxy-aminocarbonyl,

(xiii) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(xiv) aminothiocarbonyl optionally substituted by C_{6-10} aryl-C_{1-4} alkyl-carbonyl, and

(xv) 5-membered aromatic heterocyclyl-sulfonyl optionally substituted by 1 to 3 C_{1-4} alkyl,

(e) C_{1-4} alkyl-aminocarbonyl optionally having C_{6-10} aryl,

(f) 5-membered heterocyclyl-aminocarbonyl optionally substituted by 1 to 3 substituents selected from C_{1-4} alkyl and C_{6-10} aryl,

(g) C_{6-10} aryl-aminocarbonyl optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 substituents selected from a halogen atom and cyano,

(h) carboxy, and

(i) nitro,

(2) monocyclic aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) a halogen atom, and

(b) C_{6-10} aryl-carbonylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms, or

(3) fused aromatic heterocycle optionally substituted by 1 to 3 substituents selected from

(a) C_{1-4} alkyl, and

(b) C_{6-10} arylamino optionally substituted by C_{1-4} alkyl optionally substituted by 1 to 3 halogen atoms.

11. A compound selected from the group consisting of:

N-{3-[(2-{[2-(methylamino)pyrimidin-4-yl]amino}imidazo[1,2-b]pyridazin-6-yl)oxy]phenyl}-3-(trifluoromethyl)benzamide;

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-2,5-dimethyl-1,3-oxazole-4-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}sulfanyl)phenyl]-1,3-dimethyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-

yl}oxy)-2-fluorophenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]benzamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-ethyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-methoxy-1-methyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-3-ethyl-1-methyl-1H-pyrazole-5-carboxamide;

N-[2-chloro-5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-1-methyl-1H-pyrazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2,4-dimethyl-1,3-oxazole-5-carboxamide;

N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-fluorophenyl]-2-ethyl-4-methyl-1,3-oxazole-5-carboxamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide;

3-(1-cyano-1-methylethyl)-N-[5-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)-2-methylphenyl]benzamide;

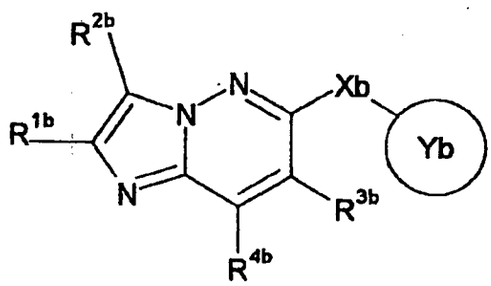
N-[3-({2-[(N,N-dimethylglycyl)amino]imidazo[1,2-b]pyridazin-6-yl}oxy)phenyl]-3-(trifluoromethyl)benzamide;

N-[3-({2-[(cyclopropylcarbonyl)amino]imidazo[1,2-b]pyridazin-6-yl}thio)phenyl]-3-(trifluoromethyl)benzamide; and

N-{6-[3-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenoxy]imidazo[1,2-

b]pyridazin-2-yl}cyclopropanecarboxamide,
or a salt thereof.

12. The compound of claim 1, which is a compound of the formula (III):



(III)

wherein
ring Yb is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted;
Xb is -O-, -S-, -S(O)-, -$S(O)_2$- or -NR^b- (wherein R^b is a hydrogen atom or a substituent);
R^{1b} is a hydrogen atom or a substituent (provided that an optionally substituted amino is excluded);
R^{2b} is a hydrogen atom or a substituent;
R^{3b} is a hydrogen atom or a substituent;
R^{4b} is a hydrogen atom or a substituent;
provided that
ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-

1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline, and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof.

13. A prodrug of the compound of claim 1.

14. A pharmaceutical agent comprising the compound of claim 1 or a prodrug thereof.

15. The pharmaceutical agent of claim 14, which is a kinase inhibitor.

16. The pharmaceutical agent of claim 14, which is an inhibitor of vascular endothelial growth factor receptor (VEGFR).

17. The pharmaceutical agent of claim 14, which is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 2.

18. The pharmaceutical agent of claim 14, which is an inhibitor of platelet-derived growth factor receptor (PDGFR).

19. The pharmaceutical agent of claim 14, which is a Raf inhibitor.

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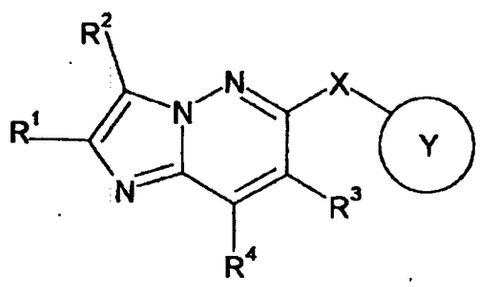
20. The pharmaceutical agent of claim 14, which is an angiogenesis inhibitor.

21. The pharmaceutical agent of claim 14, which is an agent for the prophylaxis or treatment of cancer.

22. The pharmaceutical agent of claim 14, which is a cancer growth inhibitor.

23. The pharmaceutical agent of claim 14, which is a cancer metastasis suppressor.

24. A method for the prophylaxis or treatment of cancer, which comprises administering an effective amount of a compound of the formula (I):



(I)

wherein

ring Y is an optionally substituted cyclic group;

X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;

R^4 is a hydrogen atom or a substituent;

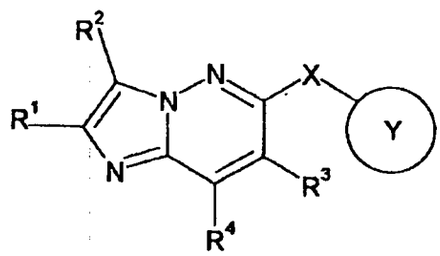
provided that

when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that

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methyl [6-(phenylthio)imidazo[1,2-b]pyridazi
methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyrida
yl]carbamate,
te,
ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazin
carboxylate,
ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,
N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,
N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline, and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof or a prodrug thereof to the mammal.

25. Use of a compound of the formula (I) for the production of an agent for the prophylaxis or treatment of cancer:



(I)

wherein

ring Y is an optionally substituted cyclic group;

X is -O-, -S-, -S(O)-, $-S(O)_2-$ or -NR- (wherein R is a hydrogen atom or a substituent);

R^1 is a hydrogen atom or a substituent;

R^2 is a hydrogen atom or a substituent;

R^3 is a hydrogen atom or a substituent;

R^4 is a hydrogen atom or a substituent;

provided that

when R^1 is other than an optionally substituted amino, ring Y is a cyclic group substituted by an optionally substituted amino, wherein the cyclic group is optionally further substituted, and that

methyl [6-(phenylthio)imidazo[1,2-b]pyridazin-2-yl]carbamate,

methyl [6-(phenylsulfinyl)imidazo[1,2-b]pyridazin-2-yl]carbamate,

ethyl 6-(4-acetamidophenoxy)imidazo[1,2-b]pyridazine-2-carboxylate,

ethyl 6-[4-(4-acetylpiperazin-1-yl)phenoxy]imidazo[1,2-b]pyridazine-2-carboxylate,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-2,5-dioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl]benzamide,

N-[1-(imidazo[1,2-b]pyridazin-6-ylamino)-7-methyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinolin-3-yl]benzamide,

N-[(5E)-5-(imidazo[1,2-b]pyridazin-6-ylhydrazono)-7-methyl-2-oxo-4a,5,6,7,8,8a-hexahydro-2H-chromen-3-yl]benzamide,
4-methoxybenzyl (6R,7R)-3-(imidazo[1,2-b]pyridazin-6-ylthio)-8-oxo-7-[(phenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,
4-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)thio]-N,N-dimethylaniline,
3-methoxy-6-(3-nitrophenoxy)-2-phenylimidazo[1,2-b]pyridazine,
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]aniline, and
3-[(3-methoxy-2-phenylimidazo[1,2-b]pyridazin-6-yl)oxy]-N,N-dimethylaniline are excluded,
or a salt thereof or a prodrug thereof.

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DERIVADO HETEROCÍCLICO FUSIONADO Y SU USO

Campo técnico

La presente invención se refiere a derivados heterocíclicos fusionados y su uso. Más particularmente, la presente invención se refiere a derivados de imidazopiridazina con potente actividad de inhibidor de quinasa y de utilidad para la prevención o el tratamiento de cáncer y similares.

Antecedentes de la invención

Para que un tumor sólido crezca hasta cierto tamaño o superior a él, es esencial la angiogénesis, a fin de asegurar suficiente suministro de nutrición y oxígeno a la célula cancerosa (ver, por ejemplo, New England Journal of Medicine, 1971, vol. 285, N.º 21, pp. 1182–1186). Uno de los factores importantes conocidos que causan angiogénesis hacia el tumor es un factor de crecimiento vascular endotelial (VEGF). VEGF está unido a un receptor del factor de crecimiento endotelial vascular (VEGFR) expresado en células vasculares endoteliales y transmite la señal para el crecimiento celular (ver, por ejemplo, Endocrine Reviews, 1997, vol. 18, N.º 1, pp. 4–25). En consecuencia, se considera que la inhibición del sistema de transducción de señales VEGF–VEGFR permite suprimir la angiogénesis y el crecimiento tumoral (ver, por ejemplo, Drug Discovery Today, 2001, vol. 6, N.º 19, pp. 1005–1024). Además, dado que los vasos sanguíneos tumorales intervienen en la metástasis hematógena del cáncer, la inhibición de la angiogénesis

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Patente de Invención

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se considera efectiva para suprimir metástasis de cáncer.

Como compuestos inhibidores de tirosinaquinasa de tipo receptor VEGFR, se conocen los derivados de ftalazina (ver, por ejemplo, WO 98/35958), los derivados pirrolsustituidos de 2–indolinona (ver, por ejemplo, WO 01/60814), los derivados de quinazolina (ver, por ejemplo, WO 01/32651), los derivados ω–carboxiarilsustituidos de difenilurea (ver, por ejemplo, WO 00/42012), los derivados de quinolina y derivados de quinazolina (ver, por ejemplo, WO 00/43366), los derivados de anillos aromáticos que contienen nitrógeno (ver, por ejemplo, WO 02/32872), y similares.

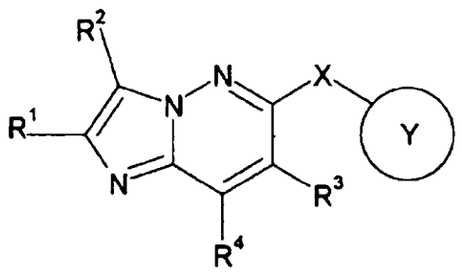
Descripción de la invención

Se espera que un inhibidor de quinasa superior en la afinidad por quinasa, eficacia de la expresión, farmacocinética, solubilidad, interacción con otros productos farmacéuticos, seguridad y estabilidad muestre un efecto terapéutico superior. Sin embargo, hasta el presente no se ha hallado dicho inhibidor superior en la afinidad por quinasa, y suficientemente satisfactorio en expresión de eficacia, farmacocinética, solubilidad, interacción con otros productos farmacéuticos, seguridad y estabilidad. En consecuencia, hay una demanda por el desarrollo de un compuesto con actividad superior de inhibidor de quinasa, y suficientemente satisfactorio como producto farmacéutico. En consecuencia, un objeto de la presente invención consiste en proveer un compuesto con superior actividad de inhibidor de quinasa, poco tóxico y suficientemente satisfactorio como producto farmacéutico.

Los presentes inventores han realizado estudios intensivos en un intento por solucionar los problemas antes mencionados y hallaron que un compuesto representado por la siguiente fórmula o una de sus sales tiene actividad superior inhibidora de quinasa, lo cual dio como resultado la realización de la presente invención.

De conformidad con ello, la presente invención provee lo siguiente.

[1] Un compuesto representado por la fórmula (I):



(I)

en donde

anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido

opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4.2.0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

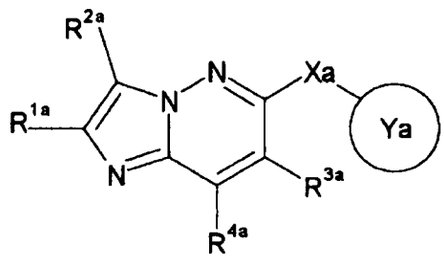
3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales.

[2] el compuesto del punto [1] antes mencionado, en donde un compuesto representado por la fórmula (II):



(II)

en donde

el anillo Ya es un grupo cíclico sustituido opcionalmente;

Xa es –O–, –S–, –S(O)–, $-S(O)_2-$ o $-NR^a-$ (en donde R^a es un átomo de hidrógeno o un sustituyente);

R^{1a} es un amino sustituido opcionalmente;

R^{2a} es un átomo de hidrógeno o un sustituyente;

R^{3a} es un átomo de hidrógeno o un sustituyente;

R^{4a} es un átomo de hidrógeno o un sustituyente;

con la condición de que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo y

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

o una de sus sales.

[3] el compuesto del punto [2] antes mencionado, en donde R^{1a} es

(1) amino,

(2) alquilcarbonilamino sustituido opcionalmente,

(3) alquenilcarbonilamino sustituido opcionalmente,

(4) alquinilcarbonilamino sustituido opcionalmente,

(5) cicloalquilcarbonilamino sustituido opcionalmente,

(6) cicloalquil–alquilcarbonilamino sustituido opcionalmente,

(7) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente,

(8) aminocarbonilamino sustituido opcionalmente,

(9) alcoxicarbonilamino sustituido opcionalmente,

(10) alquilsulfonilamino sustituido opcionalmente,

(11) cicloalquilsulfonilamino sustituido opcionalmente,

(12) arilamino sustituido opcionalmente, o

(13) heterociclilamino sustituido opcionalmente.

[4] el compuesto del punto [2] antes mencionado, en donde R^{1a} es

(1) amino,

(2) alquil C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) hidroxi,

(c) alcoxi C_{1-4},

(d) alquil C_{1-4}–carboniloxi,

(e) alquil C_{1-4}–amino,

(f) di–alquil C_{1-4}–amino,

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(g) alquilsulfonilo C_{1-4}, y

(h) un grupo heterocíclico de 6 miembros que opcionalmente tiene 1 a 3 alquilos C_{1-4},

(3) alquenil C_{2-4}–carbonilamino que opcionalmente tiene alcoxi C_{1-4},

(4) alquinil C_{2-4}–carbonilamino,

(5) cicloalquil C_{3-6}–carbonilamino sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) hidroxi,

(c) alquilo C_{1-4} que opcionalmente tiene hidroxi,

(d) alcoxi C_{1-4},

(e) alcoxi C_{1-4}–carbonilo, y

(f) alquil C_{1-4}–carboniloxi,

(6) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino,

(7) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) ciano, y

(c) alquilo C_{1-4} que opcionalmente tiene 1 a 3 átomos de halógeno,

(8) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

(a) alquilo C_{1-4} que opcionalmente tiene 1 a 3 alcoxi C_{1-4} que opcionalmente tiene 1 a 3 hidroxi, y

(b) alcoxi C_{1-4},

(9) alcoxi C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 átomos de halógeno,

(10) alquil C_{1-4}–sulfonilamino,

(11) cicloalquil C_{3-6}–sulfonilamino,

(12) aril C_{6-10}–amino, o

(13) heterociclilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) alquil C_{1-4}–amino.

[5] el compuesto del punto [2] antes mencionado, en donde R^{2a} es un átomo de hidrógeno.

[6] el compuesto del punto [2] antes mencionado, en donde R^{3a} es un átomo de hidrógeno.

[7] el compuesto del punto [2] antes mencionado, en donde R^{4a} es un átomo de hidrógeno.

[8] el compuesto del punto [2] antes mencionado, en donde Xa es –O–, –S– o –NH–.

[9] el compuesto del punto [2] antes mencionado, en donde anillo Ya es un grupo hidrocarburo aromático sustituido opcionalmente o un grupo heterocíclico aromático sustituido opcionalmente.

[10] el compuesto del punto [2] antes mencionado, en donde anillo Ya es

(1) arilo C_{6-10} sustituido opcionalmente con 1 a 3 sustituyentes

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seleccionados de

(a) un átomo de halógeno,

(b) alquilo C_{1-4},

(c) alcoxi C_{1-4},

(d) amino sustituido opcionalmente con los sustituyentes seleccionados de

(i) alquilo C_{1-4} sustituido opcionalmente con un grupo heterocíclico aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(ii) alquil C_{1-4}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') hidroxi,

(ii') alquilsulfonilo C_{1-4}, y

(iii') un grupo heterocíclico aromático de 6 miembros,

(iii) alquenil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(iv) alquinil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(v) cicloalquil C_{3-6}–carbonilo,

(vi) cicloalquenil C_{3-6}–carbonilo,

(vii) aril C_{6-10}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') un átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, ciano, hidroxi

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y cicloalquilo C_{3-6},

(iii') cicloalquilo C_{3-6} sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} sustituido opcionalmente con 1 a 5 átomos de halógeno,

(v') alcoxi C_{1-4}–carbonilo, y

(vi') un grupo heterocíclico de 5 ó 6 miembros sustituido opcionalmente con ciano u oxo,

(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') un átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, ciano, hidroxi y alcoxi C_{1-4},

(iii') arilo C_{6-10},

(iv') aril C_{6-10}–alquilo C_{1-4},

(v') alcoxi C_{1-4} sustituido opcionalmente con alcoxi C_{1-4},

(vi') alquil C_{1-4}–sulfonilo,

(vii') alquil C_{1-4}–carbonilo, y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático,

(x) alquil C_{1-4}–aminocarbonilo,

(xi) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con

alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno,

(xii) alcoxi C_{1-4}–aminocarbonilo,

(xiii) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo, y

(xv) heterociclil–sulfonilo aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(e) alquil C_{1-4}–aminocarbonilo que opcionalmente tiene arilo C_{6-10},

(f) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) aril C_{6-10}–carbonilamino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno,

o

(3) heterociclo aromático fusionado sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4}, y

(b) aril C_{6-10}–amino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno.

[11] Un compuesto seleccionado del grupo que consiste en:

N–{3–[(2–{[2–(metilamino)pirimidin–4–il]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida;

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,5–dimetil–1,3–oxazol–4–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}sulfanil)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–4–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–

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il}oxi)fenil]benzamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–4–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etil–1–metil–1H–pirazol–5–carboxamida;

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–etil–3–metil–1H–pirazol–4–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–oxazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida;

3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]benzamida;

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–

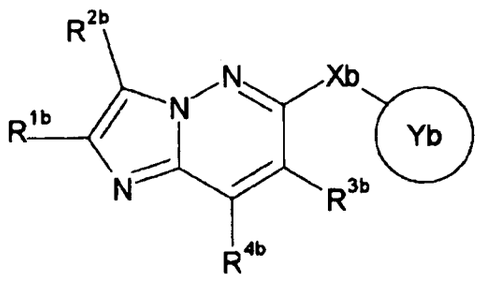
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il}tio)fenil]–3–(trifluorometil)benzamida; and

N–{6–[3–({[3–(trifluorometil)fenil]carbamoil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida,

o una de sus sales.

[12] el compuesto del punto [1] antes mencionado, que es un compuesto de la fórmula (III):



(III)

en donde

el anillo Yb es un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente;

Xb es –O–, –S–, –S(O)–, $-S(O)_2-$ o $-NR^b-$ (en donde R^b es un átomo de hidrógeno o un sustituyente);

R^{1b} es un átomo de hidrógeno o un sustituyente (con la condición de que se excluya un amino sustituido opcionalmente);

R^{2b} es un átomo de hidrógeno o un sustituyente;

R^{3b} es un átomo de hidrógeno o un sustituyente;

R^{4b} es un átomo de hidrógeno o un sustituyente;

con la condición de que se excluyan

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de

5 fls.

etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4.2.0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales.

[13] Un profármaco del compuesto del punto [1] antes mencionado.

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[14] Un agente farmacéutico que comprende el compuesto del punto [1] antes mencionado o uno de sus profármacos.

[15] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de quinasa.

[16] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de receptor del factor de crecimiento endotelial vascular (VEGFR).

[17] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de receptor del factor de crecimiento endotelial vascular (VEGFR) 2.

[18] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de receptor del factor de crecimiento derivado de plaquetas (PDGFR).

[19] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de Raf.

[20] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor de la angiogénesis.

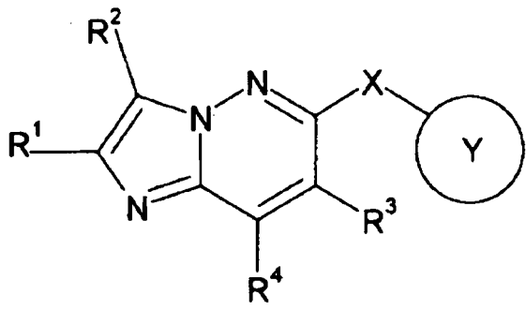
[21] El agente farmacéutico del punto [14] antes mencionado, que es un agente para la prevención o el tratamiento del cáncer.

[22] El agente farmacéutico del punto [14] antes mencionado, que es un inhibidor del crecimiento del cáncer.

[23] El agente farmacéutico del punto [14] antes mencionado, que es un supresor de la metástasis cancerosa.

[24] Un método para la prevención o el tratamiento del cáncer, que comprende la administración de una cantidad efectiva de un

compuesto de la fórmula (I):



(I)

en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

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6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4.2.0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

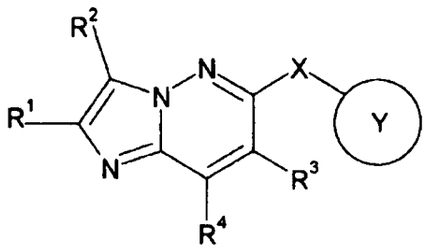
3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales o uno de sus profármacos al mamífero.

[25] Uso de un compuesto de la fórmula (I) para la producción de un agente para la prevención o el tratamiento del cáncer:



(I)

en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–

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1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4.2.0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

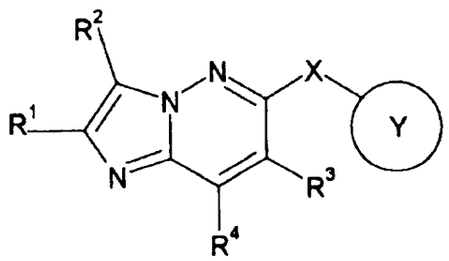
3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina, o una de sus sales o uno de sus profármacos.

La presente invención también incluye lo siguiente.

[26] Un compuesto de la fórmula (IV):



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en donde anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente,

o una de sus sales.

[27] Un inhibidor de quinasa, que comprende el compuesto del punto [26] antes mencionado o uno de sus profármacos.

[28] El inhibidor de quinasa del punto [27] antes mencionado, en donde la quinasa es un receptor del factor de crecimiento endotelial vascular (VEGFR).

[29] El inhibidor de quinasa del punto [27] antes mencionado, en donde la quinasa es un receptor del factor de crecimiento endotelial vascular (VEGFR) 2.

[30] El inhibidor de quinasa del punto [27] antes mencionado, en donde la quinasa es un receptor del factor de crecimiento derivado de plaquetas (PDGFR).

[31] El inhibidor de quinasa del punto [27] antes mencionado,

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en donde la quinasa es Raf.

[32] Un inhibidor de la angiogénesis, que comprende el compuesto del punto [26] antes mencionado o uno de sus profármacos.

[33] Un agente para la prevención o el tratamiento del cáncer, que comprende el compuesto del punto [26] antes mencionado o uno de sus profármacos.

[34] Un inhibidor del crecimiento del cáncer, que comprende el compuesto del punto [26] antes mencionado o uno de sus profármacos.

[35] Un supresor de la metástasis cancerosa, que comprende el compuesto del punto [26] antes mencionado o uno de sus profármacos.

[36] Un método para la prevención o el tratamiento del cáncer, que comprende la administración de una cantidad efectiva del compuesto del punto [26] antes mencionado o uno de sus profármacos al mamífero.

[37] Uso de el compuesto del punto [26] antes mencionado o uno de sus profármacos para la producción de un agente para la prevención o el tratamiento del cáncer.

Efecto de la invención

Los compuestos representados por las fórmulas (I) a (IV) de la presente invención o o sus sales o sus profármacos tienen una fuerte actividad inhibidora contra las quinasas, tales como: receptor del factor de crecimiento endotelial vascular, receptor del factor de

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crecimiento derivado de plaquetas, y similares, y tienen una fuerte actividad inhibidora de la angiogénesis. En consecuencia, pueden proveer un agente para la prevención o el tratamiento de cáncer de utilidad clínica, un inhibidor del crecimiento del cáncer, o un supresor de la metástasis cancerosa. Además, los compuestos representados por las fórmulas (I) a (IV) de la presente invención o sus sales o sus profármacos pueden proveer agentes clínicamente útiles para la prevención o el tratamiento para aplicaciones en enfermedades distintas del cáncer, tales como reumatismo crónico, retinopatía diabética, y similares, y tienen una excelente expresión de eficacia, propiedades farmacocinéticas, solubilidad, interacción con otros productos farmacéuticos, seguridad y estabilidad.

En lo sucesivo,, la presente invención se explica en detalle.

Se explican un compuesto representado por la fórmula (I) (en lo sucesivo,, denominado compuesto (I)) y un compuesto representado por la fórmula (IV) (en lo sucesivo,, denominado compuesto (IV)) de la presente invención.

En los compuestos (I) y (IV), los ejemplos del "grupo cíclico" del "grupo cíclico sustituido opcionalmente" para el anillo Y incluyen grupo hidrocarburo aromático, grupo heterocíclico aromático (por ejemplo, grupo heterocíclico aromático monocíclico, grupo heterocíclico aromático fusionado), grupo hidrocarburo cíclico no aromático, grupo heterocíclico no aromático, grupo de anillo fusionado de ellos, y similares.

Los ejemplos del grupo hidrocarburo aromático incluyen arilo

C_{6-14}, y similares. Específicamente, se pueden mencionar , fenilo, 1–naftilo, 2–naftilo, bifenililo, antrilo, fenantrilo, acenaftilenilo, y similares.

Los ejemplos del grupo heterocíclico aromático monocíclico incluyen grupo heterocíclico aromático monocíclico de 5 a 7 miembros que contiene, como átomo constitutivo del anillo, 1 a 4 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares.

Los ejemplos del grupo heterocíclico aromático monocíclico incluyen específicamente furilo (por ejemplo, 2–furilo, 3–furilo), tienilo (por ejemplo, 2–tienilo, 3–tienilo), piridilo (por ejemplo, 2–piridilo, 3–piridilo, 4–piridilo), pirimidinilo (por ejemplo, 2–pirimidinilo, 4–pirimidinilo, 5–pirimidinilo, 6–pirimidinilo), piridazinilo (por ejemplo, 3–piridazinilo, 4–piridazinilo), pirazinilo (por ejemplo, 2–pirazinilo), pirrolilo (por ejemplo, 1–pirrolilo, 2–pirrolilo, 3–pirrolilo), imidazolilo (por ejemplo, 1–imidazolilo, 2–imidazolilo, 4–imidazolilo, 5–imidazolilo), pirazolilo (por ejemplo, 1–pirazolilo, 3–pirazolilo, 4–pirazolilo), tiazolilo (por ejemplo, 2–tiazolilo, 4–tiazolilo, 5–tiazolilo), isotiazolilo, oxazolilo (por ejemplo, 2–oxazolilo, 4–oxazolilo, 5–oxazolilo), isoxazolilo, oxadiazolilo (por ejemplo, 1,2,4–oxadiazol–5–ilo, 1,3,4–oxadiazol–2–ilo), tiadiazolilo (por ejemplo, 1,3,4–tiadiazol–2–ilo), triazolilo (por ejemplo, 1,2,4–triazol–1–ilo, 1,2,4–triazol–3–ilo, 1,2,3–triazol–1–ilo, 1,2,3–triazol–2–ilo, 1,2,3–triazol–4–ilo), tetrazolilo (por ejemplo, tetrazol–1–ilo, tetrazol–5–ilo), triazinilo, y similares.

Los ejemplos del grupo heterocíclico aromático fusionado incluyen un grupo formado por fusión del grupo heterocíclico aromático monocíclico de 5 a 7 miembros que contiene, como átomo constitutivo del anillo, 1 a 4 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y arilo C_{6-14}, y similares; un grupo formado por fusión de los grupos heterocíclicos aromáticos monocíclicos de 5 a 7 miembros antes mencionados, y similares.

Los ejemplos del grupo heterocíclico aromático fusionado incluyen específicamente quinolilo (por ejemplo, 2–quinolilo, 3–quinolilo, 4–quinolilo, isoquinolilo), quinazolinilo (por ejemplo, 2–quinazolinilo, 4–quinazolinilo), quinoxalinilo (por ejemplo, 2–quinoxalinilo), benzofurilo (por ejemplo, 2–benzofurilo, 3–benzofurilo), benzotienilo (por ejemplo, 2–benzotienilo, 3–benzotienilo), benzoxazolilo (por ejemplo, 2–benzoxazolilo), benzotiazolilo (por ejemplo, 2–benzotiazolilo, 5–benzotiazolilo, 6–benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol–1–ilo, bencimidazol–2–ilo, bencimidazol–5–ilo, bencimidazol–6–ilo), indolilo (por ejemplo, indol–1–ilo, indol–3–ilo, indol–4–ilo, indol–5–ilo, indol–6–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), imidazopiridilo (por ejemplo, 1H–imidazo[4,5–b]piridin–2–ilo, 1H–imidazo[4,5–c]piridin–2–ilo), imidazopirazinilo (por ejemplo, 1H–imidazo[4,5–b]pirazin–2–ilo), benzisoxazolilo, benzotriazolilo, pirazolopiridilo, pirazolotienilo, pirazolotriazinilo, y

similares.

Los ejemplos del grupo hidrocarburo cíclico no aromático incluyen cicloalquilo, cicloalquenilo, cicloalcadienilo, y similares, cada uno de los cuales está opcionalmente fusionado con anillo benceno.

Los ejemplos del grupo hidrocarburo cíclico no aromático incluyen específicamente cicloalquilo C_{3-10} (por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclononilo, ciclodecilo), cicloalquenilo C_{3-10} (por ejemplo, ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclononenilo, ciclodecenilo), cicloalcadienilo C_{4-10} (por ejemplo, ciclobutadienilo, ciclopentadienilo, ciclohexadienilo, cicloheptadienilo, ciclooctadienilo, ciclononadienilo, ciclodecadienilo), anillo fusionado formado por fusión de estos grupos y anillo benceno (por ejemplo, indanilo (por ejemplo, 1–indanilo), tetrahidronaftilo (por ejemplo, 1,2,3,4–tetrahidronaftalen–1–ilo), fluorenilo (por ejemplo, 9–fluorenilo), etc.), y similares.

Los ejemplos del grupo heterocíclico no aromático incluyen grupo heterocíclico no aromático de 3 a 8 miembros (con preferencia, de 5 ó 6 miembros) saturado o insaturado (con preferencia saturado), y similares.

Los ejemplos del grupo heterocíclico no aromático incluyen específicamente oxiranilo, azetidinilo, oxetanilo, tietanilo, pirrolidinilo, tetrahidrofurilo, tiolanilo, piperidinilo, tetrahidropiranilo,

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tianilo, morfolinilo, tiomorfolinilo, piperazinilo, azepanilo, oxepanilo, tiepanilo, oxazepanilo, tiazepanilo, azocanilo, oxocanilo, tiocanilo, oxazocanilo, tiazocanilo, dioxinilo, y similares.

Como "grupo cíclico" del "grupo cíclico sustituido opcionalmente" para el anillo Y, se prefieren grupo hidrocarburo aromático, grupo heterocíclico aromático. Como el grupo hidrocarburo aromático, se prefiere arilo C_{6-14}, arilo C_{6-10} tiene mayor preferencia, y fenilo tiene particular preferencia. Como el grupo heterocíclico aromático, se prefiere grupo heterocíclico monocíclico o grupo heterocíclico aromático fusionado, anillo piridina, o grupo heterocíclico aromático fusionado formado por fusión de grupo heterocíclico aromático monocíclico de 5 miembros que contiene, como átomo constitutivo del anillo, 1 ó 2 heteroátomos seleccionados de átomo de azufre y átomo de nitrógeno, además de átomos de carbono, y anillo benceno (por ejemplo, benzotiazolilo, bencimidazolilo, indolilo, etc.) tiene mayor preferencia, y benzotiazolilo (por ejemplo, 5–benzotiazolilo, 6–benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol–5–ilo, bencimidazol–6–ilo), indolilo (por ejemplo, indol–4–ilo, indol–5–ilo, indol–6–ilo), y similares tienen particular preferencia.

El "grupo cíclico sustituido opcionalmente" para el anillo Y puede tener 1 a la cantidad máxima aceptable de sustituyentes en cualquier posición sustituible. Cuando el grupo cíclico está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y es preferible que opcionalmente tengan 1 a 5, con

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mayor preferencia, 1 a 3, con particular preferencia, 1 ó 2 sustituyentes.

Como "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Y, por ejemplo, se pueden mencionar

(i) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(ii) ciano,

(iii) nitro,

(iv) grupo hidrocarburo sustituido opcionalmente,

(v) hidroxi,

(vi) hidrocarbon–oxi sustituido opcionalmente,

(vii) aminosulfonilo sustituido opcionalmente,

(viii) aminocarbonilo sustituido opcionalmente,

(ix) acilo,

(x) amino sustituido opcionalmente,

(xi) sulfanilo sustituido opcionalmente,

(xii) grupo heterocíclico sustituido opcionalmente,

(xiii) heterociclil–oxi sustituido opcionalmente,

(xiv) oxo,

(xv) sulfinilo sustituido opcionalmente,

(xvi) aminotiocarbonilo sustituido opcionalmente,

(xvii) carboxi esterificado opcionalmente,

y similares (en la presente memoria descriptiva, mencionado como grupo sustituyente (1)).

En lo sucesivo, en la presente, se explican los sustituyentes enumerados en el grupo sustituyente (1).

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Como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv), se pueden mencionar alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, arilo, cicloalquil–alquilo, cicloalquenil–alquilo, aril–alquilo, cicloalcandienilo, y similares, cada uno de los cuales está sustituido opcionalmente.

En la presente memoria descriptiva, los ejemplos del "alquilo" pueden incluir alquilo de cadena lineal o ramificada con 1 a 8, con preferencia, 1 a 6, con mayor preferencia, 1 a 4 carbonos, y similares, específicamente metilo, etilo, propilo, isopropilo, butilo, isobutilo, sec–butilo, tert-butilo, pentilo, isopentilo, tert-pentilo, neopentilo, hexilo, isohexilo, heptilo, octilo, y similares. El "alquilo" puede tener, por ejemplo, en cualquiera de sus posiciones sustituibles, 1 a la cantidad máxima aceptable de los sustituyentes seleccionados del grupo de los siguientes sustituyentes (en lo sucesivo,, abreviados como "grupo sustituyente (2)"):

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(2) ciano;

(3) nitro;

(4) hidroxi;

(5) alcoxi C_{1-6} (por ejemplo, metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, tert-butoxi, etc.) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo) y alcoxi C_{1-6} (por ejemplo, metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, tert-butoxi, etc.);

(6) alqueniloxi C_{2-6} (por ejemplo, eteniloxi, propeniloxi,

buteniloxi, penteniloxi, hexeniloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(7) alquiniloxi C_{2-6} (por ejemplo, etiniloxi, propiniloxi, butiniloxi, pentiniloxi, hexiniloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(8) cicloalquil C_{3-6}–oxi (por ejemplo, ciclopropiloxi, ciclobutiloxi, ciclopentiloxi, ciclohexiloxi) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(9) cicloalquenil C_{3-6}–oxi (por ejemplo, ciclopropeniloxi, ciclobuteniloxi, ciclopenteniloxi, ciclohexeniloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(10) ariloxi C_{6-10} (por ejemplo, feniloxi, 1–naftiloxi, 2–naftiloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(11) cicloalquil C_{3-6}–alcoxi C_{1-6} (por ejemplo, ciclopropilmetiloxi, ciclopropiletiloxi, ciclobutilmetiloxi, ciclopentilmetiloxi, ciclohexilmetiloxi, ciclohexiletiloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(12) cicloalquenil C_{3-6}–alcoxi C_{1-6} (por ejemplo, ciclopentenilmetiloxi, ciclohexenilmetiloxi, ciclohexeniletiloxi, ciclohexenilpropiloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(13) aril C_{6-10}–alcoxi C_{1-6} (por ejemplo, fenilmetiloxi,

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feniletiloxi, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(14) alquil C_{1-6}–aminosulfonilo (por ejemplo, metilaminosulfonilo, etilaminosulfonilo, propilaminosulfonilo, etc.);

(15) di–alquil C_{1-6}–aminosulfonilo (por ejemplo, dimetilaminosulfonilo, dietilaminosulfonilo, dipropilaminosulfonilo, etc.);

(16) alquil C_{1-6}–aminocarbonilo (por ejemplo, metilaminocarbonilo, etilaminocarbonilo, propilaminocarbonilo, etc.);

(17) di–alquil C_{1-6}–aminocarbonilo (por ejemplo, dimetilaminocarbonilo, dietilaminocarbonilo, dipropilaminocarbonilo, etc.);

(18) formilo;

(19) alquil C_{1-6}–carbonilo (por ejemplo, acetilo, etilcarbonilo, propilcarbonilo, isopropilcarbonilo, etc.);

(20) alquenil C_{2-6}–carbonilo (por ejemplo, etenilcarbonilo, propenilcarbonilo, butenilcarbonilo, pentenilcarbonilo, hexenilcarbonilo, etc.);

(21) alquinil C_{2-6}–carbonilo (por ejemplo, etinilcarbonilo, propinilcarbonilo, butinilcarbonilo, pentinilcarbonilo, hexinilcarbonilo, etc.);

(22) cicloalquil C_{3-6}–carbonilo (por ejemplo, ciclopropilcarbonilo, ciclobutilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo);

(23) cicloalquenil C_{3-6}–carbonilo (por ejemplo,

ciclopropenilcarbonilo, ciclobutenilcarbonilo, ciclopentenilcarbonilo, ciclohexenilcarbonilo, etc.);

(24) aril C_{6-10}–carbonilo (por ejemplo, benzoilo, 1–naftilcarbonilo, 2–naftilcarbonilo, etc.);

(25) cicloalquil C_{3-6}–alquil C_{1-6}–carbonilo (por ejemplo, ciclopropilmetilcarbonilo, ciclopropiletilcarbonilo, ciclobutilmetilcarbonilo, ciclopentilmetilcarbonilo, ciclohexilmetilcarbonilo, ciclohexiletilcarbonilo, etc.);

(26) cicloalquenil C_{3-6}–alquil C_{1-6}–carbonilo (por ejemplo, ciclopentenilmetilcarbonilo, ciclohexenilmetilcarbonilo, ciclohexeniletilcarbonilo, ciclohexenilpropilcarbonilo, etc.);

(27) aril C_{6-10}–alquil C_{1-6}–carbonilo (por ejemplo, bencilcarbonilo, feniletilcarbonilo, etc.);

(28) heterociclil–carbonilo aromático monocíclico de 5 ó 6 miembros (por ejemplo, furilcarbonilo, tienilcarbonilo, pirrolilcarbonilo, oxazolilcarbonilo, isoxazolilcarbonilo, tiazolilcarbonilo, isotiazolilcarbonilo, imidazolilcarbonilo, piridilcarbonilo, pirazolilcarbonilo, etc.);

(29) heterociclil–carbonilo aromático fusionado de 8 a 12 miembros (por ejemplo, benzofurilcarbonilo, isobenzofurilcarbonilo, benzotienilcarbonilo, isobenzotienilcarbonilo, indolilcarbonilo, isoindolilcarbonilo, 1H–indazolilcarbonilo, bencimidazolilcarbonilo, benzoxazolilcarbonilo, etc.);

(30) heterociclil–carbonilo no aromático de 5 ó 6 miembros (por ejemplo, oxiranilcarbonilo, azetidinilcarbonilo, oxetanilcarbonilo,

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tietanilcarbonilo, pirrolidinilcarbonilo, tetrahidrofurilcarbonilo, tiolanilcarbonilo, piperidinilcarbonilo, etc.);

(31) alquil C_{1-6}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo, etc.);

(32) alquenil C_{2-6}–sulfonilo (por ejemplo, etenilsulfonilo, propenilsulfonilo, etc.);

(33) alquinil C_{2-6}–sulfonilo (por ejemplo, etinilsulfonilo, propinilsulfonilo, butinilsulfonilo, pentinilsulfonilo, hexinilsulfonilo, etc.);

(34) cicloalquil C_{3-6}–sulfonilo (por ejemplo, ciclopropilsulfonilo, ciclobutilsulfonilo, etc.);

(35) cicloalquenilsulfonilo C_{3-6} (por ejemplo, ciclopropenilsulfonilo, ciclobutenilsulfonilo, etc.);

(36) arilsulfonilo C_{6-10} (por ejemplo, fenilsulfonilo, etc.);

(37) cicloalquil C_{3-6}–alquil C_{1-6}–sulfonilo (por ejemplo, ciclopropilmetilsulfonilo, etc.);

(38) cicloalquenil C_{3-6}–alquil C_{1-6}–sulfonilo (por ejemplo, ciclopentenilmetilsulfonilo, etc.);

(39) aril C_{6-10}–alquil C_{1-6}–sulfonilo (por ejemplo, bencilsulfonilo, etc.);

(40) heterociclil–sulfonilo aromático monocíclico de 5 ó 6 miembros (por ejemplo, furilsulfonilo, tienilsulfonilo, piridilsulfonilo, etc.);

(41) heterociclil–sulfonilo aromático fusionado de 8 a 12 miembros (por ejemplo, benzofurilsulfonilo, isobenzofurilsulfonilo,

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etc.);

(42) heterociclil–sulfonilo no aromático de 5 ó 6 miembros (por ejemplo, oxiranilsulfonilo, azetidinilsulfonilo, etc.);

(43) amino;

(44) mono–alquilamino C_{1-6} (por ejemplo, metilamino, etilamino, propilamino, isopropilamino, butilamino, isobutilamino, tert-butilamino, etc.);

(45) di–alquilamino C_{1-6} (por ejemplo, dimetilamino, dietilamino, dipropilamino, diisopropilamino, dibutilamino, diisobutilamino, di–tert-butilamino, etc.);

(46) mono–(alquil C_{1-6}–carbonil)amino (por ejemplo, acetilamino, etilcarbonilamino, propilcarbonilamino, tert-butilcarbonilamino, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(47) mono–(cicloalquil C_{3-6}–carbonil)amino (por ejemplo, ciclopropilcarbonilamino, ciclobutilcarbonilamino, ciclopentilcarbonilamino, ciclohexilcarbonilamino, etc.);

(48) mono–(aril C_{6-10}–carbonil)amino (por ejemplo, benzoilamino, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo);

(49) mono–(heterociclil–carbonil aromático monocíclico de 5 ó 6 miembros)amino (por ejemplo, furilcarbonilamino, tienilcarbonilamino, pirrolilcarbonilamino, oxazolilcarbonilamino, isoxazolilcarbonilamino, tiazolilcarbonilamino, isotiazolilcarbonilamino, imidazolilcarbonilamino,

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piridilcarbonilamino, pirazolilcarbonilamino, etc.);

(50) mono–(heterociclil–carbonil aromático fusionado de 8 a 12 miembros)amino (por ejemplo, benzofurilcarbonilamino, isobenzofurilcarbonilamino, benzotienilcarbonilamino, isobenzotienilcarbonilamino, etc.);

(51) mono–(heterociclil–carbonil no aromático de 5 ó 6 miembros)amino (por ejemplo, oxiranilcarbonilamino, azetidinilcarbonilamino, oxetanilcarbonilamino, etc.);

(52) tiol;

(53) alquil C_{1-6}–sulfanilo (por ejemplo, metilsulfanilo, etilsulfanilo, etc.);

(54) alquenil C_{2-6}–sulfanilo (por ejemplo, etenilsulfanilo, propenilsulfanilo, etc.);

(55) alquinil C_{2-6}–sulfanilo (por ejemplo, etinilsulfanilo, propinilsulfanilo, butinilsulfanilo, pentinilsulfanilo, hexinilsulfanilo, etc.);

(56) cicloalquil C_{3-6}–sulfanilo (por ejemplo, ciclopropilsulfanilo, ciclobutilsulfanilo, etc.);

(57) cicloalquenil C_{3-6}–sulfanilo (por ejemplo, ciclopropenilsulfanilo, ciclobutenilsulfanilo, etc.);

(58) aril C_{6-10}–sulfanilo (por ejemplo, fenilsulfanilo, etc.);

(59) cicloalquil C_{3-6}–alquil C_{1-6}–sulfanilo (por ejemplo, ciclopropilmetilsulfanilo, etc.);

(60) cicloalquenil C_{3-6}–alquil C_{1-6}–sulfanilo (por ejemplo, ciclopentenilmetilsulfanilo, etc.);

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(61) grupo heterocíclico aromático monocíclico de 5 ó 6 miembros (por ejemplo, furilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, imidazolilo, piridilo, pirazolilo, etc.) que opcionalmente tiene 1 a 3 alquilo C_{1-4} (por ejemplo, metilo, etilo, etc.);

(62) grupo heterocíclico aromático fusionado de 8 a 12 miembros (por ejemplo, benzofurilo, isobenzofurilo, benzotienilo, isobenzotienilo, indolilo, isoindolilo, 1H–indazolilo, bencimidazolilo, benzoxazolilo, etc.);

(63) grupo heterocíclico no aromático de 5 ó 6 miembros (por ejemplo, oxiranilo, azetidinilo, oxetanilo, tietanilo, pirrolidinilo, tetrahidrofurilo, tiolanilo, piperidinilo, etc.);

(64) heterociclil–oxi aromático monocíclico de 5 ó 6 miembros (por ejemplo, furiloxi, tieniloxi, pirroliloxi, oxazoliloxi, isoxazoliloxi, tiazoliloxi, isotiazoliloxi, imidazoliloxi, piridiloxi, pirazoliloxi, etc.);

(65) heterociclil–oxi aromático fusionado de 8 a 12 miembros (por ejemplo, benzofuriloxi, isobenzofuriloxi, benzotieniloxi, isobenzotieniloxi, indoliloxi, isoindoliloxi, 1H–indazoliloxi, bencimidazoliloxi, benzoxazoliloxi, etc.);

(66) heterociclil–oxi no aromático de 5 ó 6 miembros (por ejemplo, oxiraniloxi, azetidiniloxi, oxetaniloxi, tietaniloxi, pirrolidiniloxi, tetrahidrofuriloxi, tiolaniloxi, piperidiniloxi, etc.);

(67) oxo;

(68) alquil C_{1-6}–sulfinilo (por ejemplo, metilsulfinilo, etilsulfinilo, etc.);

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(69) alquenil C_{2-6}–sulfinilo (por ejemplo, etenilsulfinilo, propenilsulfinilo, etc.);

(70) alquinil C_{2-6}–sulfinilo (por ejemplo, etinilsulfinilo, propinilsulfinilo, butinilsulfinilo, pentinilsulfinilo, hexinilsulfinilo, etc.);

(71) cicloalquil C_{3-6}–sulfinilo (por ejemplo, ciclopropilsulfinilo, ciclobutilsulfinilo, etc.);

(72) cicloalquenil C_{3-6}–sulfinilo (por ejemplo, ciclopropenilsulfinilo, ciclobutenilsulfinilo, etc.);

(73) aril C_{6-10}–sulfinilo (por ejemplo, fenilsulfinilo, etc.);

(74) cicloalquil C_{3-6}–alquil C_{1-6}–sulfinilo (por ejemplo, ciclopropilmetilsulfinilo, etc.);

(75) cicloalquenil C_{3-6}–alquil C_{1-6}–sulfinilo (por ejemplo, ciclopentenilmetilsulfinilo, etc.);

(76) aminotiocarbonil sustituido con alquilo C_{1-6} o aril C_{6-10}–alquil C_{1-4}–carbonilo (por ejemplo, metilaminotiocarbonilo, etilaminotiocarbonilo, propilaminotiocarbonilo, bencilcarbonilaminotiocarbonilo, etc.);

(77) di–alquil C_{1-6}–aminotiocarbonilo (por ejemplo, dimetilaminotiocarbonilo, dietilaminotiocarbonilo, dipropilaminotiocarbonilo, etc.);

(78) carboxi;

(79) alcoxi C_{1-6}–carbonilo (por ejemplo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, isopropoxicarbonilo, butoxicarbonilo, isobutoxicarbonilo, tert-butoxicarbonilo, etc.);

(80) alquenil C_{2-6}–oxi–carbonilo (por ejemplo,

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eteniloxicarbonilo, propeniloxicarbonilo, buteniloxicarbonilo, penteniloxicarbonilo, hexeniloxicarbonilo, etc.);

(81) alquinil C_{2-6}–oxi–carbonilo (por ejemplo, etiniloxicarbonilo, propiniloxicarbonilo, butiniloxicarbonilo, pentiniloxicarbonilo, hexiniloxicarbonilo, etc.);

(82) cicloalquil C_{3-6}–oxi–carbonilo (por ejemplo, ciclopropiloxicarbonilo, ciclobutiloxicarbonilo, ciclopentiloxicarbonilo, ciclohexiloxicarbonilo, etc.);

(83) cicloalquenil C_{3-6}–oxi–carbonilo (por ejemplo, ciclopropeniloxicarbonilo, ciclobuteniloxicarbonilo, ciclopenteniloxicarbonilo, ciclohexeniloxicarbonilo, etc.);

(84) aril C_{6-10}–oxi–carbonilo (por ejemplo, feniloxicarbonilo, 1–naftiloxicarbonilo, 2–naftiloxicarbonilo, etc.);

(85) cicloalquil C_{3-6}–alcoxi C_{1-6}–carbonilo (por ejemplo, ciclopropilmetiloxicarbonilo, ciclopropiletiloxicarbonilo, ciclobutilmetiloxicarbonilo, ciclopentilmetiloxicarbonilo, ciclohexilmetiloxicarbonilo, ciclohexiletiloxicarbonilo, etc.);

(86) cicloalquenil C_{3-6}–alcoxi C_{1-6}–carbonilo (por ejemplo, ciclopentenilmetiloxicarbonilo, ciclohexenilmetiloxicarbonilo, ciclohexeniletiloxicarbonilo, ciclohexenilpropiloxicarbonilo, etc.); y

(87) aril C_{6-10}–alcoxi C_{1-6}–carbonilo (por ejemplo, fenilmetiloxicarbonilo, feniletiloxicarbonilo, etc.).

Cuando el alquilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, y con mayor preferencia, 1 a

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Como el "alquenilo", por ejemplo, se pueden mencionar alquenilo de cadena lineal o ramificada con 2 a 8, con preferencia, 2 a 4 carbonos, y similares, y específicamente se pueden mencionar etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, butadienilo, y similares. El "alquenilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados del grupo sustituyente antes mencionado (2) y arilo C_{6-10} (por ejemplo, fenilo, etc.). Cuando el alquenilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "alquinilo", por ejemplo, se puede mencionar alquinilo de cadena lineal o ramificada con 2 a 8, con preferencia, 2 a 4 carbonos, y similares, y específicamente se pueden mencionar etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, y similares. El "alquinilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados del grupo sustituyente antes mencionado (2) y arilo C_{6-10} (por ejemplo, fenilo, etc.). Cuando el alquinilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "cicloalquilo", por ejemplo, se puede mencionar

cicloalquilo con 3 a 8, con preferencia, 3 a 6 carbonos, y similares, y se pueden mencionar específicamente ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo, y similares. El "cicloalquilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de (a) alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo) e hidroxi, y (b) sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el cicloalquilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "cicloalquenilo", por ejemplo, se puede mencionar cicloalquenilo con 3 a 8, con preferencia, 3 a 6 carbonos, y similares, y específicamente se pueden mencionar ciclopropenilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, y similares. El "cicloalquenilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo), y sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el cicloalquenilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la

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cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "arilo", por ejemplo, se puede mencionar arilo con 6 a 18, con preferencia, 6 a 14, con mayor preferencia, 6 a 10, con particular preferencia, 6 carbonos, y similares, y específicamente se pueden mencionar fenilo, 1–naftilo, 2–naftilo, bifenililo, 2–antrilo, fenantrilo, acenaftilenilo, y similares. El "arilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de (a) alquilo C_{1-4} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo), ciano, hidroxi y cicloalquilo C_{3-6} (por ejemplo, ciclopropilo, etc.), y (b) sustituyente seleccionado del grupo sustituyente antes mencionado (2) (excepto por oxo). Cuando el arilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "cicloalquil–alquilo", por ejemplo, se puede mencionar el grupo en el que el grupo cicloalquilo con 3 a 8, con preferencia, 3 a 6 carbonos, y similares, está unido con el alquilo de cadena lineal o ramificada que tiene 1 a 6, con preferencia, 1 a 4 átomos de carbono (por ejemplo, cicloalquil C_{3-8}–alquilo C_{1-4}), y similares, y específicamente se pueden mencionar ciclopropilmetilo, ciclopropiletilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo,

ciclohexiletilo, y similares. El "cicloalquil–alquilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo) y sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el cicloalquil–alquilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "cicloalquenil–alquilo", por ejemplo, se puede mencionar el grupo en el que el cicloalquenilo con 3 a 8, con preferencia, 3 a 6 carbonos está unido con el alquilo de cadena lineal o ramificada que tiene 1 a 6, con preferencia, 1 a 4 átomos de carbono (por ejemplo, grupo cicloalquenil C_{3-8}–alquilo C_{1-4}), y específicamente se pueden mencionar ciclopentenilmetilo, ciclohexenilmetilo, ciclohexeniletilo, ciclohexenilpropilo, cicloheptenilmetilo, ciclohepteniletilo, y similares. El "cicloalquenil–alquilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo) y sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el cicloalquenil–alquilo está sustituido con dos o más sustituyentes, los

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sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "aril–alquilo", por ejemplo, se puede mencionar el grupo en el que el arilo con 6 a 18, con mayor preferencia, 6 a 10, con particular preferencia, 6 carbonos está unido con el alquilo de cadena lineal o ramificada que tiene 1 a 6, con preferencia, 1 a 4 átomos de carbono (por ejemplo, aril C_{6-18}–alquilo C_{1-4}), y similares, y específicamente se pueden mencionar fenilmetilo (bencilo), feniletilo (fenetilo), y similares. El "aril–alquilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo) y sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el aril–alquilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "cicloalcandienilo", por ejemplo, se puede mencionar el grupo cicloalcandienilo C_{4-6} tales como 2,4–ciclopentadien–1–ilo, 2,4–ciclohexadien–1–ilo, 2,5–ciclohexadien–1–ilo, y similares, y otros. El "cicloalcandienilo" puede tener, en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes seleccionados de alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo,

isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor, cloro, bromo, yodo) y sustituyente seleccionado del grupo sustituyente antes mencionado (2). Cuando el cicloalcandienilo está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Como el "hidrocarbon–oxi sustituido opcionalmente" en el grupo sustituyente (1)(vi), se pueden mencionar alquil–oxi, alquenil–oxi, alquinil–oxi, cicloalquil–oxi, cicloalquenil–oxi, aril–oxi, cicloalquil–alquil–oxi, cicloalquenil–alquil–oxi, aril–alquil–oxi, y similares, cada uno de los cuales está sustituido opcionalmente. Como el "alquilo" para alquil–oxi, el "alquenilo" para alquenil–oxi, el "alquinilo" para alquinil–oxi, el "cicloalquilo" para cicloalquil–oxi, el "cicloalquenilo" para cicloalquenil–oxi, el "arilo" para aril–oxi, el "cicloalquil–alquilo" para cicloalquil–alquil–oxi, el "cicloalquenil–alquilo" para cicloalquenil–alquil–oxi, el "aril–alquilo" para aril–alquil–oxi, se pueden mencionar, respectivamente, grupos similares a los ejemplificados como "grupo hidrocarburo" del "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

El "aminosulfonilo sustituido opcionalmente" en el grupo sustituyente (1)(vii) puede tener 1 ó 2 sustituyentes. Cuando el aminosulfonilo está sustituido con dos sustituyentes, los sustituyentes pueden ser iguales o diferentes.

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Como "sustituyente" del "aminosulfonilo sustituido opcionalmente", por ejemplo, se pueden mencionar grupos similares a los ejemplificados como el "grupo hidrocarburo" del "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado y los grupos mencionados más abajo como el "grupo heterocíclico sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes mencionado.

El "aminocarbonilo sustituido opcionalmente" en el grupo sustituyente (1)(viii) puede tener 1 ó 2 sustituyentes. Cuando el aminocarbonilo está sustituido con dos sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como "sustituyente" del "aminocarbonilo sustituido opcionalmente", por ejemplo, se pueden mencionar aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes sustituido, el grupo ejemplificado como el "hidrocarbon–oxi sustituido opcionalmente" en el grupo sustituyente (1)(vi) antes mencionado, y el grupo mencionado más abajo como "heterociclo sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes mencionado.

Como el "acilo" en el grupo sustituyente (1)(ix), se pueden mencionar, por ejemplo, hidrocarbon–carbonilo sustituido opcionalmente, heterociclil–carbonilo sustituido opcionalmente, hidrocarbon–sulfonilo sustituido opcionalmente, heterociclil–sulfonilo sustituido opcionalmente, y similares.

Como el "hidrocarburo sustituido opcionalmente" del

"hidrocarburo sustituido opcionalmente–carbonilo", se pueden mencionar aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

Como el "hidrocarburo sustituido opcionalmente" del "hidrocarburo sustituido opcionalmente–sulfonilo", se pueden mencionar aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

Como el "heterociclo sustituido opcionalmente" del "heterociclil–carbonilo sustituido opcionalmente" y "heterociclil–sulfonilo sustituido opcionalmente", se pueden mencionar aquellos similares al grupo mencionado más abajo como el "grupo heterocíclico sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes mencionado.

El "amino sustituido opcionalmente" en el grupo sustituyente (1)(x) puede tener 1 ó 2 sustituyentes. Cuando el amino está sustituido con dos sustituyentes, los sustituyentes pueden ser iguales o diferentes. Como "sustituyente" del "amino sustituido opcionalmente", se pueden mencionar, por ejemplo, aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes sustituido, el grupo ejemplificado como el "aminocarbonilo sustituido opcionalmente" en el grupo sustituyente (1)(viii) antes mencionado, el grupo ejemplificado como el "acilo" en el grupo sustituyente (1)(ix)

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antes mencionado, el grupo mencionado más abajo como el "grupo heterocíclico sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes mencionado, y el grupo seleccionado del "carboxi esterificado opcionalmente" en el grupo sustituyente (1)(xviii) antes mencionado.

Como "sustituyente" del "sulfanilo sustituido opcionalmente" en el grupo sustituyente (1)(xi), se pueden mencionar, por ejemplo, aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

Como el "grupo heterocíclico" del "grupo heterocíclico sustituido opcionalmente" en el grupo sustituyente (1)(xii), se pueden mencionar grupo heterocíclico aromático (por ejemplo, grupo heterocíclico aromático monocíclico, grupo heterocíclico aromático fusionado), grupo heterocíclico no aromático, y similares, y por ejemplo, se pueden mencionar grupo heterocíclico aromático de 5 a 12 miembros (grupo heterocíclico aromático monocíclico o grupo heterocíclico aromático fusionado etc.), heterociclo no aromático saturado o insaturado, y similares que tiene, como átomo constitutivo del anillo, 1 o más (con preferencia, 1 a 4, con mayor preferencia, 1 ó 2) de 1 a 3, con preferencia, 1 ó 2 tipos de heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno opcionalmente oxidados, y similares (con preferencia, átomo de oxígeno, átomo de azufre y átomo de nitrógeno, etc.) además de átomos de carbono.

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Como el grupo heterocíclico aromático monocíclico, se pueden mencionar, por ejemplo, grupo heterocíclico aromático monocíclico de 5 ó 6 miembros, y similares.

Como el grupo heterocíclico aromático monocíclico, se pueden mencionar específicamente furilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, imidazolilo, pirazolilo, oxadiazolilo (por ejemplo, 1,2,3–oxadiazolilo, 1,2,4–oxadiazolilo, 1,3,4–oxadiazolilo), furazanilo, tiadiazolilo (por ejemplo, 1,2,3–tiadiazolilo, 1,2,4–tiadiazolilo, 1,3,4–tiadiazolilo), triazolilo (por ejemplo, 1,2,3–triazolilo, 1,2,4–triazolilo), tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, y similares.

Como el grupo heterocíclico aromático fusionado, se pueden mencionar en particular, por ejemplo, grupo heterocíclico aromático fusionado de 8 a 12 miembros, y grupo heterocíclico formado por fusión del grupo heterocíclico aromático monocíclico de 5 ó 6 miembros antes mencionado y anillo benceno o grupo heterocíclico formado por fusión de dos de los grupos heterocíclicos aromáticos monocíclicos de 5 ó 6 miembros antes mencionados, iguales o diferentes.

Los ejemplos del grupo heterocíclico aromático fusionado incluyen específicamente benzofurilo, isobenzofurilo, benzotienilo, isobenzotienilo, indolilo, isoindolilo, 1H–indazolilo, bencimidazolilo, benzoxazolilo, 1,2–benzisoxazolilo, benzotiazolilo, 1,2–benzoisotiazolilo, 1H–benzotriazolilo, quinolilo, isoquinolilo, cinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, naftiridinilo,

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purinilo, pteridinilo, carbazolilo, α–carbolinilo, β–carbolinilo, γ–carbolinilo, acridinilo, fenoxazinilo, fenotiazinilo, fenazinilo, fenoxatiinilo, tiantrenilo, fenantridinilo, fenantrolinilo, indolizinilo, pirrolo[1,2–b]piridazinilo, pirazolo[1,5–a]piridilo, imidazo[1,2–a]piridilo, imidazo[1,5–a]piridilo, imidazo[1,2–b]piridazinilo, imidazo[1,2–a]pirimidinilo, 1,2,4–triazolo[4,3–a]piridilo, 1,2,4–triazolo[4,3–b]piridazinilo, y similares.

Los ejemplos del grupo heterocíclico no aromático incluyen grupo heterocíclico no aromático de 3 a 8 miembros (con preferencia, de 5 ó 6 miembros) saturado o insaturado (con preferencia saturado), y similares.

Los ejemplos del grupo heterocíclico no aromático incluyen específicamente oxiranilo, azetidinilo, oxetanilo, tietanilo, pirrolidinilo, tetrahidrofurilo, tiolanilo, piperidinilo, tetrahidropiranilo, tianilo, morfolinilo, tiomorfolinilo, piperazinilo, azepanilo, oxepanilo, tiepanilo, oxazepanilo, tiazepanilo, azocanilo, oxocanilo, tiocanilo, oxazocanilo, tiazocanilo, dioxinilo, y similares.

De modo alternativo, el grupo heterocíclico no aromático puede estar fusionado con el anillo benceno o el grupo heterocíclico aromático monocíclico antes mencionado para formar grupo heterocíclico no aromático fusionado. Como el grupo heterocíclico no aromático fusionado formado por fusión de grupo heterocíclico no aromático y anillo benceno, se pueden mencionar, por ejemplo, benzodioxinilo, tetrahidroisoquinolilo, y similares.

El "grupo heterocíclico sustituido opcionalmente" puede tener,

en cualquier posición sustituible, 1 a la cantidad máxima aceptable de sustituyentes. Cuando el grupo heterocíclico está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y la cantidad preferible de los sustituyentes es 1 a 5, con mayor preferencia, 1 a 3.

Los ejemplos del "sustituyente" del "grupo heterocíclico sustituido opcionalmente" pueden incluir (a) alquilo C_{1-6} (por ejemplo, metilo, etilo, propilo, isopropilo, butilo, isobutilo, tert-butilo, etc.) que opcionalmente tiene 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo), ciano, hidroxi y alcoxi C_{1-4} (por ejemplo, metoxi), (b) arilo C_{6-10} (por ejemplo, fenilo), (c) aril C_{6-10}–alquilo C_{1-4} (por ejemplo, bencilo, etc.) y (d) aquellos similares al grupo seleccionado del grupo sustituyente (2) antes mencionado.

Por ejemplo, entre los grupos heterocíclicos sustituidos con oxo en el grupo sustituyente (2) antes mencionado, se pueden mencionar como ejemplos específicos del grupo heterocíclico no aromático sustituido con oxo, 2–oxoazetidinilo, 2–oxopirrolidinilo, 2–oxopiperidinilo, 2–oxoazepanilo, 2–oxoazocanilo, 2–oxotetrahidrofurilo, 2–oxotetrahidropiranilo, 2–oxotiolanilo, 2–oxotianilo, 2–oxopiperazinilo, 2–oxooxepanilo, 2–oxooxazepanilo, 2–oxotiepanilo, 2–oxotiazepanilo, 2–oxooxocanilo, 2–oxotiocanilo, 2–oxooxazocanilo, 2–oxotiazocanilo, 2–oxodioxinilo, y similares.

Como el "heterociclo sustituido opcionalmente" del "heterociclil–oxi sustituido opcionalmente," en el grupo sustituyente

(1)(xiii), se pueden mencionar aquellos similares al grupo ejemplificado como el "heterociclo sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes mencionado.

Como "sustituyente" del "sulfinilo sustituido opcionalmente" en el grupo sustituyente (1)(xv), se pueden mencionar, por ejemplo, aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

El "aminotiocarbonilo sustituido opcionalmente" en el grupo sustituyente (1)(xvi) puede tener 1 ó 2 sustituyentes. Cuando el aminotiocarbonilo está sustituido con 2 sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como "sustituyente" del "aminotiocarbonilo sustituido opcionalmente", se pueden mencionar, por ejemplo, 1 ó 2 grupos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

Como el "carboxi esterificado opcionalmente" en el grupo sustituyente (1)(xvii), se pueden mencionar, por ejemplo, carboxi esterificado opcionalmente por el grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes mencionado.

El "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Y es, con preferencia,

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

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(2) alquilo sustituido opcionalmente,

(3) alcoxi sustituido opcionalmente,

(4) aminocarbonilo sustituido opcionalmente,

(5) amino sustituido opcionalmente,

(6) carboxi esterificado opcionalmente,

(7) nitro,

y similares.

De ellos, se prefieren

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(2) alquilo sustituido opcionalmente,

(3) amino sustituido opcionalmente,

y similares.

En lo sucesivo, en la presente, los ejemplos preferidos del "sustituyente" antes mencionado del "grupo cíclico sustituido opcionalmente" para el anillo Y se ejemplifican en detalle.

(1) Como átomo de halógeno, se prefieren flúor, cloro, bromo, y similares.

(2) Como el alquilo sustituido opcionalmente, es prefiere el alquilo C_{1-8} sustituido opcionalmente, el alquilo C_{1-4} sustituido opcionalmente tiene mayor preferencia, y alquilo C_{1-4} no sustituido es mucho más preferido. Específicamente, se prefieren metilo, etilo, y similares.

(3) Como el alcoxi sustituido opcionalmente, se prefiere alcoxi C_{1-8} sustituido opcionalmente, alcoxi C_{1-4} sustituido opcionalmente tiene mayor preferencia, alcoxi C_{1-4} no sustituido es mucho más

preferido. Específicamente, se prefieren metoxi, y similares.

(4) Como "sustituyente" para el aminocarbonilo sustituido opcionalmente, se prefieren, por ejemplo, alquilo C_{1-8}, alquenilo C_{2-8}, alquinilo C_{2-8}, cicloalquilo C_{3-8}, cicloalquenilo C_{3-8}, cicloalquinilo C_{3-8}, arilo C_{6-18}, grupo heterocíclico, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquilo C_{1-4} sustituido opcionalmente, arilo C_{6-12} sustituido opcionalmente y grupo heterocíclico sustituido opcionalmente de 5 miembros, y similares. En particular, se prefieren (a) alquilo C_{1-4} (por ejemplo, metilo, etilo) que opcionalmente tiene arilo C_{6-12} (por ejemplo, fenilo) (ejemplos específicos son bencilo, etilo), (b) grupo heterocíclico 5 miembros (por ejemplo, pirazolilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo) y arilo C_{6-12} (por ejemplo, fenilo), (c) arilo C_{6-12} sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor) y ciano (ejemplos específicos: trifluorometilo, tert-butilo, 1–ciano–1–metiletil).

(5) Como "sustituyente" para el amino sustituido opcionalmente, se prefieren alquilo sustituido opcionalmente, aminocarbonilo sustituido opcionalmente, acilo, aminotiocarbonilo sustituido opcionalmente, y similares.

Como el amino sustituido opcionalmente, es preferible amino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de (a) alquilo sustituido opcionalmente, (b) aminocarbonilo sustituido

opcionalmente, (c) acilo y (d) aminotiocarbonilo sustituido opcionalmente.

Como el alquilo sustituido opcionalmente, es preferible alquilo C_{1-4} sustituido opcionalmente. De ellos, es preferible alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con grupo heterocíclico 5 miembros (por ejemplo, pirazolilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo) (ejemplo específico: 1,3–dimetil–1H–pirazol–5–ilmetilo).

Como el aminocarbonilo sustituido opcionalmente, se prefieren alquil C_{1-8}–aminocarbonilo, aril C_{6-18}–aminocarbonilo, aril C_{6-18}–alquil C_{1-4}–aminocarbonilo, heterociclil–aminocarbonilo, cicloalquil C_{3-8}–aminocarbonilo, alcoxi C_{1-8}–aminocarbonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–aminocarbonilo sustituido opcionalmente, aril C_{6-18}–aminocarbonilo sustituido opcionalmente, heterociclil–aminocarbonilo sustituido opcionalmente, alcoxi C_{1-8}–aminocarbonilo sustituido opcionalmente, y similares. En particular, se prefieren (i) alquil C_{1-4}–aminocarbonilo (por ejemplo, etilaminocarbonilo), (ii) aril C_{6-10}–aminocarbonilo (por ejemplo, fenilaminocarbonilo) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–(trifluorometil)fenilcarbonilo), (iii) alcoxi C_{1-4}–aminocarbonilo (por ejemplo, metoxiaminocarbonilo, isobutoxiaminocarbonilo), (iv) heterociclil–aminocarbonilo de 5 miembros (por ejemplo, pirazolilo)

sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo) y arilo C_{6-10} (ejemplo específico: 1,3–dimetil–1H–pirazol–5–il–aminocarbonilo), y similares.

Como el acilo, se prefieren alquil C_{1-8}–carbonilo, alquenil C_{2-8}–carbonilo, alquinil C_{2-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, cicloalquenil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, aril C_{6-18}–alquil C_{1-4}–carbonilo, alquil C_{1-8}–sulfonilo, aril C_{6-18}–sulfonilo, heterociclil–carbonilo, heterociclil–sulfonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–carbonilo, alquenil C_{2-8}–carbonilo, alquinil C_{2-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, cicloalquenil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, heterociclil–carbonilo, cada uno de los cuales está sustituido opcionalmente.

Como el alquil C_{1-8}–carbonilo sustituido opcionalmente, es preferible el alquil C_{1-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquil C_{1-4}–carbonilo (por ejemplo, metilcarbonilo, tert-butilcarbonilo, 3–metilbutanoílo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) hidroxi, (b) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo) y (c) grupo heterocíclico de 6 miembros (por ejemplo, piridilo) (ejemplos específicos: metilsulfonilmetilcarbonilo, 2–piridilmetilcarbonilo, tert-butilcarbonilo, 3–hidroxi–3–metilbutanoílo).

Como el alquenil C_{2-8}–carbonilo sustituido opcionalmente, se prefiere alquenilo C_{2-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquenil C_{2-4}–carbonilo (por ejemplo, 3–metil–

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2–butenoílo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo) (ejemplo específico: 3–metil–2–butenoílo).

Como el alquinil C_{2-8}–carbonilo sustituido opcionalmente, se prefiere alquinil C_{2-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquinil C_{2-4}–carbonilo (por ejemplo, 2–butinoilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo) (ejemplo específico: 2–butinoilo).

Como el cicloalquil C_{3-8}–carbonilo sustituido opcionalmente, se prefiere cicloalquil C_{3-6}–carbonilo, y específicamente se prefieren ciclopropilcarbonilo, ciclopentilcarbonilo y ciclohexilcarbonilo.

Como el cicloalquenil C_{3-8}–carbonilo sustituido opcionalmente, se prefiere cicloalquenil C_{3-6}–carbonilo (por ejemplo, ciclopentenecarbonilo) (ejemplo específico: 1–ciclopentenecarbonil).

Como el aril C_{6-18}–carbonilo sustituido opcionalmente, se prefiere aril C_{6-10}–carbonilo sustituido opcionalmente. En particular, se prefieren aril C_{6-10}–carbonilo (por ejemplo, benzoilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor), (b) alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y cicloalquilo C_{3-6} (por ejemplo, ciclopropilo) (ejemplo específico: trifluorometilo), (c) cicloalquilo C_{3-6} (por ejemplo, ciclopropilo, ciclobutilo, ciclohexilo) sustituido opcionalmente con ciano, (d) alcoxi C_{1-4} (por ejemplo, isopropoxi, tert-butoxi) sustituido opcionalmente con 1 a 5 átomos de halógeno

(por ejemplo, flúor), (e) alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y (f) grupo heterocíclico de 5 o 6 miembros (por ejemplo, tetrahidropiranilo, pirrolidinilo) sustituido opcionalmente con ciano u oxo. Específicamente, se prefieren fenilcarbonilo (benzoilo), 3–(trifluorometil)fenilcarbonilo, 4–(trifluorometil)fenilcarbonilo, 3–fluorofenilcarbonilo, 3–clorofenilcarbonilo, 3–(1–cianociclopropil)fenilcarbonilo, 3–(1–cianociclobutil)fenilcarbonilo, 3–(1–cianociclohexil)fenilcarbonilo, 2–fluoro–3–(trifluorometil)fenilcarbonilo, 2–fluoro–5–(trifluorometil)fenilcarbonilo, 3–fluoro–5–(trifluorometil)fenilcarbonilo, 4–cloro–3–(trifluorometil)fenilcarbonilo, 2–cloro–3–(trifluorometil)fenilcarbonilo, 2–cloro–5–(trifluorometil)fenilcarbonilo, 3–isopropoxifenilcarbonilo, 3–(tert-butoxi)fenilcarbonilo, 3–(1–ciano–1–metiletil)fenilcarbonilo, 3–metoxifenilcarbonilo, 3–metoxicarbonilfenilcarbonilo, 3–(trifluorometoxi)carbonilfenilcarbonilo, 3–(1,1,2,2–tetrafluoroetoxi)fenilcarbonilo, 3–(4–cianotetrahidropiran–4–il)fenilcarbonilo, 3,5–di(trifluorometil)fenilcarbonilo, 3–(2–oxopirrolidin–1–il)fenilcarbonilo, 4–(tert-butil)fenilcarbonilo, 3–(1–cianoetil)fenilcarbonilo, 3–(1–ciano–2–ciclopropil–1–metiletil)fenilcarbonilo, y similares.

Como el aril C_{6-18}–alquil C_{1-4}–carbonilo sustituido opcionalmente, se prefiere aril C_{6-10}–alquil C_{1-4}–carbonilo.

Como el alquil C_{1-8}–sulfonilo sustituido opcionalmente, se prefiere alquil C_{1-8}–sulfonilo.

Como el aril C_{6-18}–sulfonilo sustituido opcionalmente, se

prefiere aril C_{6-10}–sulfonilo.

Como la porción "heterociclo" para el heterociclil–carbonilo sustituido opcionalmente, se prefiere un grupo heterocíclico monocíclico de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y específicamente se prefieren piridilo, furilo, tetrahidrofurilo, tienilo, pirazolilo, imidazolilo, tiazolilo, oxazolilo, isoxazolilo, 1,2,3–triazolilo, 1,2,3–tiadiazolilo, dihidrooxazolilo, piridazinilo, pirazinilo, dihidropirazolilo, pirrolilo, pirrolidinilo, pirimidinilo, y similares. Como "sustituyente" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren (1) átomo de halógeno (por ejemplo, cloro), (2) alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y alcoxi C_{1-4} (por ejemplo, metoxi) (ejemplos específicos: metilo, trifluorometilo, etilo, metoxietilo, 2,2,2–trifluoroetilo, isopropilo, tert-butilo), (3) arilo C_{6-18} (por ejemplo, fenilo), (4) aril C_{6-10}–alquilo C_{1-4} (por ejemplo, bencilo), (5) alcoxi C_{1-4} (por ejemplo, metoxi, etoxi) sustituido opcionalmente con alcoxi C_{1-4} (por ejemplo, metoxi) (ejemplos específicos: metoxi, etoxi, metoxietoxi), (6) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo), (7) alquil C_{1-4}–carbonilo (por ejemplo, acetilo), (8) oxo, y similares.

Como el heterociclil–carbonilo sustituido opcionalmente, se

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prefieren específicamente 2–piridilcarbonilo, 3–piridilcarbonilo, 4–piridilcarbonilo, 2–metil–6–piridilcarbonilo, 3–metil–2–piridilcarbonilo, 4–metil–2–piridilcarbonilo, 2–metil–3–piridilcarbonilo, 2–(trifluorometil)–3–piridilcarbonilo, 2–(trifluorometil)–4–piridilcarbonilo, 2–(trifluorometil)–6–piridilcarbonilo, 2–cloro–6–metil–4—piridilcarbonilo, 2,6–dicloro–4–piridilcarbonilo, 2–furilcarbonilo, 2,5–dimetilfuran–3–carbonilo, 5–metil–2–(trifluorometil)–3–furancarbonilo, 3–metiltiofen–2–carbonilo, 5–acetilsulfoniltiofen–2–carbonilo, 5–etilsulfoniltiofen–2–carbonilo, 4–metil–1,2,3–tiadiazol–5–carbonilo, isoxazol–5–carbonilo, 1H–pirazol–5–carbonilo, 1–metil–1H–pirazol–3–carbonilo, 1–metil–1H–pirazol–5–carbonilo, 1–etil–1H–pirazol–3–carbonilo, 1–etil–1H–pirazol–5–carbonilo, 3–metil–1H–pirazol–5–carbonilo, 3–cloro–1–metil–1H–pirazol–5–carbonilo, 4–cloro–1–metil–1H–pirazol–3–carbonilo, 1–metil–3–metoxi–1H–pirazol–5–carbonilo, 1–metil–3–(trifluorometil)–1H–pirazol–5–carbonilo, 3–metoxi–1–metil–1H–pirazol–4–carbonilo, 3–metoxi–1–metil–1H–pirazol–5–carbonilo, 3–etoxi–1–metil–1H–pirazol–5–carbonilo, 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carbonilo, 1–etil–3–metil–1H–pirazol–4–carbonilo, 1–etil–3–metil–1H–pirazol–5–carbonilo, 3–metil–1–fenil–1H–pirazol–5–carbonilo, 5–metil–1–fenil–1H–pirazol–3–carbonilo, 3–etil–1–metil–1H–pirazol–5–carbonilo, 3–isopropil–1–metil–1H–pirazol–5–carbonilo, 3–metoxi–1–metil–1H–pirazol–5–carbonilo, 1–tert-butil–3–metil–1H–pirazol–5–carbonilo, 3–tert-butil–1–metil–1H–pirazol–5–carbonilo, 1–metoxietil–3–metil–1H–pirazol–5–carbonilo, 1,3–dimetil–1H–pirazol–4–carbonilo, 1,3–

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dimetil–1H–pirazol–5–carbonilo, 1,4–dimetil–1H–pirazol–3–carbonilo, 1,4–dimetil–1H–pirazol–5–carbonilo, 1,5–dimetil–1H–pirazol–3–carbonilo, 3–metilisoxazol–4–carbonilo, 3–metilisoxazol–5–carbonilo, 5–metilisoxazol–3–carbonilo, 5–metilisoxazol–4–carbonilo, 3,5–dimetilisoxazol–4–carbonilo, 1,3–tiazol–2–carbonilo, 2–metil–1,3–tiazol–4–carbonilo, 4–metil–1,3–tiazol–5–carbonilo, 5–metil–1,3–tiazol–4–carbonilo, 2,4–dimetil–1,3–tiazol–5–carbonilo, 2–cloro–4–metil–1,3–tiazol–5–carbonilo, 4–metoxi–2–metil–1,3–tiazol–5–carbonilo, 2–(1–hidroxi–1–metiletil)–1,3–tiazol–5–carbonilo, 2–(1–ciano–1–metiletil)–1,3–tiazol–5–carbonilo, 2–metil–1,3–oxazol–4–carbonilo, 4–metil–1,3–oxazol–5–carbonilo, 2–etil–4–metil–1,3–oxazol–5–carbonilo, 2,4–dimetil–1,3–oxazol–5–carbonilo, 2,5–dimetil–1,3–oxazol–4–carbonilo, 1–metil–1H–1,2,3–triazol–5–carbonilo, 1–metil–1H–1,2,3–triazol–4–carbonilo, 1–metil–1H–imidazol–2–carbonilo, 1–metil–1H–imidazol–5–carbonilo, 2–pirazinilcarbonilo, 1–metilpirrol–2–carbonilo, 1–bencilpirrol–3–carbonilo, 1,2,5–trimetilpirrol–3–carbonilo, 1–metilpirrolidin–2–carbonilo, 2–(trifluorometil)pirimidin–4–carbonilo, y similares.

Como la porción "heterociclo" para el heterociclil–sulfonilo sustituido opcionalmente, se prefieren grupo heterocíclico aromático monocíclico de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y se prefieren específicamente tiazolilo, y similares. Como "sustituyente" para el heterociclil–

carbonilo sustituido opcionalmente, se prefieren alquilo C_{1-4} (por ejemplo, metilo), y similares.

Como el heterociclil–sulfonilo sustituido opcionalmente, se prefieren específicamente 2,5–dimetil–1,3–tiazol–4–sulfonilo, y similares.

Como el aminotiocarbonilo sustituido opcionalmente, se prefieren aminotiocarbonilo sustituido opcionalmente con aril C_{6-18}–alquil C_{1-4}–carbonilo (por ejemplo, bencilcarbonilo), y similares.

(6) Como el carboxi esterificado opcionalmente, se prefieren carboxi y alcoxi C_{1-6}–carbonilo (por ejemplo, metoxicarbonilo).

Con preferencia, el anillo Y es

(1) arilo C_{6-10} (por ejemplo, fenilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro, bromo),

(b) alquilo C_{1-4} (por ejemplo, metilo, etilo),

(c) alcoxi C_{1-4} (por ejemplo, metoxi),

(d) amino sustituido opcionalmente con sustituyentes seleccionados de

(i) alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con grupo heterocíclico 5 miembros aromático (por ejemplo, pirazolilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(ii) alquil C_{1-4}–carbonilo (por ejemplo, metilcarbonilo, isobutilcarbonilo, tert-butilcarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

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(i') hidroxi,

(ii') alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo), y

(iii') grupo heterocíclico de 6 miembros aromático (por ejemplo, piridilo),

(iii) alquenil C_{2-4}–carbonilo (por ejemplo, 2–metil–1–propenilcarbonilo, vinilcarbonilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo),

(iv) alquinil C_{2-4}–carbonilo (por ejemplo, acetilencarbonilo, 1–propinilcarbonilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo),

(v) cicloalquil C_{3-6}–carbonilo (por ejemplo, ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo),

(vi) cicloalquenil C_{3-6}–carbonilo (por ejemplo, ciclopentenilcarbonilo),

(vii) aril C_{6-10}–carbonilo (por ejemplo, benzoilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno (por ejemplo, flúor, cloro),

(ii') alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y cicloalquilo C_{3-6} (por ejemplo, ciclopropilo),

(iii') cicloalquilo C_{3-6} (por ejemplo, ciclopropilo, ciclobutilo, ciclohexilo) sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} (por ejemplo, metoxi, etoxi, isopropoxi, tert-butoxi) sustituido opcionalmente con 1 a 5 átomos de halógeno (por

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ejemplo, flúor),

(v') alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y

(vi') grupo heterocíclico de 5 ó 6 miembros (por ejemplo, tetrahidropiranilo, pirrolidinilo) sustituido opcionalmente con ciano u oxo,

(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono (por ejemplo, furilcarbonilo, tetrahidrofurilcarbonilo, tienilcarbonilo, pirrolilcarbonilo, pirrolidinilcarbonilo, imidazolilcarbonilo, tiazolilcarbonilo, tiadiazolilcarbonilo, dihidrooxazolilcarbonilo, oxazolilcarbonilo, isoxazolilcarbonilo, pirazolilcarbonilo, dihidropirazolilcarbonilo, triazolilcarbonilo, piridilcarbonilo, pirimidinilcarbonilo, pirazinilcarbonilo, piridazinilcarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno (por ejemplo, cloro),

(ii') alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, terc-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y alcoxi C_{1-4} (por ejemplo, metoxi),

(iii') arilo C_{6-10} (por ejemplo, fenilo),

(iv') aril C_{6-10}–alquilo C_{1-4} (por ejemplo, bencilo),

(v') alcoxi C_{1-4} (por ejemplo, metoxi, etoxi) sustituido opcionalmente con alcoxi C_{1-4} (por ejemplo, metoxi),

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(vi') alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo),

(vii') alquil C_{1-4}–carbonilo (por ejemplo, acetilo), y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático (por ejemplo, benzopirazolilcarbonilo, indolilcarbonilo),

(x) alquil C_{1-4}–aminocarbonilo (por ejemplo, etilaminocarbonilo),

(xi) aril C_{6-10}–aminocarbonilo (por ejemplo, fenilaminocarbonilo) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(xii) alcoxi C_{1-4}–aminocarbonilo (por ejemplo, metoxiaminocarbonilo, isobutoxiaminocarbonilo),

(xiii) heterociclil–aminocarbonilo de 5 miembros (por ejemplo, isoxazolilaminocarbonilo, pirazolilaminocarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo, tert-butilo) y arilo C_{6-10} (por ejemplo, fenilo),

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo (por ejemplo, bencilcarbonilo), y

(xv) heterociclil–sulfonilo aromático de 5 miembros (por ejemplo, tiazolilsulfonilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(e) alquil C_{1-4}–aminocarbonilo (por ejemplo, metilaminocarbonilo) que opcionalmente tiene arilo C_{6-10} (por

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ejemplo, fenilo),

(f) heterociclil–aminocarbonilo de 5 miembros (por ejemplo, pirazolilaminocarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo) y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo (por ejemplo, fenilaminocarbonilo) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor) y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico (por ejemplo, piridilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, bromo), y

(b) aril C_{6-10}–carbonilamino (por ejemplo, benzoilamino) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor), o

(3) heterociclo aromático fusionado (por ejemplo, indolilo, benzotiazolilo, bencimidazolilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4} (por ejemplo, metilo), y

(b) aril C_{6-10}–amino (por ejemplo, fenilamino) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido

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opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor), y similares.

Como anillo Y, se prefieren específicamente 3–[(1,3–dimetil–1H–pirazol–5–il)aminocarbonil]–3–fenilo, 3–aminofenilo, 4–aminofenilo, 3–{[(etilamino)carbonil]amino}fenilo, 4–{[(fenilamino) carbonil]amino}fenilo, 3–{[(fenilamino)carbonil]amino}fenilo, 3–({[3–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–({[4–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–[(tert-butilcarbonil) amino]fenilo, 3–[(ciclopropilcarbonil)amino]fenilo, 3–[(ciclohexilcarbonil)amino]fenilo, 3–[(fenilcarbonil)amino]fenilo, 3–{[3–(trifluorometilfenil)carbonil]amino}fenilo, 3–{[3–(fluorofenil) carbonil]amino}fenilo, 3–{[3–(clorofenil)carbonil]amino}fenilo, 3–{[3–(piridil)carbonil]amino}fenilo, 3–{[2–(furil)carbonil]amino}fenilo, 3–{[3–(2,5–dimetilfuran)carbonil]amino}fenilo, 3–{[2–(3–metiltiofeno) carbonil]amino}fenilo, 3–{[5–(4–metil–1,2,3–tiadiazol)carbonil] amino}fenilo, 3–{[5–(isoxazol)carbonil]amino}fenilo, 3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[5–(3–metilisoxazol) carbonil]amino}fenilo, 3–{[3–(5–metilisoxazol)carbonil]amino}fenilo, 3–({5–[1–metil–3–(trifluorometil)–1H–pirazol]carbonil}amino)fenilo, 5–metil–2–(trifluorometil)–3–furancarbonilaminofenilo, 3–{[5–(2,4–dimetil–1,3–tiazol)carbonil]amino}fenilo, 3–{[4–(2,5–dimetil–1,3–oxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–pirazol)carbonil] amino}fenilo, 3–{[3–(1,5–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[4–(3,5–dimetilisoxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–1,2,3–triazol)carbonil]amino}fenilo, 3–{[4–(1–metil–1H–1,2,3–

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triazol)carbonil]amino}fenilo, 3–{[2–(1–metil–1H–imidazole)carbonil] amino}fenilo, 3–{[5–(1–metil–1H–imidazole)carbonil]amino}fenilo, 1H–indol–6–ilo, 2–metil–1H–indol–6–ilo, 1,2–dimetil–1H–bencimidazol–5–ilo, 1H–indol–4–ilo, 2–metil–1,3–benzotiazol–5–ilo, 2–metil–1,3–benzotiazol–6–ilo, 5–amino–2–metilfenilo, 3–amino–2–metilfenilo, 3–amino–4–metilfenilo, 3–amino–4–clorofenilo, 5–amino–2–clorofenilo, 5–amino–2–metoxifenilo, 6–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 2–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–fluoro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–metoxi–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–(ciclopropilcarbonilamino) fenilo, 3–amino–4–fluorofenilo, 4–fluoro–3–{[4–(1–etil–3–metil–1H–pirazol)carbonil]amino}fenilo, y similares.

En los compuestos (I) y (IV), como el sustituyente para R de NR definido por X, se pueden mencionar aquellos similares al grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" en el grupo sustituyente (1)(iv) antes sustituido, el grupo ejemplificado como el "aminocarbonilo sustituido opcionalmente" en el grupo sustituyente (1)(viii) antes mencionado, el grupo ejemplificado como el "acilo" en el grupo sustituyente (1)(ix) antes mencionado y el grupo ejemplificado como el "grupo heterocíclico sustituido opcionalmente" en el grupo sustituyente (1)(xii) antes

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mencionado.

Como el sustituyente para R, se prefieren grupo hidrocarburo sustituido opcionalmente, y similares.

X es con preferencia, –O–, –S– o –NH–, con mayor preferencia, –O– o –S–, y con particular preferencia, –O–.

En los compuestos (I) y (IV), R^1 es átomo de hidrógeno o sustituyente (con la condición de que cuando R1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente).

Como "sustituyente" para R^1, se pueden citar aquellos similares al sustituyente del grupo sustituyente (1) antes mencionado. De ellos, se prefieren amino sustituido opcionalmente, aminocarbonilo sustituido opcionalmente, alquilo sustituido opcionalmente, y similares.

El R^1 preferible es

(1) átomo de hidrógeno,

(2) amino,

(3) alquilcarbonilamino sustituido opcionalmente,

(4) alquenilcarbonilamino sustituido opcionalmente,

(5) alquinilcarbonilamino sustituido opcionalmente,

(6) cicloalquilcarbonilamino sustituido opcionalmente,

(7) cicloalquil–alquilcarbonilamino sustituido opcionalmente,

(8) heterociclil–carbonilamino sustituido opcionalmente de 6 miembros,

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(9) aminocarbonilamino sustituido opcionalmente,

(10) alcoxicarbonilamino sustituido opcionalmente,

(11) alquilsulfonilamino sustituido opcionalmente,

(12) cicloalquilsulfonilamino sustituido opcionalmente,

(13) arilamino sustituido opcionalmente,

(14) heterociclilamino sustituido opcionalmente,

(15) aminocarbonilo sustituido opcionalmente,

(16) alquilo sustituido opcionalmente,

(17) carboxi esterificado opcionalmente, y similares.

De ellos, el R^1 preferible es

(1) átomo de hidrógeno,

(2) amino,

(3) alquil C_{1-4}–carbonilamino (por ejemplo, acetilamino, etilcarbonilamino, isopropilcarbonilamino, isobutilcarbonilamino, tert-butilcarbonilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, cloro), (b) hidroxi, (c) alcoxi C_{1-4} (por ejemplo, metoxi), (d) alquil C_{1-4}–carboniloxi (por ejemplo, metilcarboniloxi), (e) alquil C_{1-4}–amino (por ejemplo, metilamino), (f) di–alquil C_{1-4}–amino (por ejemplo, dimetilamino), (g) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo), y (h) grupo heterocíclico de 6 miembros (por ejemplo, piperazinilo, morfolinilo) que opcionalmente tiene 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(4) alquenil C_{2-4}–carbonilamino (por ejemplo, vinilcarbonilamino, 2–metil–1–propenilcarbonilamino) que

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opcionalmente tiene alcoxi C_{1-4} (por ejemplo, metoxi),

(5) alquinil C_{2-4}–carbonilamino (por ejemplo, 1–propenilcarbonilamino),

(6) cicloalquil C_{3-6}–carbonilamino (por ejemplo, ciclopropilcarbonilamino, ciclobutilcarbonilamino, ciclopentilcarbonilamino, ciclohexilcarbonilamino) sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor), (b) hidroxi, (c) alquilo C_{1-4} (por ejemplo, metilo, isopropilo) que opcionalmente tiene hidroxi, (d) alcoxi C_{1-4} (por ejemplo, metoxi), (e) alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y (f) alquil C_{1-4}–carboniloxi (por ejemplo, acetoxi),

(7) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino (por ejemplo, ciclopropilmetilcarbonilamino),

(8) heterociclil–carbonilamino de 6 miembros (por ejemplo, tetrahidropiranilcarbonilamino, piridilcarbonilamino, pirimidinilcarbonilamino, morfolinilcarbonilamino, piperazinilcarbonilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor, cloro), (b) ciano, y (c) alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene 1 a 3 átomos de halógeno (por ejemplo, flúor),

(9) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de (a) alquilo C_{1-4} (por ejemplo, etilo) que opcionalmente tiene 1 a 3 alcoxi C_{1-4} (por ejemplo, etoxi) que opcionalmente tiene 1 a 3 hidroxi, y (b) alcoxi C_{1-4} (por ejemplo,

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metoxi),

(10) alcoxi C_{1-4}–carbonilamino (por ejemplo, metoxicarbonilamino, etoxicarbonilamino, tert-butoxicarbonilamino) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, cloro),

(11) alquil C_{1-4}–sulfonilamino (por ejemplo, metilsulfonilamino),

(12) cicloalquil C_{3-6}–sulfonilamino (por ejemplo, ciclopropilsulfonilamino),

(13) aril C_{6-10}–amino (por ejemplo, fenilamino),

(14) heterociclilamino (por ejemplo, tiazolilamino, pirimidinilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, cloro), y (b) alquil C_{1-4}–amino (por ejemplo, metilamino),

(15) aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo),

(16) alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con hidroxi,

(17) carboxi,

(18) alcoxi C_{1-6}–carbonilo (por ejemplo, etoxicarbonilo),

y similares.

El R^1 específico puede incluir átomo de hidrógeno, amino, acetilamino, cloroacetilamino, 4–morfolinilacetilamino, metilcarboniloximetilcarbonilamino, metilaminometilcarbonilamino, hidroximetilcarbonilamino, metoximetilcarbonilamino, etilcarbonilamino, isopropilcarbonilamino,

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dimetilaminometilcarbonilamino, 4–metilpiperazin–1–ilacetilamino, metilsulfonilmetilcarbonilamino, 3–hidroxi–3–metilbutanoilamino, hidroxietilcarbonilamino, 3–metil–2–butenoilamino, 3–metoxi–2–propenoilamino, 2–butinoilamino, (ciclopropilcarbonil)amino, (1–metoxicarbonilciclopropilcarbonil)amino, (1–hidroxiciclopropilcarbonil)amino, (2–metilciclopropilcarbonil)amino, (2–metoxiciclopropilcarbonil)amino, (2–metilcarbonilciclopropilcarbonil)amino, (2–hidroximetilcarbonilciclopropilcarbonil)amino, (2–(1–hidroxi–1–metiletil)ciclopropil)carbonilamino, (2,2–dimetilciclopropilcarbonil)amino, (2,2–difluorociclopropilcarbonil)amino, (2,2,3,3–tetrametilciclopropilcarbonil)amino, (ciclobutilcarbonil)amino, (ciclopentilcarbonil)amino, (ciclohexilcarbonil)amino, ciclopropilmetilcarbonilamino, (tetrahidro–2H–piran–4–ilcarbonil)amino, (3–piridilcarbonil)amino, (4–piridilcarbonil)amino, (6–metil–3–piridilcarbonil)amino, (6–fluoro–3–piridilcarbonil)amino, (6–cloro–3–piridilcarbonil)amino, (6–ciano–3–piridilcarbonil)amino, (6–(trifluorometil)–3–piridilcarbonil)amino, (5–pirimidinilcarbonil)amino, 4–morfolinilcarbonilamino, metoxiureído, etilureído, 2–hidroxietoxietilureído, metoxicarbonilamino, etoxicarbonilamino, 2,2,2–tricloroetoxicarbonilamino, tert-butoxicarbonilamino, metilsulfonilamino, (ciclopropilsulfonil)amino, fenilamino, 2–metilaminopirimidin–4–ilamino, 2–cloropirimidin–4–ilamino, 1,3–tiazol–2–ilamino, metilaminocarbonilo, hidroximetilo,

carboxi, etoxicarbonilo, y similares.

En los compuestos (I) y (IV), se pueden mencionar como el "sustituyente" para R^2 a aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, el R^2 preferible es el átomo de hidrógeno.

En los compuestos (I) y (IV), se pueden citar como el "sustituyente" para R^3 aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, R^3 preferible es átomo de hidrógeno.

En los compuestos (I) y (IV), se pueden citar como el "sustituyente" para R^4 a aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, el R^4 preferible es el átomo de hidrógeno.

Como ejemplos preferibles de los compuestos (I) y (IV), por ejemplo, se pueden mencionar los siguientes compuestos.

Un compuesto en el que

el anillo Y es

(1) arilo C_{6-10} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) alquilo C_{1-4},

(c) alcoxi C_{1-4},

(d) amino sustituido opcionalmente con los sustituyentes seleccionados de

(i) alquilo C_{1-4} sustituido opcionalmente con un grupo

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heterocíclico aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(ii) alquil C_{1-4}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') hidroxi,

(ii') alquil C_{1-4}–sulfonilo, y

(iii') grupo heterocíclico de 6 miembros aromático,

(iii) alquenil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(iv) alquinil C_{2-6}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(v) cicloalquil C_{3-6}–carbonilo,

(vi) cicloalquenil C_{3-6}–carbonilo,

(vii) aril C_{6-10}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno, ciano, hidroxi y cicloalquilo C_{3-6},

(iii') cicloalquilo C_{3-6} sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} sustituido opcionalmente con 1 a 5 átomos de halógeno,

(v') alcoxi C_{1-4}–carbonilo, y

(vi') grupo heterocíclico de 5 ó 6 miembros sustituido opcionalmente con ciano u oxo,

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(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno, ciano, hidroxi y alcoxi C_{1-4},

(iii') arilo C_{6-10},

(iv') aril C_{6-10}–alquilo C_{1-4},

(v') alcoxi C_{1-4} sustituido opcionalmente con alcoxi C_{1-4},

(vi') alquil C_{1-4}–sulfonilo,

(vii') alquil C_{1-4}–carbonilo, y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático,

(x) alquil C_{1-4}–aminocarbonilo,

(xi) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno,

(xii) alcoxi C_{1-4}–aminocarbonilo,

(xiii) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo, y

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(xv) heterociclil–sulfonilo aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(e) alquil C_{1-4}–aminocarbonilo que opcionalmente tiene arilo C_{6-10},

(f) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno, y

(b) aril C_{6-10}–carbonilamino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno, o

(3) heterociclo aromático fusionado sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4}, y

(b) aril C_{6-10}–amino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno;

X es –O–, –S– o –NH– (con mayor preferencia, –O– o –S–, con particular preferencia, –O–);

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R^1 es

(1) átomo de hidrógeno,

(2) amino,

(3) alquil C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) hidroxi,

(c) alcoxi C_{1-4},

(d) alquil C_{1-4}–carboniloxi,

(e) alquil C_{1-4}–amino,

(f) di–alquil C_{1-4}–amino,

(g) alquil C_{1-4}–sulfonilo, y

(h) grupo heterocíclico de 6 miembros que opcionalmente tiene 1 a 3 alquilo C_{1-4},

(4) alquenil C_{2-4}–carbonilamino que opcionalmente tiene alcoxi C_{1-4},

(5) alquinil C_{2-4}–carbonilamino,

(6) cicloalquil C_{3-6}–carbonilamino sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) hidroxi,

(c) alquilo C_{1-4} que opcionalmente tiene hidroxi,

(d) alcoxi C_{1-4},

(e) alcoxi C_{1-4}–carbonilo, y

(f) alquil C_{1-4}–carboniloxi,

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(7) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino,

(8) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) ciano, y

(c) alquilo C_{1-4} que opcionalmente tiene 1 a 3 átomo de halógeno,

(9) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

(a) alquilo C_{1-4} que opcionalmente tiene 1 a 3 alcoxi C_{1-4} que opcionalmente tiene 1 a 3 hidroxi, y

(b) alcoxi C_{1-4},

(10) alcoxi C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 átomos de halógeno,

(11) alquil C_{1-4}–sulfonilamino,

(12) cicloalquil C_{3-6}–sulfonilamino,

(13) aril C_{6-10}–amino,

(14) heterociclilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno, y

(b) alquil C_{1-4}–amino,

(15) aminocarbonilo sustituido con alquilo C_{1-4} (por ejemplo, metilo, etc.),

(16) alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con hidroxi,

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(17) carboxi, o

(18) alcoxi C_{1-6}–carbonilo (por ejemplo, etoxicarbonilo); y

R^2, R^3 y R^4 son cada uno átomo de hidrógeno.

Como ejemplos específicos de los compuestos (I) y (IV), se pueden mencionar, por ejemplo, compuestos de los Ejemplos 1 a 440, 442 y 445.

Los ejemplos particular preferidos pueden incluir los siguientes compuestos o sus sales.

N–{3–[(2–{[2–(metilamino)pirimidin–4–il]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (Ejemplo 70);

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 97);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 111);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida (Ejemplo 114);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,5–dimetil–1,3–oxazol–4–carboxamida (Ejemplo 117);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 148);

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 149);

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N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}sulfanil)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 150);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–4–carboxamida (Ejemplo 161);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida (Ejemplo 165);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–4–carboxamida (Ejemplo 173);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–5–carboxamida (Ejemplo 174);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida (Ejemplo 180);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etil–1–metil–1H–pirazol–5–carboxamida (Ejemplo 208);

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–etil–3–metil–1H–pirazol–4–carboxamida (Ejemplo 254);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida (Ejemplo

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N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–oxazol–5–carboxamida (Ejemplo 289);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida (Ejemplo 314);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (Ejemplo 319);

3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]benzamida (Ejemplo 330);

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (Ejemplo 398);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–3–(trifluorometil)benzamida (Ejemplo 427);

N–{6–[3–({[3–(trifluorometil)fenil]carbamoil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (Ejemplo 431).

Ahora se explica el compuesto representado por la fórmula (II) (de ahora en adelante, compuesto (II)) de la presente invención.

Como "grupo cíclico" del "grupo cíclico sustituido opcionalmente" para el anillo Ya, se pueden mencionar aquellos similares al grupo ejemplificado como el "grupo cíclico" del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I).

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Como "grupo cíclico" del "grupo cíclico sustituido opcionalmente" indicado por el anillo Ya, se prefieren grupo hidrocarburo aromático, grupo heterocíclico aromático. Como el grupo hidrocarburo aromático, se prefiere arilo C_{6-14}, arilo C_{6-10} tiene mayor preferencia, y fenilo tiene particular preferencia. Como el grupo heterocíclico aromático, se prefieren grupo heterocíclico aromático monocíclico, grupo heterocíclico aromático fusionado, anillo piridina, y grupo heterocíclico aromático fusionado formado por fusión de anillo benceno y grupo heterocíclico aromático monocíclico de 5 miembros que contiene, como átomo constitutivo del anillo, 1 ó 2 heteroátomos seleccionados de átomo de azufre y átomo de nitrógeno además de átomos de carbono (por ejemplo, benzotiazolilo, bencimidazolilo, indolilo, etc.) tiene mayor preferencia, y benzotiazolilo (por ejemplo, 5–benzotiazolilo, 6–benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol–5–ilo, bencimidazol–6–ilo), indolilo (por ejemplo, indol–4–ilo, indol–5–ilo, indol–6–ilo), y similares tienen particular preferencia.

El "grupo cíclico sustituido opcionalmente" para el anillo Ya puede tener 1 a la cantidad máxima aceptable de sustituyentes en cualquier posición sustituible. Cuando el grupo cíclico está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes, y el grupo cíclico tiene opcionalmente con preferencia, 1 a 5, con mayor preferencia, 1 a 3 sustituyentes.

Como "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Ya, se pueden mencionar aquellos

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similares al grupo ejemplificado como el "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I).

El "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Ya es con preferencia,

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(2) alquilo sustituido opcionalmente,

(3) alcoxi sustituido opcionalmente,

(4) aminocarbonilo sustituido opcionalmente,

(5) amino sustituido opcionalmente,

(6) carboxilo,

y similares.

De ellos, se prefieren

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(2) alquilo sustituido opcionalmente,

(3) amino sustituido opcionalmente,

y similares.

En lo sucesivo, en la presente, los ejemplos preferibles antes mencionados del "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Ya se explican en detalle.

(1) Como átomo de halógeno, se prefieren flúor, cloro, bromo, y similares.

(2) Como el alquilo sustituido opcionalmente, se prefiere alquilo C_{1-8} sustituido opcionalmente, alquilo C_{1-4} sustituido opcionalmente tiene mayor preferencia, y alquilo C_{1-4} no sustituido tiene mayor preferencia. Específicamente, son preferibles metilo,

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etilo, y similares.

(3) Como el alcoxi sustituido opcionalmente, se prefiere alcoxi C_{1-8} sustituido opcionalmente, alcoxi C_{1-4} sustituido opcionalmente tiene mayor preferencia, alcoxi C_{1-4} no sustituido es mucho más preferido. Específicamente, se prefieren metoxi, y similares.

(4) Como "sustituyente" para el aminocarbonilo sustituido opcionalmente, se prefieren, por ejemplo, alquilo C_{1-8}, alquenilo C_{2-8}, alquinilo C_{2-8}, cicloalquilo C_{3-8}, cicloalquenilo C_{3-8}, cicloalquinilo C_{3-8}, arilo C_{6-18}, grupo heterocíclico, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquilo C_{1-4} sustituido opcionalmente, arilo C_{6-12} sustituido opcionalmente y grupo heterocíclico sustituido opcionalmente de 5 miembros, y similares. En particular, arilo C_{6-12} sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) alquilo C_{1-4} que opcionalmente tiene arilo C_{6-12}, (b) grupo heterocíclico 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-12}, (c) átomo de halógeno y (d) ciano.

(5) Como "sustituyente" para el amino sustituido opcionalmente, se prefieren alquilo sustituido opcionalmente, aminocarbonilo sustituido opcionalmente, acilo, aminotiocarbonilo sustituido opcionalmente, heterociclil–sulfonilo sustituido opcionalmente, y similares.

Como el amino sustituido opcionalmente, se prefiere amino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

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(a) alquilo sustituido opcionalmente, (b) aminocarbonilo sustituido opcionalmente, (c) acilo, (d) aminotiocarbonilo sustituido opcionalmente, y (e) heterociclil–sulfonilo sustituido opcionalmente.

Como el alquilo sustituido opcionalmente, se prefiere alquilo C_{1-4} sustituido opcionalmente. De ellos, se prefiere alquilo C_{1-4} sustituido opcionalmente con grupo heterocíclico 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4}.

Como el aminocarbonilo sustituido opcionalmente, se prefieren alquil C_{1-8}–aminocarbonilo, aril C_{6-18}–aminocarbonilo, aril C_{6-18}–alquil C_{1-4}–aminocarbonilo, heterociclil–aminocarbonilo, cicloalquil C_{3-8}–aminocarbonilo, alcoxi C_{1-8}–aminocarbonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–aminocarbonilo sustituido opcionalmente, aril C_{6-18}–aminocarbonilo sustituido opcionalmente, heterociclil–aminocarbonilo sustituido opcionalmente, alcoxi C_{1-8}–aminocarbonilo sustituido opcionalmente, y similares. En particular, se prefieren (i) alquil C_{1-4}–aminocarbonilo, (ii) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno, (iii) alcoxi C_{1-4}–aminocarbonilo, (iv) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10}, y similares.

Como el acilo, se prefieren alquil C_{1-8}–carbonilo, alquenil C_{2-8}–carbonilo, alquinil C_{2-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, cicloalquenil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, aril C_{6-18}–alquil C_{1-}

$_4$–carbonilo, alquil C_{1-8}–sulfonilo, aril C_{6-18}–sulfonilo, heterociclil–carbonilo, heterociclil–sulfonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–carbonilo, alquenil C_{2-8}–carbonilo, alquinil C_{2-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, cicloalquenil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, heterociclil–carbonilo, cada uno de los cuales está sustituido opcionalmente.

Como el alquil C_{1-8}–carbonilo sustituido opcionalmente, se prefiere alquil C_{1-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquil C_{1-4}–carbonilo (por ejemplo, metilcarbonilo, tert-butilcarbonilo, 3–metilbutanoilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) hidroxi, (b) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo) y (c) grupo heterocíclico de 6 miembros (por ejemplo, piridilo) (ejemplos específicos: metilsulfonilmetilcarbonilo, 2–piridilmetilcarbonilo, tert-butilcarbonilo, 3–hidroxi–3–metilbutanoil).

Como el alquenil C_{2-8}–carbonilo sustituido opcionalmente, se prefiere alquenilo C_{2-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquenil C_{2-4}–carbonilo (por ejemplo, 3–metil–2–butenoílo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo) (ejemplos específicos: 3–metil–2–butenoílo).

Como el alquinil C_{2-8}–carbonilo sustituido opcionalmente, se prefiere alquinil C_{2-4}–carbonilo sustituido opcionalmente. En particular, se prefiere alquinil C_{2-4}–carbonilo (por ejemplo, 2–butinoilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo,

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fenilo) (ejemplo específico: 2–butinoilo).

Como el cicloalquil C_{3-8}–carbonilo sustituido opcionalmente, se prefiere cicloalquil C_{3-6}–carbonilo, y se prefieren específicamente ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo, y similares.

Como el cicloalquenil C_{3-8}–carbonilo sustituido opcionalmente, se prefiere cicloalquenil C_{3-6}–carbonilo (por ejemplo, ciclopentenecarbonilo) (ejemplo específico: 1–ciclopentenecarbonilo).

Como el aril C_{6-18}–carbonilo sustituido opcionalmente, se prefiere aril C_{6-10}–carbonilo sustituido opcionalmente. En particular, se prefiere aril C_{6-10}–carbonilo (por ejemplo, benzoilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor), (b) alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y cicloalquilo C_{3-6} (por ejemplo, ciclopropilo) (ejemplo específico: trifluorometilo), (c) cicloalquilo C_{3-6} (por ejemplo, ciclopropilo, ciclobutilo, ciclohexilo) sustituido opcionalmente con ciano, (d) alcoxi C_{1-4} (por ejemplo, isopropoxi, tert-butoxi) sustituido opcionalmente con 1 a 5 átomos de halógeno (por ejemplo, flúor), (e) alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y (f) grupo heterocíclico de 5 o 6 miembros (por ejemplo, tetrahidropiranilo, pirrolidinilo) sustituido opcionalmente con ciano u oxo. Específicamente, se prefieren fenilcarbonil(benzoilo), 3–

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(trifluorometil)fenilcarbonilo, 4–(trifluorometil)fenilcarbonilo, 3–fluorofenilcarbonilo, 3–clorofenilcarbonilo, 3–(1–cianociclopropil)fenilcarbonilo, 3–(1–cianociclobutil)fenilcarbonilo, 3–(1–cianociclohexil)fenilcarbonilo, 2–fluoro–3–(trifluorometil)fenilcarbonilo, 2–fluoro–5–(trifluorometil)fenilcarbonilo, 3–fluoro–5–(trifluorometil)fenilcarbonilo, 4–cloro–3–(trifluorometil)fenilcarbonilo, 2–cloro–3–(trifluorometil)fenilcarbonilo, 2–cloro–5–(trifluorometil)fenilcarbonilo, 3–isopropoxifenilcarbonilo, 3–(tert-butoxi)fenilcarbonilo, 3–(1–ciano–1–metiletil)fenilcarbonilo, 3–metoxifenilcarbonilo, 3–metoxicarbonilfenilcarbonilo, 3–(trifluorometoxi)carbonilfenilcarbonilo, 3–(1,1,2,2–tetrafluoroetoxi)fenilcarbonilo, 3–(4–cianotetrahidropiran–4–il)fenilcarbonilo, 3,5–di(trifluorometil)fenilcarbonilo, 3–(2–oxopirrolidin–1–il)fenilcarbonilo, 4–(tert-butil)fenilcarbonilo, 3–(1–cianoetil)fenilcarbonilo, 3–(1–ciano–2–ciclopropil–1–metiletil)fenilcarbonilo, y similares.

Como el aril C_{6-18}–alquil C_{1-4}–carbonilo sustituido opcionalmente, se prefiere aril C_{6-10}–alquil C_{1-4}–carbonilo.

Como el alquil C_{1-8}–sulfonilo sustituido opcionalmente, se prefiere alquil C_{1-8}–sulfonilo.

Como el aril C_{6-18}–sulfonilo sustituido opcionalmente, se prefiere aril C_{6-10}–sulfonilo.

Como la porción "heterociclo" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren grupo heterocíclico monocíclico de 5 ó 6 miembros que contiene, como átomo

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constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y se prefieren específicamente piridilo, furilo, tetrahidrofurilo, tienilo, pirazolilo, imidazolilo, tiazolilo, oxazolilo, isoxazolilo, 1,2,3–triazolilo, 1,2,3–tiadiazolilo, dihidrooxazolilo, piridazinilo, pirazinilo, dihidropirazolilo, pirrolilo, pirrolidinilo, pirimidinilo, y similares. Como "sustituyente" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren (1) átomo de halógeno (por ejemplo, cloro), (2) alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y alcoxi C_{1-4} (por ejemplo, metoxi) (ejemplos específicos: metilo, trifluorometilo, etilo, metoxietilo, 2,2,2–trifluoroetilo, isopropilo, tert-butilo), (3) arilo C_{6-18} (por ejemplo, fenilo), (4) aril C_{6-10}–alquilo C_{1-4} (por ejemplo, bencilo), (5) alcoxi C_{1-4} (por ejemplo, metoxi, etoxi) sustituido opcionalmente con alcoxi C_{1-4} (por ejemplo, metoxi) (ejemplos específicos: metoxi, etoxi, metoxietoxi), (6) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo), (7) alquil C_{1-4}–carbonilo (por ejemplo, acetilo), (8) oxo, y similares.

Como el heterociclil–carbonilo sustituido opcionalmente, se prefieren el heterociclil–carbonilo aromático monocíclico de 5 ó 6 miembros antes mencionado, y similares sustituido opcionalmente con alquilo C_{1-4} opcionalmente halogenado, y similares. Específicamente, se prefieren 2–piridilcarbonilo, 3–piridilcarbonilo,

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4–piridilcarbonilo, 2–metil–6–piridilcarbonilo, 3–metil–2–piridilcarbonilo, 4–metil–2–piridilcarbonilo, 2–metil–3–piridilcarbonilo, 2–(trifluorometil)–3–piridilcarbonilo, 2–(trifluorometil)–4–piridilcarbonilo, 2–(trifluorometil)–6–piridilcarbonilo, 2–cloro–6–metil–4—piridilcarbonilo, 2,6–dicloro–4–piridilcarbonilo, 2–furilcarbonilo, 2,5–dimetilfuran–3–carbonilo, 5–metil–2–(trifluorometil)–3–furancarbonilo, 3–metiltiofen–2–carbonilo, 5–acetilsulfoniltiofen–2–carbonilo, 5–etilsulfoniltiofen–2–carbonilo, 4–metil–1,2,3–tiadiazol–5–carbonilo, isoxazol–5–carbonilo, 1H–pirazol–5–carbonilo, 1–metil–1H–pirazol–3–carbonilo, 1–metil–1H–pirazol–5–carbonilo, 1–etil–1H–pirazol–3–carbonilo, 1–etil–1H–pirazol–5–carbonilo, 3–metil–1H–pirazol–5–carbonilo, 3–cloro–1–metil–1H–pirazol–5–carbonilo, 4–cloro–1–metil–1H–pirazol–3–carbonilo, 1–metil–3–metoxi–1H–pirazol–5–carbonilo, 1–metil–3–(trifluorometil)–1H–pirazol–5–carbonilo, 3–metoxi–1–metil–1H–pirazol–4–carbonilo, 3–metoxi–1–metil–1H–pirazol–5–carbonilo, 3–etoxi–1–metil–1H–pirazol–5–carbonilo, 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carbonilo, 1–etil–3–metil–1H–pirazol–4–carbonilo, 1–etil–3–metil–1H–pirazol–5–carbonilo, 3–metil–1–fenil–1H–pirazol–5–carbonilo, 5–metil–1–fenil–1H–pirazol–3–carbonilo, 3–etil–1–metil–1H–pirazol–5–carbonilo, 3–isopropil–1–metil–1H–pirazol–5–carbonilo, 3–metoxi–1–metil–1H–pirazol–5–carbonilo, 1–tert-butil–3–metil–1H–pirazol–5–carbonilo, 3–tert-butil–1–metil–1H–pirazol–5–carbonilo, 1–metoxietil–3–metil–1H–pirazol–5–carbonilo, 1,3–dimetil–1H–pirazol–4–carbonilo, 1,3–dimetil–1H–pirazol–5–carbonilo, 1,4–dimetil–1H–pirazol–3–carbonilo,

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1,4–dimetil–1H–pirazol–5–carbonilo, 1,5–dimetil–1H–pirazol–3–carbonilo, 3–metilisoxazol–4–carbonilo, 3–metilisoxazol–5–carbonilo, 5–metilisoxazol–3–carbonilo, 5–metilisoxazol–4–carbonilo, 3,5–dimetilisoxazol–4–carbonilo, 1,3–tiazol–2–carbonilo, 2–metil–1,3–tiazol–4–carbonilo, 4–metil–1,3–tiazol–5–carbonilo, 5–metil–1,3–tiazol–4–carbonilo, 2,4–dimetil–1,3–tiazol–5–carbonilo, 2–cloro–4–metil–1,3–tiazol–5–carbonilo, 4–metoxi–2–metil–1,3–tiazol–5–carbonilo, 2–(1–hidroxi–1–metiletil)–1,3–tiazol–5–carbonilo, 2–(1–ciano–1–metiletil)–1,3–tiazol–5–carbonilo, 2–metil–1,3–oxazol–4–carbonilo, 4–metil–1,3–oxazol–5–carbonilo, 2–etil–4–metil–1,3–oxazol–5–carbonilo, 2,4–dimetil–1,3–oxazol–5–carbonilo, 2,5–dimetil–1,3–oxazol–4–carbonilo, 1–metil–1H–1,2,3–triazol–5–carbonilo, 1–metil–1H–1,2,3–triazol–4–carbonilo, 1–metil–1H–imidazol–2–carbonilo, 1–metil–1H–imidazol–5–carbonilo, 2–pirazinilcarbonilo, 1–metilpirrol–2–carbonilo, 1–bencilpirrol–3–carbonilo, 1,2,5–trimetilpirrol–3–carbonilo, 1–metilpirrolidin–2–carbonilo, 2–(trifluorometil)pirimidin–4–carbonilo, y similares.

Como la porción "heterociclo" para el heterociclil–sulfonilo sustituido opcionalmente, se prefieren grupo heterocíclico aromático monocíclico de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y se prefieren específicamente tiazolilo, y similares. Como "sustituyente" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren alquilo C_{1-4} (por

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ejemplo, metilo), y similares.

Como el heterociclil–sulfonilo sustituido opcionalmente, se prefieren específicamente 2,5–dimetil–1,3–tiazol–4–sulfonilo, y similares.

Como el aminotiocarbonilo sustituido opcionalmente, se prefieren aminotiocarbonilo sustituido opcionalmente con aril C_{6-18}–alquil C_{1-4}–carbonilo (por ejemplo, bencilcarbonilo), y similares.

Con preferencia, el anillo Ya es

(1) arilo C_{6-10} (por ejemplo, fenilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, flúor, cloro, bromo),

(b) alquilo C_{1-4} (por ejemplo, metilo, etilo),

(c) alcoxi C_{1-4} (por ejemplo, metoxi),

(d) amino sustituido opcionalmente con sustituyentes seleccionados de

(i) alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con grupo heterocíclico 5 miembros aromático (por ejemplo, pirazolilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(ii) alquil C_{1-4}–carbonilo (por ejemplo, metilcarbonilo, isobutilcarbonilo, tert-butilcarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') hidroxi,

(ii') alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo), y

(iii') grupo heterocíclico de 6 miembros aromático (por ejemplo,

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piridilo),

(iii) alquenil C_{2-4}–carbonilo (por ejemplo, 2–metil–1–propenilcarbonilo, vinilcarbonilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo),

(iv) alquinil C_{2-4}–carbonilo (por ejemplo, acetilencarbonilo, 1–propinilcarbonilo) sustituido opcionalmente con arilo C_{6-10} (por ejemplo, fenilo),

(v) cicloalquil C_{3-6}–carbonilo (por ejemplo, ciclopropilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo),

(vi) cicloalquenil C_{3-6}–carbonilo (por ejemplo, ciclopentenilcarbonilo),

(vii) aril C_{6-10}–carbonilo (por ejemplo, benzoilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno (por ejemplo, flúor, cloro),

(ii') alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, terc-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y cicloalquilo C_{3-6} (por ejemplo, ciclopropilo),

(iii') cicloalquilo C_{3-6} (por ejemplo, ciclopropilo, ciclobutilo, ciclohexilo) sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} (por ejemplo, metoxi, etoxi, isopropoxi, terc-butoxi) sustituido opcionalmente con 1 a 5 átomos de halógeno (por ejemplo, flúor),

(v') alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y

(vi') grupo heterocíclico de 5 ó 6 miembros (por ejemplo,

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tetrahidropiranilo, pirrolidinilo) sustituido opcionalmente con ciano u oxo,

(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono (por ejemplo, furilcarbonilo, tetrahidrofurilcarbonilo, tienilcarbonilo, pirrolilcarbonilo, pirrolidinilcarbonilo, imidazolilcarbonilo, tiazolilcarbonilo, tiadiazolilcarbonilo, dihidrooxazolilcarbonilo, oxazolilcarbonilo, isoxazolilcarbonilo, pirazolilcarbonilo, dihidropirazolilcarbonilo, triazolilcarbonilo, piridilcarbonilo, pirimidinilcarbonilo, pirazinilcarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno (por ejemplo, cloro),

(ii') alquilo C_{1-4} (por ejemplo, metilo, etilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor), ciano, hidroxi y alcoxi C_{1-4} (por ejemplo, metoxi),

(iii') arilo C_{6-10} (por ejemplo, fenilo),

(iv') aril C_{6-10}–alquilo C_{1-4} (por ejemplo, bencilo),

(v') alcoxi C_{1-4} (por ejemplo, metoxi, etoxi) sustituido opcionalmente con alcoxi C_{1-4} (por ejemplo, metoxi),

(vi') alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo),

(vii') alquil C_{1-4}–carbonilo (por ejemplo, acetilo), y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático (por ejemplo, benzopirazolilcarbonilo, indolilcarbonilo),

(x) alquil C_{1-4}–aminocarbonilo (por ejemplo, etilaminocarbonilo),

(xi) aril C_{6-10}–aminocarbonilo (por ejemplo, fenilaminocarbonilo) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor),

(xii) alcoxi C_{1-4}–aminocarbonilo (por ejemplo, metoxiaminocarbonilo, isobutoxiaminocarbonilo),

(xiii) heterociclil–aminocarbonilo de 5 miembros (por ejemplo, isoxazolilaminocarbonilo, pirazolilaminocarbonilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo, tert-butilo) y arilo C_{6-10} (por ejemplo, fenilo),

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo (por ejemplo, bencilcarbonilo), y

(xv) heterociclil–sulfonilo aromático de 5 miembros (por ejemplo, tiazolilsulfonilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(e) alquil C_{1-4}–aminocarbonilo (por ejemplo, metilaminocarbonilo) que opcionalmente tiene arilo C_{6-10} (por ejemplo, fenilo),

(f) heterociclil–aminocarbonilo de 5 miembros (por ejemplo, pirazolilaminocarbonilo) sustituido opcionalmente con 1 a 3

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sustituyentes seleccionados de alquilo C_{1-4} (por ejemplo, metilo) y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo (por ejemplo, fenilaminocarbonilo) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo, isopropilo, tert-butilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno (por ejemplo, flúor) y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico (por ejemplo, piridilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno (por ejemplo, bromo), y

(b) aril C_{6-10}–carbonilamino (por ejemplo, benzoilamino) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor), o

(3) heterociclo aromático fusionado (por ejemplo, indolilo, benzotiazolilo, bencimidazolilo) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4} (por ejemplo, metilo), y

(b) aril C_{6-10}–amino (por ejemplo, fenilamino) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) sustituido opcionalmente con 1 a 3 átomos de halógeno (por ejemplo, flúor).

Como anillo Ya, se pueden mencionar específicamente (1,3–dimetil–1H–pirazol–5–il)aminocarbonil–3–fenilo, 3–aminofenilo, 4–

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aminofenilo, 3–{[(etilamino)carbonil]amino}fenilo, 4–{[(fenilamino)carbonil]amino}fenilo, 3–{[(fenilamino)carbonil]amino}fenilo, 3–({[3–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–({[4–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–[(tert-butilcarbonil)amino]fenilo, 3–[(ciclopropilcarbonil)amino]fenilo, 3–[(ciclohexilcarbonil)amino]fenilo, 3–[(fenilcarbonil)amino]fenilo, 3–{[3–(trifluorometilfenil)carbonil]amino}fenilo, 3–{[3–(fluorofenil)carbonil]amino}fenilo, 3–{[3–(clorofenil)carbonil]amino}fenilo, 3–{[3–(piridil)carbonil]amino}fenilo, 3–{[2–(furil)carbonil]amino}fenilo, 3–{[3–(2,5–dimetilfuran)carbonil]amino}fenilo, 3–{[2–(3–metiltiofeno)carbonil]amino}fenilo, 3–{[5–(4–metil–1,2,3–tiadiazol)carbonil]amino}fenilo, 3–{[5–(isoxazol)carbonil]amino}fenilo, 3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[5–(3–metilisoxazol)carbonil]amino}fenilo, 3–{[3–(5–metilisoxazol)carbonil]amino}fenilo, 3–({5–[1–metil–3–(trifluorometil)–1H–pirazol]carbonil}amino)fenilo, 5–metil–2–(trifluorometil)–3–furancarbonilaminofenilo, 3–{[5–(2,4–dimetil–1,3–tiazol)carbonil]amino}fenilo, 3–{[4–(2,5–dimetil–1,3–oxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–pirazol)carbonil]amino}fenilo, 3–{[3–(1,5–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[4–(3,5–dimetilisoxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–1,2,3–triazol)carbonil]amino}fenilo, 3–{[4–(1–metil–1H–1,2,3–

triazol)carbonil]amino}fenilo, 3–{[2–(1–metil–1H–imidazole)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–imidazole)carbonil]amino}fenilo, 1H–indol–6–ilo, 2–metil–1H–indol–6–ilo, 1,2–dimetil–1H–bencimidazol–5–ilo, 1H–indol–4–ilo, 2–metil–1,3–benzotiazol–5–ilo, 2–metil–1,3–benzotiazol–6–ilo, 5–amino–2–metilfenilo, 3–amino–2–metilfenilo, 3–amino–4–metilfenilo, 3–amino–4–clorofenilo, 5–amino–2–clorofenilo, 5–amino–2–metoxifenilo, 6–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 2–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–fluoro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–metoxi–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–(ciclopropilcarbonilamino)fenilo, 3–amino–4–fluorofenilo, 4–fluoro–3–{[4–(1–etil–3–metil–1H–pirazol)carbonil]amino}fenilo, y similares.

En el compuesto (II), como el sustituyente para R^a de NR^a definido por Xa, se pueden mencionar aquellos similares al sustituyente seleccionado del grupo ejemplificado como el "grupo hidrocarburo sustituido opcionalmente" para el grupo sustituyente (1)(iv) antes sustituido, el grupo ejemplificado como el "aminocarbonilo sustituido opcionalmente" para el grupo sustituyente (1)(viii) antes mencionado, el grupo ejemplificado como el "acilo" para el grupo sustituyente (1)(ix) antes mencionado y el grupo ejemplificado como el "grupo heterocíclico sustituido opcionalmente"

para el grupo sustituyente (1)(xii) antes mencionado.

Como el sustituyente para R^a, se prefieren grupo hidrocarburo sustituido opcionalmente, y similares.

Xa es con preferencia, –O–, –S– o –NH–, con mayor preferencia, –O– o –S–, y con particular preferencia, –O–.

Como el "amino sustituido opcionalmente" para R^{1a} en el compuesto (II), se pueden mencionar aquellos similares al "amino sustituido opcionalmente" ejemplificado en el grupo sustituyente (1)(x) antes mencionado.

Como el "amino sustituido opcionalmente" para R^{1a}, se prefieren (1) amino, (2) alquilcarbonilamino sustituido opcionalmente, (3) alquenilcarbonilamino sustituido opcionalmente, (4) alquinilcarbonilamino sustituido opcionalmente, (5) cicloalquilcarbonilamino sustituido opcionalmente, (6) cicloalquil–alquilcarbonilamino sustituido opcionalmente, (7) heterociclil–carbonilamino sustituido opcionalmente de 6 miembros, (8) aminocarbonilamino sustituido opcionalmente, (9) alcoxicarbonilamino sustituido opcionalmente, (10) alquilsulfonilamino sustituido opcionalmente, (11) cicloalquilsulfonilamino sustituido opcionalmente, (12) arilamino sustituido opcionalmente y (13) heterociclilamino sustituido opcionalmente.

De ellos, el R^{1a} preferido es

(1) amino,

(2) alquil C_{1-4}–carbonilamino (por ejemplo, acetilamino,

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etilcarbonilamino, isopropilcarbonilamino, isobutilcarbonilamino, tert-butilcarbonilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, cloro), (b) hidroxi, (c) alcoxi C_{1-4} (por ejemplo, metoxi), (d) alquil C_{1-4}–carboniloxi (por ejemplo, metilcarboniloxi), (e) alquil C_{1-4}–amino (por ejemplo, metilamino), (f) di–alquil C_{1-4}–amino (por ejemplo, dimetilamino), (g) alquil C_{1-4}–sulfonilo (por ejemplo, metilsulfonilo), y (h) grupo heterocíclico de 6 miembros (por ejemplo, piperazinilo, morfolinilo) sustituido opcionalmente con 1 a 3 alquilo C_{1-4} (por ejemplo, metilo),

(3) alquenil C_{2-4}–carbonilamino (por ejemplo, vinilcarbonilamino, 2–metil–1–propenilcarbonilamino) que opcionalmente tiene alcoxi C_{1-4} (por ejemplo, metoxi),

(4) alquinil C_{2-4}–carbonilamino (por ejemplo, 1–propenilcarbonilamino),

(5) cicloalquil C_{3-6}–carbonilamino (por ejemplo, ciclopropilcarbonilamino, ciclobutilcarbonilamino, ciclopentilcarbonilamino, ciclohexilcarbonilamino) sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor), (b) hidroxi, (c) alquilo C_{1-4} (por ejemplo, metilo, isopropilo) que opcionalmente tiene hidroxi, (d) alcoxi C_{1-4} (por ejemplo, metoxi), (e) alcoxi C_{1-4}–carbonilo (por ejemplo, metoxicarbonilo), y (f) alquil C_{1-4}–carboniloxi (por ejemplo, acetoxi),

(6) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino (por ejemplo,

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ciclopropilmetilcarbonilamino),

(7) heterociclil–carbonilamino de 6 miembros (por ejemplo, tetrahidropiranilcarbonilamino, piridilcarbonilamino, pirimidinilcarbonilamino, morfolinilcarbonilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, flúor, cloro), (b) ciano, y (c) alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene 1 a 3 átomo de halógeno (por ejemplo, flúor),

(8) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de (a) alquilo C_{1-4} (por ejemplo, etilo) que opcionalmente tiene 1 a 3 alcoxi C_{1-4} (por ejemplo, etoxi) que opcionalmente tiene 1 a 3 hidroxi, y (b) alcoxi C_{1-4} (por ejemplo, metoxi),

(9) alcoxi C_{1-4}–carbonilamino (por ejemplo, metoxicarbonilamino, etoxicarbonilamino, tert-butoxicarbonilamino) sustituido opcionalmente con 1 a 3 átomo de halógeno (por ejemplo, cloro),

(10) alquil C_{1-4}–sulfonilamino (por ejemplo, metilsulfonilamino),

(11) cicloalquil C_{3-6}–sulfonilamino (por ejemplo, ciclopropilsulfonilamino),

(12) aril C_{6-10}–amino (por ejemplo, fenilamino), y

(13) heterociclilamino (por ejemplo, tiazolilamino, pirimidinilamino) sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de (a) átomo de halógeno (por ejemplo, cloro), y (b) alquil C_{1-4}–amino (por ejemplo, metilamino), y similares.

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Como R^{1a}, se pueden mencionar específicamente amino, acetilamino, cloroacetilamino, 4–morfolinilacetilamino, metilcarboniloximetilcarbonilamino, metilaminometilcarbonilamino, hidroximetilcarbonilamino, metoximetilcarbonilamino, etilcarbonilamino, isopropilcarbonilamino, dimetilaminometilcarbonilamino, 4–metilpiperazin–1–ilacetilamino, metilsulfonilmetilcarbonilamino, 3–hidroxi–3–metilbutanoilamino, hidroxietilcarbonilamino, 3–metil–2–butenoilamino, 3–metoxi–2–propenoilamino, 2–butinoilamino, (ciclopropilcarbonil)amino, (1–metoxicarbonilciclopropilcarbonil)amino, (1–hidroxiciclopropilcarbonil)amino, (2–metilciclopropilcarbonil)amino, (2–metoxiciclopropilcarbonil)amino, (2–metilcarbonilciclopropilcarbonil)amino, (2–hidroximetilcarbonilciclopropilcarbonil)amino, (2–(1–hidroxi–1–metiletil)ciclopropil)carbonilamino, (2,2–dimetilciclopropilcarbonil)amino, (2,2–difluorociclopropilcarbonil)amino, (2,2,3,3–tetrametilciclopropilcarbonil)amino, (ciclobutilcarbonil)amino, (ciclopentilcarbonil)amino, (ciclohexilcarbonil)amino, ciclopropilmetilcarbonilamino, (tetrahidro–2H–piran–4–ilcarbonil)amino, (3–piridilcarbonil)amino, (4–piridilcarbonil)amino, (6–metil–3–piridilcarbonil)amino, (6–fluoro–3–piridilcarbonil)amino, (6–cloro–3–piridilcarbonil)amino, (6–ciano–3–piridilcarbonil)amino, (6–(trifluorometil)–3–piridilcarbonil)amino, (5–pirimidinilcarbonil)amino, 4–morfolinilcarbonilamino, metoxiureído,

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etilureído, 2–hidroxietoxietilureído, metoxicarbonilamino, etoxicarbonilamino, 2,2,2–tricloroetoxicarbonilamino, tert-butoxicarbonilamino, metilsulfonilamino, (ciclopropilsulfonil)amino, fenilamino, 2–metilaminopirimidin–4–ilamino, 2–cloropirimidin–4–ilamino, 1,3–tiazol–2–ilamino, y similares.

En el compuesto (II), como el "sustituyente" para R^{2a}, se pueden citar aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, el R^{2a} preferido es el átomo de hidrógeno.

En el compuesto (II), como el "sustituyente" para R^{3a}, se pueden citar aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, R^{3a} preferido es átomo de hidrógeno.

En el compuesto (II), como el "sustituyente" para R^{4a}, se pueden citar aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, el R^{4a} preferido es el átomo de hidrógeno.

Como ejemplos preferibles de el compuesto (II), por ejemplo, se pueden citar los siguientes compuestos.

Un compuesto en el que

el anillo Ya es

(1) arilo C_{6-10} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) alquilo C_{1-4},

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(c) alcoxi C_{1-4},

(d) amino sustituido opcionalmente con los sustituyentes seleccionados de

(i) alquilo C_{1-4} sustituido opcionalmente con un grupo heterocíclico aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(ii) alquil C_{1-4}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') hidroxi,

(ii') alquil C_{1-4}–sulfonilo, y

(iii') grupo heterocíclico de 6 miembros aromático,

(iii) alquenil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(iv) alquinil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(v) cicloalquil C_{3-6}–carbonilo,

(vi) cicloalquenil C_{3-6}–carbonilo,

(vii) aril C_{6-10}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno, ciano, hidroxi y cicloalquilo C_{3-6},

(iii') cicloalquilo C_{3-6} sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} sustituido opcionalmente con 1 a 5 átomos de

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halógeno,

(v') alcoxi C_{1-4}–carbonilo, y

(vi') grupo heterocíclico de 5 ó 6 miembros sustituido opcionalmente con ciano u oxo,

(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno, ciano, hidroxi y alcoxi C_{1-4},

(iii') arilo C_{6-10},

(iv') aril C_{6-10}–alquilo C_{1-4},

(v') alcoxi C_{1-4} sustituido opcionalmente con alcoxi C_{1-4},

(vi') alquil C_{1-4}–sulfonilo,

(vii') alquil C_{1-4}–carbonilo, y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático,

(x) alquil C_{1-4}–aminocarbonilo,

(xi) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno,

(xii) alcoxi C_{1-4}–aminocarbonilo,

(xiii) heterociclil–aminocarbonilo de 5 miembros sustituido

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opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo, y

(xv) heterociclil–sulfonilo aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(e) alquil C_{1-4}–aminocarbonilo que opcionalmente tiene arilo C_{6-10},

(f) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de átomo de halógeno y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) halógeno, y

(b) aril C_{6-10}–carbonilamino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno, o

(3) heterociclo aromático fusionado sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4}, y

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(b) aril C_{6-10}–amino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno;

Xa es –O–, –S– o –NH– (con mayor preferencia, –O– o –S–, con particular preferencia, –O–);

R^{1a} es

(1) amino,

(2) alquil C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) hidroxi,

(c) alcoxi C_{1-4},

(d) alquil C_{1-4}–carboniloxi,

(e) alquil C_{1-4}–amino,

(f) di–alquil C_{1-4}–amino,

(g) alquil C_{1-4}–sulfonilo, y

(h) grupo heterocíclico de 6 miembros que opcionalmente tiene 1 a 3 alquilo C_{1-4},

(3) alquenil C_{2-4}–carbonilamino que opcionalmente tiene alcoxi C_{1-4},

(4) alquinil C_{2-4}–carbonilamino,

(5) cicloalquil C_{3-6}–carbonilamino sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) hidroxi,

(c) alquilo C_{1-4} que opcionalmente tiene hidroxi,

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(d) alcoxi C_{1-4}, y

(e) alcoxi C_{1-4}–carbonilo,

(6) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino,

(7) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno,

(b) ciano, y

(c) alquilo C_{1-4} que opcionalmente tiene 1 a 3 átomos de halógeno,

(8) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

(a) alquilo C_{1-4} que opcionalmente tiene 1 a 3 alcoxi C_{1-4} que opcionalmente tiene 1 a 3 hidroxi, y

(b) alcoxi C_{1-4},

(9) alcoxi C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 átomos de halógeno,

(10) alquil C_{1-4}–sulfonilamino,

(11) cicloalquil C_{3-6}–sulfonilamino,

(12) aril C_{6-10}–amino, y

(13) heterociclilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) átomo de halógeno, y

(b) alquil C_{1-4}–amino; y

R^{2a}, R^{3a} y R^{4a} son cada uno átomo de hidrógeno.

Como ejemplos específicos del compuesto (II), por ejemplo, se

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pueden mencionar los compuestos de los Ejemplos 1 a 60, 64, 66 a 72, 74 a 123, 126 a 138 y 147 a 439.

De ellos, se prefieren los siguientes compuestos o sus sales.

N–{3–[(2–{[2–(metilamino)pirimidin–4–il]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (Ejemplo 70);

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 97);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 111);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida (Ejemplo 114);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,5–dimetil–1,3–oxazol–4–carboxamida (Ejemplo 117);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 148);

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 149);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}sulfanil)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida (Ejemplo 150);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–4–carboxamida

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(Ejemplo 161);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida (Ejemplo 165);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–4–carboxamida (Ejemplo 173);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–5–carboxamida (Ejemplo 174);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida (Ejemplo 180);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etil–1–metil–1H–pirazol–5–carboxamida (Ejemplo 208);

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–etil–3–metil–1H–pirazol–4–carboxamida (Ejemplo 254);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida (Ejemplo 287);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–oxazol–5–carboxamida (Ejemplo 289);

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–

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il}oxi)–2–fluorofenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida (Ejemplo 314);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (Ejemplo 319);

3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]benzamida (Ejemplo 330);

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (Ejemplo 398);

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–3–(trifluorometil)benzamida (Ejemplo 427);

N–{6–[3–({[3–(trifluorometil)fenil]carbamoil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (Ejemplo 431).

A continuación se explica el compuesto representado por la fórmula (III) (de ahora en adelante, compuesto (III)) de la presente invención.

Como "grupo cíclico" del "grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente", para el anillo Yb, se pueden citar aquellos similares a los grupos ejemplificados como el "grupo cíclico" del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I).

Como "grupo cíclico" del "grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está

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sustituido opcionalmente" para el anillo Yb, se prefieren grupo hidrocarburo aromático, grupo heterocíclico aromático. Como el grupo hidrocarburo aromático, se prefiere arilo C_{6-14}, arilo C_{6-10} tiene mayor preferencia, y fenilo tiene particular preferencia. Como el grupo heterocíclico aromático, se prefiere grupo heterocíclico aromático fusionado, grupo heterocíclico aromático fusionado formado por fusión de grupo heterocíclico aromático monocíclico de 5 miembros que contiene, como átomo constitutivo del anillo, 1 ó 2 heteroátomos seleccionados de átomo de azufre y átomo de nitrógeno, además de átomos de carbono, y anillo benceno (por ejemplo, benzotiazolilo, bencimidazolilo, indolilo, etc.) tiene mayor preferencia, y benzotiazolilo (por ejemplo, 5–benzotiazolilo, 6–benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol–5–ilo, bencimidazol–6–ilo), indolilo (por ejemplo, indol–4–ilo, indol–5–ilo, indol–6–ilo), y similares tienen particular preferencia.

El "grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente" para el anillo Yb está sustituido, en cualquiera de sus posiciones sustituibles, con amino sustituido opcionalmente que también puede tener 1 a la cantidad máxima aceptable, con preferencia, 1 a 5, con mayor preferencia, 1 a 3, sustituyentes en cualquier posición sustituible. Cuando el grupo cíclico está sustituido con dos o más sustituyentes, los sustituyentes pueden ser iguales o diferentes.

Como el "amino sustituido opcionalmente" del "grupo cíclico

sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente" para el anillo Yb, se prefieren aquellos similares al grupo ejemplificado como el "amino sustituido opcionalmente" (grupo sustituyente (1)(x)) entre los grupos ejemplificados como el "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I). Como el sustituyente que también se puede usar para la ulterior sustitución, se pueden mencionar aquellos similares al grupo ejemplificado como el "sustituyente" del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I).

Como "sustituyente" del "amino sustituido opcionalmente" en el "grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente" para el anillo Yb, se prefieren el "aminocarbonilo sustituido opcionalmente" del grupo sustituyente (1)(viii) antes mencionado, y el "acilo" del grupo sustituyente (1)(ix) antes mencionado entre los sustituyentes referenciados y ejemplificados con anterioridad. De ellos, se prefieren (1) aril C_{6-18}–aminocarbonilo (por ejemplo, fenilaminocarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–trifluorometilfenilaminocarbonilo, 4–trifluorometilfenilaminocarbonilo, etc.), (2) aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor)

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(ejemplos específicos: fenilcarbonilo, 3–trifluorometilfenilcarbonilo, etc.) y (3) heterociclo aromático monocíclico de 5 ó 6 miembros (por ejemplo, pirazolilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo), y similares (ejemplos específicos: 1,3–dimetil–1H–pirazol–5–carbonilo, etc.), y similares.

De los sustituyentes referenciados y ejemplificados con anterioridad, el "sustituyente" con el que el "grupo cíclico" está sustituido opcionalmente, es preferentemente

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(2) alquilo sustituido opcionalmente,

(3) alcoxi sustituido opcionalmente,

(4) aminocarbonilo sustituido opcionalmente,

(5) amino sustituido opcionalmente,

y similares.

De ellos, se prefieren

(1) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo),

(2) alquilo sustituido opcionalmente,

(3) amino sustituido opcionalmente,

y similares.

En lo sucesivo, en la presente, se ejemplifican en detalle los ejemplos preferibles antes mencionados del sustituyente con el que el grupo cíclico está también sustituido del "grupo cíclico sustituido

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con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente" para el anillo Yb.

(1) Como átomo de halógeno, se prefieren flúor, cloro, bromo, y similares.

(2) Como el alquilo sustituido opcionalmente, se prefiere alquilo C_{1-8} sustituido opcionalmente, alquilo C_{1-4} sustituido opcionalmente tiene mayor preferencia, y alquilo C_{1-4} no sustituido es mucho más preferido. Específicamente, se prefieren metilo, etilo, y similares.

(3) Como el alcoxi sustituido opcionalmente, se prefiere alcoxi C_{1-8} sustituido opcionalmente, alcoxi C_{1-4} sustituido opcionalmente tiene mayor preferencia, y alcoxi C_{1-4} no sustituido tiene mayor preferencia. Específicamente, se prefieren metoxi, y similares.

(4) Como "sustituyente" para el aminocarbonilo sustituido opcionalmente, se prefieren, por ejemplo, alquilo C_{1-8}, alquenilo C_{2-8}, alquinilo C_{2-8}, cicloalquilo C_{3-8}, cicloalquenilo C_{3-8}, cicloalquinilo C_{3-8}, arilo C_{6-18}, grupo heterocíclico, y similares, cada uno de los cuales está sustituido opcionalmente, son más preferidos el grupo heterocíclico sustituido opcionalmente, y similares, y el grupo heterocíclico aromático sustituido opcionalmente tiene particular preferencia. Como el aminocarbonilo sustituido opcionalmente, se prefieren aminocarbonilo sustituido opcionalmente con grupo heterocíclico aromático alquilo C_{1-4} sustituido opcionalmente, y similares, y se prefieren específicamente 1,3–dimetil–1H–pirazol–5–il–aminocarbonilo, y similares.

(5) Como "sustituyente" para el amino sustituido opcionalmente, se prefieren aminocarbonilo sustituido opcionalmente, acilo, y similares.

Como el amino sustituido opcionalmente, se prefieren amino no sustituido; amino sustituido opcionalmente con aminocarbonilo sustituido opcionalmente; amino sustituido opcionalmente con acilo, y similares.

Como el aminocarbonilo sustituido opcionalmente, se prefieren alquil C_{1-8}–aminocarbonilo, aril C_{6-18}–aminocarbonilo, aril C_{6-18}–alquil C_{1-4}–aminocarbonilo, heterociclil–aminocarbonilo, cicloalquil C_{3-8}–aminocarbonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–aminocarbonilo sustituido opcionalmente, y similares, y alquil C_{1-4}–aminocarbonilo sustituido opcionalmente tiene mayor preferencia. Específicamente, se prefieren etilaminocarbonilo, y similares. De modo alternativo, se prefieren aril C_{6-18}–aminocarbonilo sustituido opcionalmente, y similares, aril C_{6-10}–aminocarbonilo sustituido opcionalmente tiene mayor preferencia, y aquellos en donde el resto de arilo es fenilo no sustituido; fenilo sustituido opcionalmente con átomo de halógeno (por ejemplo, flúor, cloro), alquilo C_{1-4} opcionalmente halogenado (por ejemplo, trifluorometilo), y similares, y similares tienen particular preferencia. Específicamente, se prefieren fenilaminocarbonilo (anilinocarbonilo), 3–trifluorometilfenilaminocarbonilo (3–trifluorometilanilinocarbonilo), 4–trifluorometilfenilaminocarbonilo (4–trifluorometilanilinocarbonilo), y

similares.

Como el acilo, se prefieren alquil C_{1-8}–carbonilo, aril C_{6-18}–carbonilo, aril C_{6-18}–alquil C_{1-4}–carbonilo, alquil C_{1-8}–sulfonilo, aril C_{6-18}–sulfonilo, heterociclil–carbonilo, heterociclil–sulfonilo, cicloalquil C_{3-8}–carbonilo, y similares, cada uno de los cuales está sustituido opcionalmente. De ellos, se prefieren alquil C_{1-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, heterociclil–carbonilo, cada uno de los cuales está sustituido opcionalmente.

Como el alquil C_{1-8}–carbonilo sustituido opcionalmente, se prefiere alquil C_{1-4}–carbonilo, y se prefieren específicamente tert-butilcarbonilo, y similares.

Como el cicloalquil C_{3-8}–carbonilo sustituido opcionalmente, se prefiere cicloalquil C_{3-6}–carbonilo, y se prefieren específicamente ciclopropilcarbonilo, ciclohexilcarbonilo, y similares.

Como el aril C_{6-18}–carbonilo sustituido opcionalmente, se prefiere aril C_{6-10}–carbonilo sustituido opcionalmente, y fenil–carbonilo sustituido opcionalmente tiene mayor preferencia. Como "sustituyente" para el aril C_{6-18}–carbonilo sustituido opcionalmente, se prefieren átomo de halógeno (por ejemplo, flúor, cloro), alquilo C_{1-4} opcionalmente halogenado (por ejemplo, trifluorometilo), y similares. Como el aril C_{6-18}–carbonilo sustituido opcionalmente, se prefieren en donde el resto de "arilo" es fenilo no sustituido; fenilo sustituido opcionalmente con átomo de halógeno (por ejemplo, flúor, cloro), alquilo C_{1-4} opcionalmente halogenado (por ejemplo, trifluorometilo), y similares, y similares. Específicamente, se

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prefieren fenilcarbonil(benzoilo), 3–trifluorometilfenilcarbonilo, 3–fluorofenilcarbonilo, 3–clorofenilcarbonilo, y similares.

Como la porción "heterociclo" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren grupo heterocíclico aromático monocíclico de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, y similares, y se prefieren específicamente piridilo, furilo, tienilo, pirazolilo, imidazolilo, tiazolilo, oxazolilo, isoxazolilo, 1,2,3–triazolilo, 1,2,3–tiadiazolilo, piridazinilo, y similares. Como "sustituyente" para el heterociclil–carbonilo sustituido opcionalmente, se prefieren alquilo C_{1-4} opcionalmente halogenado (por ejemplo, metilo, trifluorometilo), y similares.

Como el heterociclil–carbonilo sustituido opcionalmente, se prefieren el heterociclil–carbonilo aromático monocíclico de 5 ó 6 miembros antes mencionado, y similares sustituido opcionalmente con alquilo C_{1-4} opcionalmente halogenado, y similares. Específicamente, se prefieren 3–piridilcarbonilo, 2–furilcarbonilo, 2,5–dimetilfuran–3–carbonilo, 3–metiltiofen–2–carbonilo, 4–metil–1,2,3–tiadiazol–5–carbonilo, isoxazol–5–carbonilo, 1,3–dimetil–1H–pirazol–5–carbonilo, 3–metilisoxazol–5–carbonilo, 5–metilisoxazol–3–carbonilo, 1–metil–3–(trifluorometil)–1H–pirazol–5–carbonilo, 5–metil–2–(trifluorometil)–3–furancarbonilo, 2,4–dimetil–1,3–tiazol–5–carbonilo, 2,5–dimetil–1,3–oxazol–4–carbonilo, 1–metil–1H–pirazol–5–carbonilo, 1,5–dimetil–1H–pirazol–3–carbonilo, 3,5–

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dimetilisoxazol–4–carbonilo, 1–metil–1H–1,2,3–triazol–5–carbonilo, 1–metil–1H–1,2,3–triazol–4–carbonilo, 1–metil–1H–imidazol–2–carbonilo, 1–metil–1H–imidazol–5–carbonilo, y similares.

Con preferencia, el anillo Yb es

(1) arilo C_{6-14} (por ejemplo, fenilo, etc.) sustituido con amino sustituido opcionalmente con sustituyente seleccionado de (1') aril C_{6-18}–aminocarbonilo (por ejemplo, fenilaminocarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–trifluorometilfenilaminocarbonilo, 4–trifluorometilfenilaminocarbonilo, etc.), (2') aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilcarbonilo, 3–trifluorometilfenilcarbonilo, etc.), y (3') heterociclo aromático monocíclico de 5 ó 6 miembros (por ejemplo, pirazolilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo), y similares (ejemplos específicos: 1,3–dimetil–1H–pirazol–5–carbonilo, etc.), en donde dicho arilo C_{6-14} también está sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

(i) átomo de halógeno (por ejemplo, flúor, cloro, bromo, yodo

etc.),

(ii) alquilo C_{1-4} (por ejemplo, metilo, etc.),

(iii) alcoxi C_{1-4} (por ejemplo, metoxi, etc.),

(iv) aminocarbonilo sustituido con grupo heterocíclico aromático (por ejemplo, pirazolilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo, etc.), y

(v) amino sustituido opcionalmente con sustituyente seleccionado de

(a) alquil C_{1-4}–carbonilo (por ejemplo, tert-butilcarbonilo, etc.),

(b) cicloalquil C_{3-6}–carbonilo (por ejemplo, ciclopropilcarbonilo, ciclohexilcarbonilo, etc.),

(c) aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con sustituyente seleccionado de átomo de halógeno (por ejemplo, flúor, cloro) y alquilo C_{1-4} opcionalmente halogenado (por ejemplo, trifluorometilo) (ejemplos específicos: fenilcarbonilo (benzoilo), 3–trifluorometilfenilcarbonilo, 3–fluorofenilcarbonilo, 3–clorofenilcarbonilo, etc.), y

(d) grupo heterocíclico aromático monocíclico de 5 ó 6 miembros (por ejemplo, piridilo, furilo, tienilo, pirazolilo, imidazolilo, tiazolilo, oxazolilo, isoxazolilo, 1,2,3–triazolilo, 1,2,3–tiadiazolilo, piridazinilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por

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ejemplo, flúor), y similares (ejemplos específicos: 3–piridilcarbonilo, 2–furilcarbonilo, 2,5–dimetilfuran–3–carbonilo, 3–metiltiofen–2–carbonilo, 4–metil–1,2,3–tiadiazol–5–carbonilo, isoxazol–5–carbonilo, 1,3–dimetil–1H–pirazol–5–carbonilo, 3–metilisoxazol–5–carbonilo, 5–metilisoxazol–3–carbonilo, 1–metil–3–(trifluorometil)–1H–pirazol–5–carbonilo, 5–metil–2–(trifluorometil)–3–furancarbonilo, 2,4–dimetil–1,3–tiazol–5–carbonilo, 2,5–dimetil–1,3–oxazol–4–carbonilo, 1–metil–1H–pirazol–5–carbonilo, 1,5–dimetil–1H–pirazol–3–carbonilo, 3,5–dimetilisoxazol–4–carbonilo, 1–metil–1H–1,2,3–triazol–5–carbonilo, 1–metil–1H–1,2,3–triazol–4–carbonilo, 1–metil–1H–imidazol–2–carbonilo, 1–metil–1H–imidazol–5–carbonilo, etc.),

y similares,

(2) heterociclo aromático fusionado (por ejemplo, benzotiazolilo (por ejemplo, 5–benzotiazolilo, 6–benzotiazolilo), bencimidazolilo (por ejemplo, bencimidazol–5–ilo, bencimidazol–6–ilo), indolilo (por ejemplo, indol–4–ilo, indol–5–ilo, indol–6–ilo), etc.) sustituido con amino sustituido opcionalmente con (1') aril C_{6-18}–aminocarbonilo (por ejemplo, fenilaminocarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–trifluorometilfenilaminocarbonilo, 4–trifluorometilfenilaminocarbonilo, etc.), (2') aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilcarbonilo, 3–

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trifluorometilfenilcarbonilo, etc.), y (3') heterociclo aromático monocíclico de 5 ó 6 miembros (por ejemplo, pirazolilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo), y similares (ejemplos específicos: 1,3–dimetil–1H–pirazol–5–carbonilo, etc.), en donde dicho heterociclo aromático fusionado también tiene 1 ó 2 alquilo C_{1-4} (por ejemplo, metilo, etc.), y similares.

En particular, se prefiere arilo C_{6-14} (por ejemplo, fenilo, etc.) sustituido con amino sustituido opcionalmente con (1) aril C_{6-18}–aminocarbonilo (por ejemplo, fenilaminocarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–trifluorometilfenilaminocarbonilo, 4–trifluorometilfenilaminocarbonilo, etc.), (2) aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilcarbonilo, 3–trifluorometilfenilcarbonilo, etc.), y (3) heterociclo aromático monocíclico de 5 ó 6 miembros (por ejemplo, pirazolilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo

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C_{1-4} (por ejemplo, metilo), y similares (ejemplos específicos: 1,3–dimetil–1H–pirazol–5–carbonilo, etc.), en donde dicho arilo C_{6-14} no tieneotros sustituyentes.

Como anillo Yb, se prefieren específicamente 3–aminofenilo, 4–aminofenilo, 3–{[(etilamino)carbonil]amino}fenilo, 4–{[(fenilamino)carbonil]amino}fenilo, 3–{[(fenilamino)carbonil]amino}fenilo, 3–({[3–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–({[4–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–[(tert-butilcarbonil)amino]fenilo, 3–[(ciclopropilcarbonil)amino]fenilo, 3–[(ciclohexilcarbonil)amino]fenilo, 3–[(fenilcarbonil)amino]fenilo, 3–{[3–(trifluorometilfenil)carbonil]amino}fenilo, 3–{[3–(fluorofenil)carbonil]amino}fenilo, 3–{[3–(clorofenil)carbonil]amino}fenilo, 3–{[3–(piridil)carbonil]amino}fenilo, 3–{[2–(furil)carbonil]amino}fenilo, 3–{[3–(2,5–dimetilfuran)carbonil]amino}fenilo, 3–{[2–(3–metiltiofeno)carbonil]amino}fenilo, 3–{[5–(4–metil–1,2,3–tiadiazol)carbonil]amino}fenilo, 3–{[5–(isoxazol)carbonil]amino}fenilo, 3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[5–(3–metilisoxazol)carbonil]amino}fenilo, 3–{[3–(5–metilisoxazol)carbonil]amino}fenilo, 3–({5–[1–metil–3–(trifluorometil)–1H–pirazol]carbonil}amino)fenilo, 5–metil–2–(trifluorometil)–3–furancarbonilaminofenilo, 3–{[5–(2,4–dimetil–1,3–tiazol)carbonil]amino}fenilo, 3–{[4–(2,5–dimetil–1,3–oxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–

pirazol)carbonil]amino}fenilo, 3–{[3–(1,5–dimetil–1H–pirazol)carbonil]amino}fenilo, 3–{[4–(3,5–dimetilisoxazol)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–1,2,3–triazol)carbonil]amino}fenilo, 3–{[4–(1–metil–1H–1,2,3–triazol)carbonil]amino}fenilo, 3–{[2–(1–metil–1H–imidazole)carbonil]amino}fenilo, 3–{[5–(1–metil–1H–imidazole)carbonil]amino}fenilo, 5–amino–2–metilfenilo, 3–amino–2–metilfenilo, 3–amino–4–metilfenilo, 3–amino–4–clorofenilo, 5–amino–2–clorofenilo, 5–amino–2–metoxifenilo, 6–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 2–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–metil–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–cloro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–fluoro–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 6–metoxi–3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–cloro–3–(ciclopropilcarbonilamino)fenilo, 3–amino–4–fluorofenilo, y similares. De ellos, 3–aminofenilo, 4–aminofenilo, 4–{[(fenilamino)carbonil]amino}fenilo, 3–{[(fenilamino)carbonil]amino}fenilo, 3–({[3–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–({[4–(trifluorometilfenil)amino]carbonil}amino)fenilo, 3–{[5–(1,3–dimetil–1H–pirazol)carbonil]amino}fenilo, 4–fluoro–3–{[4–(1–etil–3–metil–1H–pirazol)carbonil]amino}fenilo, y similares.

En el compuesto (III), como el sustituyente para R^b de NR^b

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definido por Xb, se pueden mencionar aquellos similares al sustituyente seleccionado del grupo sustituyente (1) antes mencionado.

Como el sustituyente para R^b, se prefieren grupo hidrocarburo sustituido opcionalmente, y similares.

Xb es con preferencia, –O–, –S– o –NH–, y con particular preferencia, –O–.

Como el "sustituyente (excepto por sustituido opcionalmente amino)" para R^{1b}, se prefieren aquellos similares al grupo de los sustituyentes del grupo sustituyente (1) antes mencionado excepto por el "amino sustituido opcionalmente". De ellos, se prefieren aminocarbonilo sustituido opcionalmente, y similares.

Los R^{1b} preferidos son

(1) átomo de hidrógeno,

(2) aminocarbonilo sustituido opcionalmente,

(3) alquilo sustituido opcionalmente,

(4) carboxi esterificado opcionalmente,

y similares.

De ellos, los R^{1b} de mayor preferencia son

(1) átomo de hidrógeno,

(2) aminocarbonilo sustituido opcionalmente con alquilo sustituido opcionalmente,

(3) alquilo sustituido opcionalmente con hidroxi,

(4) carboxi,

(5) alcoxi C_{1-6}–carbonilo (por ejemplo, etoxicarbonilo),

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y similares.

En lo sucesivo, en la presente, los ejemplos preferidos del "sustituyente" para R^{1b} se explican en detalle.

Como el "alquilo" del "alquilo sustituido opcionalmente" del (2) antes mencionado, se prefieren alquilo C_{1-8}, y similares, alquilo C_{1-4}, y similares tienen mayor prefefencia, y se prefieren específicamente metilo, y similares.

Como el "alquilo" del "alquilo sustituido opcionalmente hidroxi" del (3) antes mencionado, se prefieren alquilo C_{1-8}, y similares, alquilo C_{1-4}, y similares tienen mayor preferencia, y se prefieren específicamente metilo, y similares.

Como R^{1b}, se pueden mencionar específicamente hidroximetilo, $-C(O)NH-CH_3$, átomo de hidrógeno, carboxi, etoxicarbonilo, y similares.

En el compuesto (III), se pueden mencionar como el "sustituyente" para R^{2b}, aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, R^{2b} preferido es átomo de hidrógeno.

En el compuesto (III), se pueden mencionar como el "sustituyente" para R^{3b}, aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

De ellos, R^{3b} preferido es átomo de hidrógeno.

En el compuesto (III), se pueden mencionar como el "sustituyente" para R^{4b}, aquellos similares a los sustituyentes del grupo sustituyente (1) antes mencionado.

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De ellos, R^{4b} preferido es átomo de hidrógeno.

Como el ejemplo preferido del compuesto (III), se puede mencionar, por ejemplo, el siguiente compuesto.

Un compuesto en donde

El anillo Yb es arilo C_{6-14} (por ejemplo, fenilo, etc.) sustituido con amino sustituido opcionalmente con (1) aril C_{6-18}–aminocarbonilo (por ejemplo, fenilaminocarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilaminocarbonilo, 3–trifluorometilfenilaminocarbonilo, 4–trifluorometilfenilaminocarbonilo, etc.), (2) aril C_{6-18}–carbonilo (por ejemplo, fenilcarbonilo, etc.) sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo) que opcionalmente tiene átomo de halógeno (por ejemplo, flúor) (ejemplos específicos: fenilcarbonilo, 3–trifluorometilfenilcarbonilo, etc.), y (3) heterociclo aromático monocíclico de 5 ó 6 miembros (por ejemplo, pirazolilo, etc.)–carbonilo que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con alquilo C_{1-4} (por ejemplo, metilo), y similares (ejemplos específicos: 1,3–dimetil–1H–pirazol–5–carbonilo, etc.), en donde dicho arilo C_{6-14} no tiene otro sustituyente;

Xb es –O–, –S– o –NH– (con preferencia, –O–);

R^{1b} es

(1) átomo de hidrógeno,

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(2) $-C(O)NH-CH_3$, o

(3) hidroximetilo; y

R^{2b}, R^{3b} y R^{4b} son cada uno átomo de hidrógeno.

Los ejemplos específicos del compuesto (III) incluyen los Ejemplos 61 a 63, 65, 73, 124, 125, 139 a 146, 440, 442 y 445.

Los ejemplos de la sal de los compuestos (I) – (IV) incluyen una sal metálica, una sal de amonio, una sal con base orgánica, una sal con ácido inorgánico, una sal con ácido orgánico, una sal con aminoácido básico o ácido, y similares. Los ejemplos preferidos de la sal metálica incluyen sal de metal alcalino tales como sal de sodio, sal de potasio, y similares; sal de metal alcalinotérreo tal como sal de calcio, sal de magnesio, sal de bario, y similares; sal de aluminio, y similares. Los ejemplos preferidos de la sal con la base orgánica incluyen una sal con trimetilamina, trietilamina, piridina, picolina, 2,6–lutidina, etanolamina, dietanolamina, trietanolamina, ciclohexilamina, diciclohexilamina, N,N'–dibenciletilendiamina, y similares. Los ejemplos preferidos de la sal con el 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 el 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 el aminoácido básico incluyen una sal con

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arginina, lisina, ornitina, y similares. Los ejemplos preferidos de la sal con el aminoácido ácido incluyen una sal con ácido aspártico, ácido glutámico, y similares.

De ellos, se prefiere la sal farmacéuticamente aceptable. Por ejemplo, cuando el compuesto tiene un grupo funcional ácido, se puede mencionar una sal inorgánica como sal de metal alcalino (por ejemplo, sal de sodio, sal de potasio etc.), sal de metal alcalinotérreo (por ejemplo, sal de calcio, sal de magnesio etc.), y similares, sal de amonio, y similares. De modo alternativo, cuando el compuesto tiene un grupo funcional básico, por ejemplo, una sal con ácido inorgánico como ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido fosfórico, y similares, o una sal con ácido orgánico como acético, ácido ftálico, ácido fumárico, ácido oxálico, ácido tartárico, ácido maleico, ácido cítrico, ácido succínico, ácido metansulfónico, ácido bencensulfónico, ácido p–toluensulfónico, y similares.

En lo sucesivo, se explican los métodos de producción de los compuestos (I) – (IV) de la presente invención.

Se pueden obtener los compuestos (I) – (IV) de la presente invención, por ejemplo, de acuerdo con los métodos indicados en los siguientes esquemas o un método análogo, y similares (mientras los métodos de producción de los compuestos (II) y (III) se muestran abajo a modo de ejemplo, los compuestos (I) y (IV) también se pueden obtener de acuerdo con un método indicado por un esquema similar o un método análogo, y similares).

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Cada compuesto en los siguientes esquemas incluye sales, y como tales sales se pueden usar, por ejemplo, aquellas similares a las sales de los compuestos (I) – (IV), y similares.

El compuesto obtenido en cada paso se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. Además, el compuesto se puede aislar de una mezcla de reacción de acuerdo con un método convencional, y se puede purificar con facilidad por un medio de separación como recristalización, destilación, cromatografía, y similares.

Las fórmulas de reacción esquemáticas se indican a continuación, en donde cada símbolo en los compuestos es como se definió con anterioridad.

Más aún, los términos respectivos en los métodos de producción significan lo siguiente.

El "átomo de halógeno" significa flúor, cloro, bromo o yodo.

El "alquilsulfonilo sustituido opcionalmente" significa alquil C_{1-6}–sulfonilo (por ejemplo, metilsulfonilo, etilsulfonilo, etc.) sustituido opcionalmente con sustituyente(s) seleccionados de átomo de halógeno, alquilo C_{1-6} opcionalmente halogenado (por ejemplo, metilo, etilo, trifluorometilo) y nitro.

El "alquilsulfoniloxi sustituido opcionalmente" significa alquil C_{1-6}–sulfoniloxi (por ejemplo, metilsulfoniloxi, etilsulfoniloxi, etc.) sustituido opcionalmente con sustituyente(s) seleccionados de átomo de halógeno, alquilo C_{1-6} opcionalmente halogenado (por ejemplo, metilo, etilo, trifluorometilo) y nitro.

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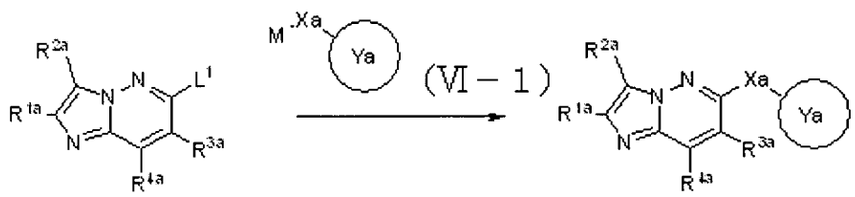
El "arilsulfoniloxi sustituido opcionalmente" significa aril C_{6-14}–sulfoniloxi (por ejemplo, fenilsulfoniloxi, etc.) sustituido opcionalmente con sustituyente(s) seleccionados de átomo de halógeno, alquilo C_{1-6} opcionalmente halogenado (por ejemplo, metilo, etilo, trifluorometilo) y nitro.

El "ariloxi sustituido opcionalmente" significa aril C_{6-14}–oxi (por ejemplo, feniloxi, etc.) sustituido opcionalmente con sustituyente(s) seleccionados de átomo de halógeno, alquilo C_{1-6} opcionalmente halogenado (por ejemplo, metilo, etilo, trifluorometilo) y nitro.

El "alcoxi sustituido opcionalmente" significa alcoxi C_{1-6} (por ejemplo, metoxi, etoxi, etc.) sustituido opcionalmente con sustituyente(s) seleccionados de átomo de halógeno, alquilo C_{1-6} opcionalmente halogenado (por ejemplo, metilo, etilo, trifluorometilo) y nitro.

Método de producción 1

Esquema 1



(V−1) (II)

en donde L^1 es un grupo saliente, M es un átomo de hidrógeno o un átomo de metal, y los otros símbolos son como se definieron con anterioridad.

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Como el grupo saliente para L^1, por ejemplo, se puede usar un átomo de halógeno, alquilsulfonilo sustituido opcionalmente, alquilsulfoniloxi sustituido opcionalmente, arilsulfoniloxi sustituido opcionalmente, y similares.

M es principalmente un átomo de hidrógeno, pero puede ser un metal alcalino como litio, sodio, potasio, cesio, y similares, o un metal alcalinotérreo como magnesio, calcio, y similares.

El compuesto (II) se puede producir haciendo reaccionar el compuesto (V–1) con el compuesto (VI–1). El compuesto (VI–1) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–1). Se añade una base de ser necesario. Como la base, se pueden usar base inorgánica o base orgánica, y similares. Específicamente, se pueden mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, carbonato de sodio, carbonato de potasio, carbonato de cesio, bicarbonato de sodio, trietilamina, N–etildiisopropilamina, N–metilmorfolina, 1,8–diazabiciclo[5,4,0]undec–7–eno, piridina, 4–(dimetilamino)piridina, N,N–dimetilanilina, metóxido de sodio, etóxido de sodio, tert-butóxido de potasio, hidruro de sodio, amida de sodio, diisopropilamida de litio, y similares. La base se usa en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como el solvente no está particularmente limitado cuando procede la reacción, se pueden usar solos o en mezcla, por ejemplo, alcoholes tales como metanol, etanol, 2–propanol, 2–metil–

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2–propanol, y similares, éteres tales como éter dietílico, tetrahidrofurano, 1,4–dioxano, 1,2–dimetoxietano, y similares, hidrocarburos tales como benceno, tolueno, ciclohexano, hexano, y similares, ésteres tales como acetato de etilo, y similares, cetonas tales como acetona, metiletilcetona, y similares, amidas tales como N,N–dimetilformamida, N,N–dimetilacetamida, 1–metil–2–pirrolidona, y similares, hidrocarburos halogenados tales como diclorometano, cloroformo, tetracloruro de carbono, 1,2–dicloroetano, y similares, nitrilos tales como acetonitrilo, y similares, sulfóxidos tales como dimetilsulfóxido, y similares, piridina, agua, y similares. Como el tiempo de reacción varía según el tipo de reactivo y solvente por usar, oscila en general de 1 min a 200 h, con preferencia, de 10 min a 100 h. Como la temperatura de reacción varía según el tipo de reactivo y solvente por usar, varía en general de –100 a 250 °C, con preferencia, de –78 a 200 °C. La reacción se puede llevar a cabo usando un sintetizador de microondas.

Un compuesto dentro del alcance de la presente invención también se puede producir aplicando un medio conocido *per se* al compuesto (II) obtenido de la presente invención para la introducción de sustituyentes y la conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden usar conversión en carboxi por hidrólisis del éster, conversión en carbamoílo por amidación de carboxi, conversión en hidroximetilo por reducción de carboxi, conversión en compuesto alcohólico por reducción o alquilación de

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carbonilo, aminación reductiva de carbonilo, oximación de carbonilo, acilación, ureación, sulfonilación o alquilación de amino, sustitución y aminación de halógeno activo por amina, aminación de nitro por reducción, alquilación de hidroxi, sustitución y aminación de hidroxi, y similares. Cuando está presente un sustituyente reactivo que causa una reacción no objetivo durante la introducción de sustituyentes y la conversión de grupos funcionales, se introduce un grupo protector con anterioridad en el sustituyente reactivo a través de un medio conocido en sí, y el grupo protector se elimina con un medio conocido en sí después de la reacción objetivo, con lo cual se puede producir también el compuesto dentro del alcance de la presente invención.

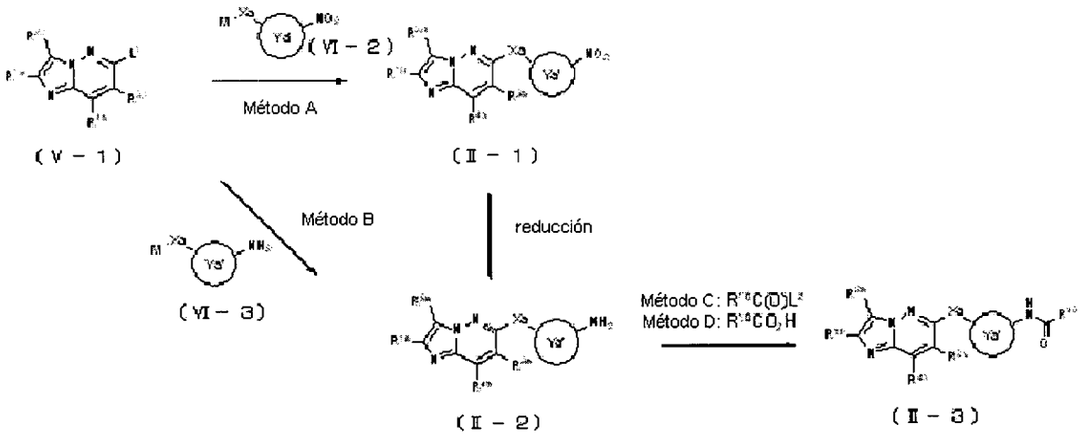
El compuesto (VI–1) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 2

El compuesto (II), en donde Ya es sustituido con amida opcionalmente sustituida, que también está opcionalmente sustituida, también se puede producir, por ejemplo, de acuerdo con un método indicado en el Esquema 2. Los compuestos (II–1), (II–2) y (II–3) están incluidos en el compuesto (II).

Esquema 2

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en donde L^2 es un grupo saliente, Ya' es un grupo cíclico de Ya, R^{10} es un grupo indicado por el resto de acilo excepto por resto de carbonilo, cuyo acilo está ejemplificado como el sustituyente del "amino sustituido opcionalmente" que es uno de los sustituyentes del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I), y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^2, por ejemplo, se pueden usar átomo de halógeno, ariloxi sustituido opcionalmente, alcoxi sustituido opcionalmente, 1–imidazolilo, y similares.

En el método A, el compuesto (II–2) se produce haciendo reaccionar el compuesto (V–1) y el compuesto (VI–2) en presencia de una base, y reduciendo el nitro del compuesto (II–1). El compuesto (VI–2) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–1). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. La base se usa en 1 a 30 equivalentes, con preferencia,

1 a 10 equivalentes, respecto del compuesto (V–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–2) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo. El compuesto obtenido (II–1) se puede usar como una mezcla de reacción o como un producto crudo en la siguiente reacción. Se puede aislar de una mezcla de reacción de acuerdo con un método convencional. La reducción de nitro se puede llevar a cabo de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en la cuarta serie de experimentos químicos, vol. 20, 279–280, y similares, o un método análogo.

En el método B, el compuesto (II–2) se produce haciendo reaccionar el compuesto (V–1) con el compuesto (VI–3) en presencia de una base. El compuesto (VI–3) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–1). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. La base se usa en 1 a 30

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equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–3) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método C, el compuesto (II–3) se produce haciendo reaccionar el compuesto (II–2) con un compuesto representado por la fórmula $R^{10}C(O)L^2$. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–2). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C,

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con preferencia, de –78 °C a 200°C. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método D, (II–3) se produce haciendo reaccionar el compuesto (II–2) con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (II–2) se hace reaccionar con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{10}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. El agente de condensación se usa en 1 a 10 equivalentes, con preferencia, 1 a 5 equivalentes, respecto del compuesto (II–2). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). El promotor de la condensación se usa en 0.1 a 10

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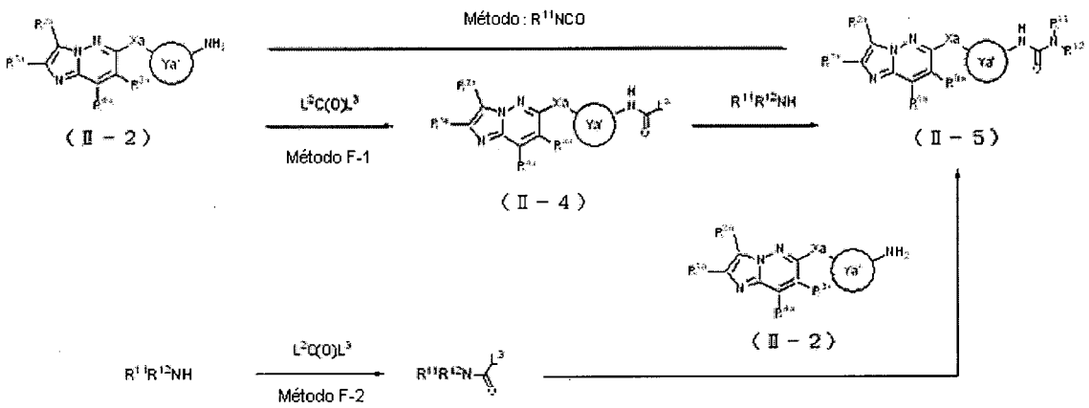
equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a las bases ejemplificadas en el Esquema 1. La base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte para la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El ácido carboxílico ($R^{10}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 3

En el compuesto (II), cuando Ya está sustituido con ureído sustituido opcionalmente, y está sustituido opcionalmente, por ejemplo, el compuesto también se puede producir por medio del método indicado en el Esquema 3. Los compuestos (II–2), (II–4) y (II–5) están incluidos en el compuesto (II).

Esquema 3

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en donde L^3 es un grupo saliente, $-NR^{11}R^{12}$ es un grupo indicado por el resto de aminocarbonilo sustituido opcionalmente excepto por el resto de carbonilo, cuyo aminocarbonilo sustituido opcionalmente se ejemplifica como el sustituyente del "amino sustituido opcionalmente" que es uno de los sustituyentes del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I), y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^3, se puede usar, por ejemplo, un átomo de halógeno, ariloxi sustituido opcionalmente, alcoxi sustituido opcionalmente, 1–imidazolilo, y similares.

En el método E, el compuesto (II–5) se produce haciendo reaccionar el compuesto (II–2) con el derivado de isocianato ($R^{11}NCO$). El derivado de isocianato ($R^{11}NCO$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.01 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un

solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de isocianato ($R^{11}NCO$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método F–1, el compuesto (II–5) se produce haciendo reaccionar primero el compuesto (II–2) con un compuesto representado por la fórmula $L^2C(O)L^3$ para dar el compuesto (II–4), y luego haciendo reaccionar el compuesto (II–4) con un derivado de amina ($R^{11}R^{12}NH$). El compuesto representado por la fórmula $L^2C(O)L^3$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h.

La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $L^2C(O)L^3$ se puede conseguir en comercios, o se puede producir por un método en sí conocido. El compuesto obtenido (II–4) se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. También se puede usar para la siguiente reacción después del aislamiento y la purificación de una mezcla de reacción de acuerdo con un método convencional. El derivado de amina ($R^{11}R^{12}NH$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–4). Además, se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de amina ($R^{11}R^{12}NH$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método F–2, el compuesto (II–5) se produce haciendo

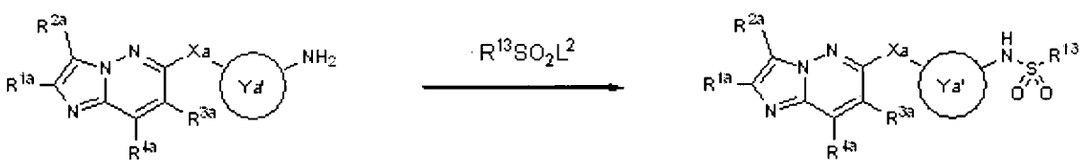
reaccionar primero un compuesto representado por la fórmula $R^{11}R^{12}NH$ con un compuesto representado por la fórmula $L^2C(O)L^3$, sucesivamente el compuesto (II–2) para dar el compuesto (II–5). El compuesto representado por la fórmula $L^2C(O)L^3$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto de un derivado de amina ($R^{11}R^{12}NH$). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de amina ($R^{11}R^{12}NH$) y el compuesto representado por la fórmula $L^2C(O)L^3$ se puede conseguir en comercios, o se puede producir por un método en sí conocido por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo. El compuesto obtenido representado por la fórmula $R^{11}R^{12}NC(O)L^3$ se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. También se puede usar para la siguiente reacción después del aislamiento y la purificación de una mezcla de reacción de acuerdo con un método convencional. El compuesto (II–2) se usa en

0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto representado por la fórmula $R^{11}R^{12}NC(O)L^3$. Además, se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C.

Método de producción 4

En el compuesto (II), cuando Ya está sustituido con sulfonamida opcionalmente sustituida, y está sustituido opcionalmente, por ejemplo, el compuesto también se puede producir por medio del método indicado en el Esquema 4. El compuesto (II–6) está comprendido en el compuesto (II).

(Esquema 4)



(Ⅱ－2) (Ⅱ－6)

en donde R^{13} es un grupo indicado por el resto de acilo excepto por resto de carbonilo, cuyo acilo está ejemplificado como el sustituyente del "amino sustituido opcionalmente" que es uno de los

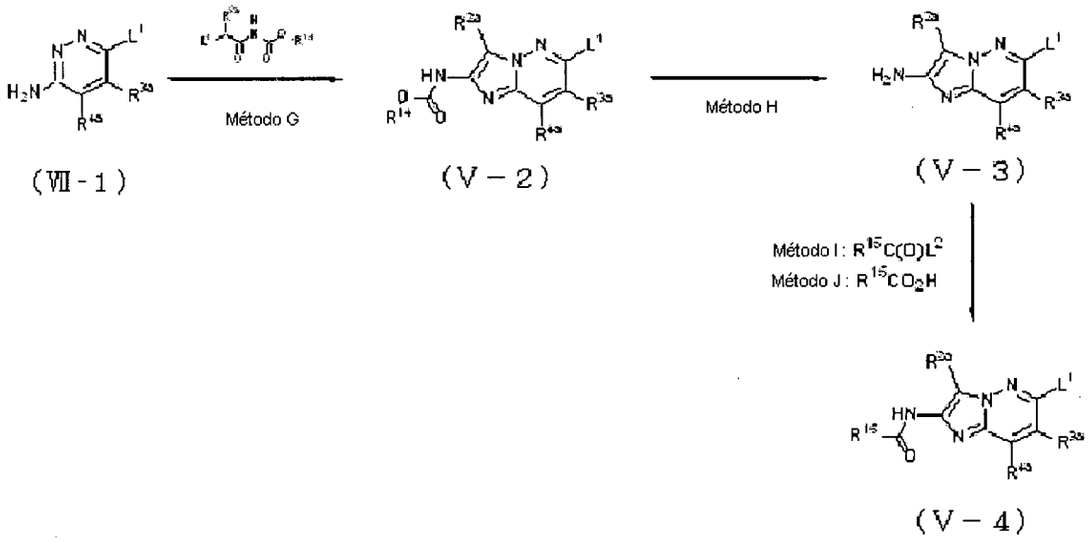
sustituyentes del "grupo cíclico sustituido opcionalmente" para el anillo Y del compuesto (I), y los otros símbolos son como se definieron con anterioridad.

El compuesto (II–6) se puede producir haciendo reaccionar el compuesto (II–2) con un derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$). El derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–2). En el presente método, la reacción se lleva a cabo en general en presencia de una base, a pesar de que no siempre es esencial. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 5

El compuesto (V–1) indicado en los Esquemas 1 y 2 se puede obtener, por ejemplo, por medio del método indicado en el siguiente Esquema o un método análogo, y similares. Los compuestos (V–2), (V–3) y (V–4) están incluidos en el compuesto (V–1).

Esquema 5



en donde L^4 es un grupo saliente, R^{14} es un grupo hidrocarburo sustituido opcionalmente, R^{15} es un grupo hidrocarburo sustituido opcionalmente o grupo cíclico sustituido opcionalmente, y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^4, se pueden usar cloro, bromo, yodo, y similares.

Los ejemplos del grupo hidrocarburo sustituido opcionalmente para R^{14} incluyen metilo, etilo, propilo, isopropilo, tert-butilo, y similares.

Los ejemplos del grupo hidrocarburo sustituido opcionalmente, grupo cíclico sustituido opcionalmente para R^{15} incluyen un grupo

indicado por el resto de acilo excepto por grupo carbonilo, cuyo acilo está ejemplificado como el sustituyente del "amino sustituido opcionalmente" para R^{1a} del compuesto (II), y similares.

En el método G, el compuesto (V–2) se produce haciendo reaccionar el compuesto (VII–1) con un derivado de ácido acetilcarbámico ($L^4CHR^{2a}C(O)NHC(O)OR^{14}$). El derivado de ácido acetilcarbámico se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 5 equivalentes, respecto del compuesto (VII–1). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 5 equivalentes, respecto del compuesto (VII–1). Como base, se pueden usar base inorgánica o base orgánica, y similares, específicamente se pueden usar, por ejemplo, carbonato de sodio, carbonato de potasio, carbonato de cesio, bicarbonato de sodio, hidrógeno–fosfato disódico, hidrógeno–fosfato dipotásico, hidrógeno–fosfato de calcio, trietilamina, N–etildiisopropilamina, N–metilmorfolina, 1,8–diazabiciclo[5,4,0]undec–7–eno, piridina, 4–(dimetilamino)piridina, N,N–dimetilanilina, y similares. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de ácido acetilcarbámico ($L^4CHR^{2a}C(O)NHC(O)OR^{14}$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí

conocido, por ejemplo, los métodos descritos en "Journal of Organic Chemistri, 50, 2480–2499 (1985)", y similares o un método análogo.

En el método H, el compuesto (V–3) se produce al tratar el compuesto (V–2) con una base o un ácido. Como base, se pueden mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, hidróxido de cesio, hidróxido de bario, y similares. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (V–2). Como ácido, se pueden usar, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido trifluoroacético, y similares. Un ácido se usa en 0.1 a 20 equivalentes, con preferencia, 0.3 a 10 equivalentes, respecto del compuesto (V–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1.

En el método I, el compuesto (V–4) se produce haciendo reaccionar el compuesto (V–3) con un compuesto representado por la fórmula $R^{15}C(O)L^2$. El compuesto representado por la fórmula $R^{15}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–3). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (V–3). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los

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solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $R^{15}C(O)L^2$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

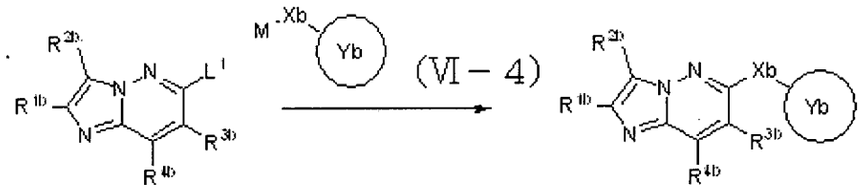
En el método J, (V–4) se produce haciendo reaccionar el compuesto (V–3) con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (V–3) se hace reaccionar con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{15}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–3). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con

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preferencia, 1 a 5 equivalentes, respecto del compuesto (V–3). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–3). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Estas bases se usan en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (V–3). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El ácido carboxílico ($R^{15}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 6

Esquema 6



(V – 5) (III)

en donde cada símbolo es como se definió con anterioridad.

El compuesto (III) se puede producir haciendo reaccionar el compuesto (V–5) con el compuesto (VI–4). El compuesto (VI–4) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto de compuesto (V–5). De ser necesario, se puede añadir una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Estas bases se usan en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–5). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía según el tipo de reactivo y solvente por usar, y es generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. Como la temperatura de reacción varía según el tipo de reactivo y solvente por usar, generalmente de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. la reacción se puede llevar a cabo usando un sintetizador de microondas.

Un compuesto dentro del alcance de la presente invención también se puede producir aplicando un medio conocido en sí al compuesto obtenido (III) de la presente invención para la

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introducción de sustituyentes y la conversión de grupos funcionales. Para la conversión de sustituyentes, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar conversión en carboxi por hidrólisis del éster, conversión en carbamoílo por amidación de carboxi, conversión en hidroximetilo por reducción de carboxi, conversión en compuesto alcohólico por reducción o alquilación de carbonilo, aminación reductiva de carbonilo, oximación de carbonilo, acilación, ureación, sulfonilación o alquilación de amino, sustitución y aminación de halógeno activo por amina, alquilación de hidroxi, sustitución y aminación de hidroxi, y similares. Cuando está presente un sustituyente reactivo que causa una reacción no objetivo durante la introducción de sustituyentes y la conversión de grupos funcionales, se introduce un grupo protector con anterioridad en el sustituyente reactivo a través de un medio conocido en sí, y el grupo protector se elimina con un medio conocido en sí después de la reacción objetivo, con lo cual se puede producir también el compuesto dentro del alcance de la presente invención.

El compuesto (VI–4) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

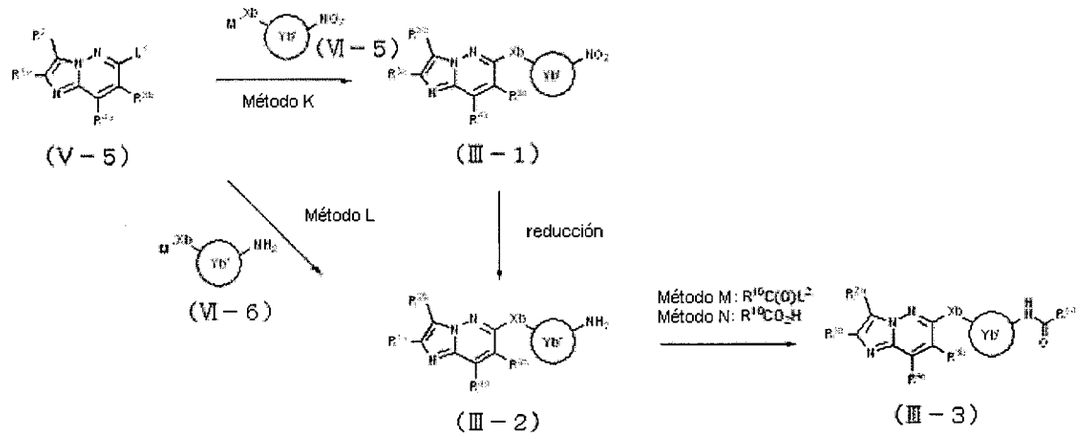
Método de producción 7

En el compuesto (III), cuando el sustituyente de amino

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sustituido opcionalmente para Yb es acilo, por ejemplo, el compuesto también se puede producir por medio del método indicado en el Esquema 7. Los compuestos (III–1), (III–2) y (III–3) están incluidos en el compuesto (III).

Esquema 7



en donde Yb' es un grupo cíclico de Yb, y los otros símbolos son como se definieron con anterioridad.

En el método K, el compuesto (III–2) se produce haciendo reaccionar primero el compuesto (V–5) con el compuesto (VI–5) en presencia de una base para dar el compuesto (III–1), y luego reduciendo nitro del compuesto (III–1). El compuesto (VI–5) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–5). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–5). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes

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ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–5) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, el método descrito en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares, o un método análogo. El compuesto obtenido (III–1) se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. De modo alternativo, se puede usar para la siguiente reacción después del aislamiento y la purificación de la mezcla de reacción de acuerdo con un método convencional. La reducción de nitro se puede llevar a cabo por un método en sí conocido, por ejemplo, el método descrito en la cuarta serie de experimentos químicos, vol. 20, 279–280, y similares, o un método análogo.

En el método L, el compuesto (III–2) se produce haciendo reaccionar el compuesto (V–5) con el compuesto (VI–6) en presencia de una base. El compuesto (VI–6) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–5). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 1 a 5 equivalentes, con preferencia, 1 a 2 equivalentes, respecto del compuesto (V–5). Esta reacción se lleva a cabo ventajosamente

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usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–6) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, el método descrito en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares, o un método análogo.

En el método M, el compuesto (III–3) se produce haciendo reaccionar el compuesto (III–2) con un compuesto representado por la fórmula $R^{10}C(O)L^2$. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–2). Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (III–2). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se puede

conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

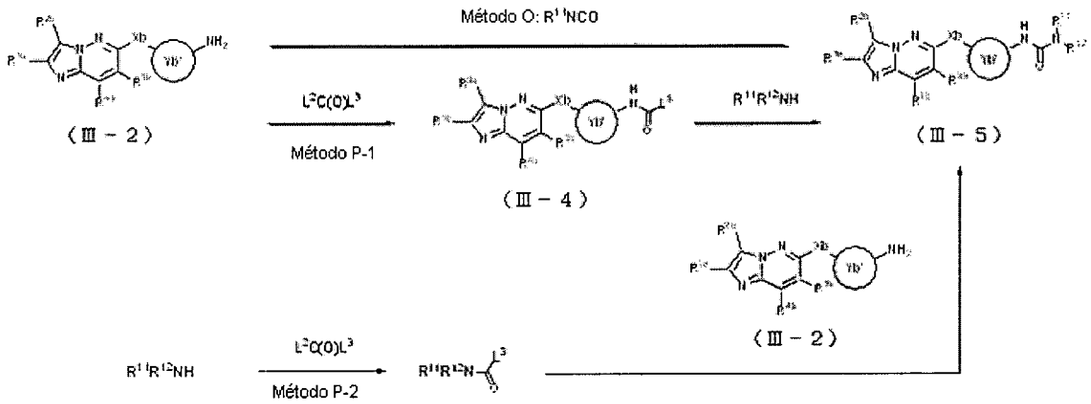
En el método N, el compuesto (III–3) se produce haciendo reaccionar el compuesto (III–2) con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (III–2) se hace reaccionar con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{10}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–2). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con preferencia, 1 a 5 equivalentes, respecto del compuesto (III–2). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del

compuesto (III–2). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (III–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El ácido carboxílico ($R^{10}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 8

El compuesto (III) en donde Yb está sustituido con ureído sustituido opcionalmente, y está sustituido opcionalmente también se puede producir, por ejemplo, por medio del método indicado en el Esquema 8. Los compuestos (III–2), (III–4) y (III–5) están incluidos en el compuesto (III).

Esquema 8



en donde cada símbolo es como se definió con anterioridad.

En el método O, el compuesto (III–5) se produce haciendo reaccionar el compuesto (III–2) con un derivado de isocianato ($R^{11}NCO$). El derivado de isocianato ($R^{11}NCO$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–2). Además, se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.01 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. Un derivado de isocianato ($R^{11}NCO$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en “Advanced Organic Chemistry, 4a. Ed.” (Jerry March), “Comprehensive Organic Transformations, 2a. Ed.” (Richard C. Larock), y similares o un

método análogo.

En el método P–1, el compuesto (III–5) se produce haciendo reaccionar primero el compuesto (III–2) con un compuesto representado por la fórmula $L^2C(O)L^3$ para dar el compuesto (III–4), y luego haciendo reaccionar el compuesto (III–4) con un derivado de amina ($R^{11}R^{12}NH$). El compuesto representado por la fórmula $L^2C(O)L^3$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–2). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $L^2C(O)L^3$ se puede conseguir en comercios, o se puede producir por un método en sí conocido. El compuesto obtenido (III–4) se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. Se puede usar para la siguiente reacción después del aislamiento y la purificación de la mezcla de reacción de acuerdo con un método convencional. Un derivado de amina ($R^{11}R^{12}NH$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–4). Se puede usar

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una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de amina ($R^{11}R^{12}NH$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método P–2, el compuesto (III–5) se produce haciendo reaccionar un derivado de amina ($R^{11}R^{12}NH$) con un compuesto representado por la fórmula $L^2C(O)L^3$ sucesivamente con el compuesto (III–2). El compuesto representado por la fórmula $L^2C(O)L^3$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del derivado de amina ($R^{11}R^{12}NH$). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes

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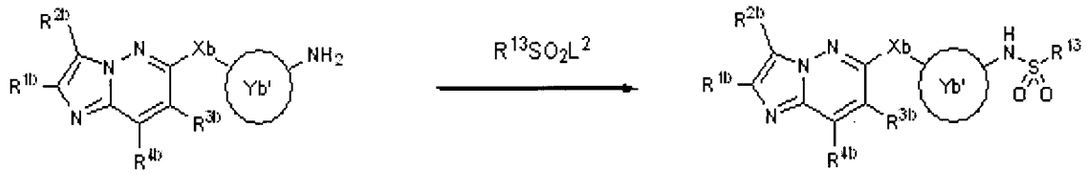
ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de amina ($R^{11}R^{12}NH$) y el compuesto representado por la fórmula $L^2C(O)L^3$ se puede conseguir en comercios, o se puede producir por un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo. El compuesto obtenido representado por la fórmula $R^{11}R^{12}NC(O)L^3$ se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. Se puede usar para la siguiente reacción después del aislamiento y la purificación de la mezcla de reacción de acuerdo con un método convencional. El compuesto (III–2) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto representado por la fórmula $R^{11}R^{12}NC(O)L^3$. Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C.

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Método de producción 9

El compuesto (III) en donde el sustituyente del amino sustituido opcionalmente para Yb es sulfonilo también se puede producir, por ejemplo, por medio del método indicado en el Esquema 9. El compuesto (III–6) está comprendido en el compuesto (III).

Esquema 9



(Ⅲ – 2) (Ⅲ – 6)

en donde cada símbolo es como se definió con anterioridad.

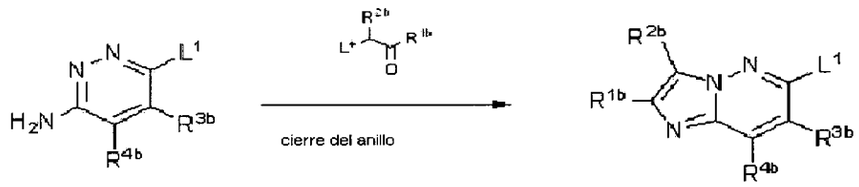
El compuesto (III–6) se puede producir haciendo reaccionar el compuesto (III–2) con un derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$). El derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (III–2). En el presente método, la reacción se lleva a cabo en general en presencia de una base, que no siempre es esencial. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto de compuesto (III–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en

general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado reactivo de ácido sulfónico ($R^{13}SO_2L^2$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 10

El compuesto (V–5) indicado en los Esquemas 6 y 7 se puede obtener, por ejemplo, por medio del método descrito en el documento WO00/23450 o un método análogo, y similares.

Esquema 10



(VII – 2) (V – 5)

en donde cada símbolo es como se definió con anterioridad.

El compuesto (V–5) se puede producir haciendo reaccionar el compuesto (VII–2) con derivado de carbonilo ($L^4CHR^{2b}C(O)R^{1b}$). Un derivado de carbonilo se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 5 equivalentes, respecto del compuesto (VII–2). Se puede usar una base en 0.1 a 10 equivalentes, con preferencia, 0.3 a 5 equivalentes, respecto del compuesto (VII–2). Como base, se pueden usar aquellas similares a las bases ejemplificadas en el Esquema 5. Esta reacción se lleva a cabo ventajosamente usando un

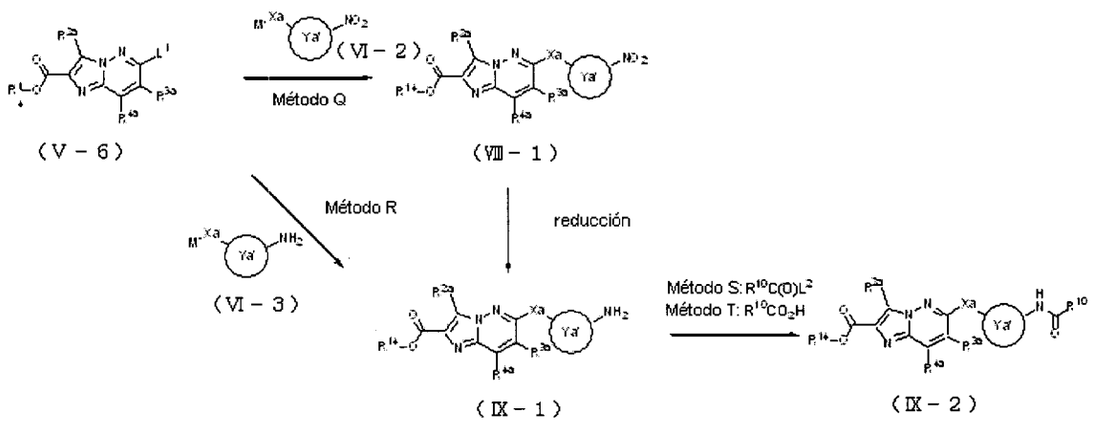
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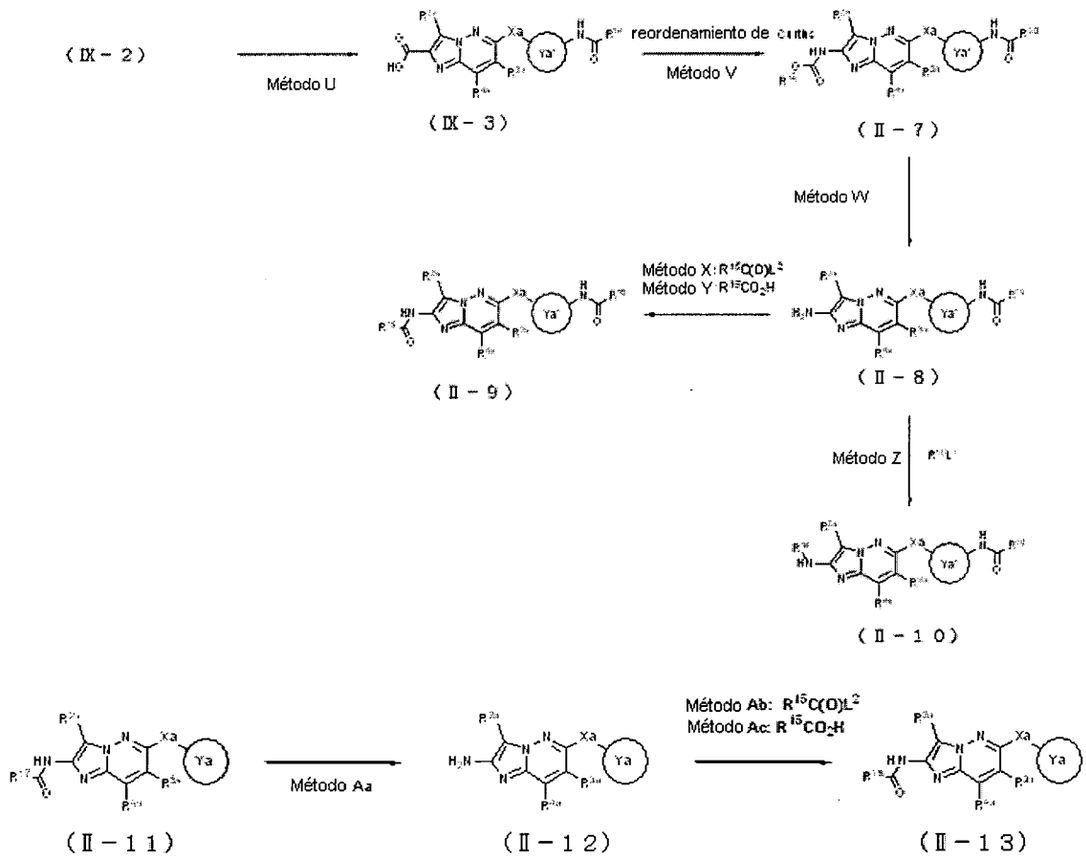
solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de carbonilo ($L^4CHR^{2b}C(O)R^{1b}$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 11

El compuesto (II) también se puede producir por medio del método indicado en el Esquema 11. Los compuestos (IX–1), (IX–2) y (IX–3) están incluidos en el compuesto (III), y compuestos (II–7), (II–8), (II–9), (II–10), (II–11), (II–12) y (II–13) están incluidos en el compuesto (II).

Esquema 11





en donde R^{16} es un arilo sustituido opcionalmente o grupo heterocíclico sustituido opcionalmente, R^{17} es un alquilo sustituido opcionalmente o cicloalquilo sustituido opcionalmente, y los otros símbolos son como se definieron con anterioridad.

R^{16} es un grupo que va a ser, como $R^{16}NH$–, el "arilamino sustituido opcionalmente" o "heterociclilamino sustituido opcionalmente" ejemplificado como un sustituyente preferible para el R^1 mencionado anteriormente.

R^{17} – es un grupo que va a ser, como $R^{17}CONH$–, el "alquilcarbonilamino sustituido opcionalmente" o "cicloalquilcarbonilamino sustituido opcionalmente" ejemplificado

como un sustituyente preferible para el R^1 antes mencionado.

En el método Q, el compuesto (IX–1) se produce haciendo reaccionar primero el compuesto (V–6) con el compuesto (VI–2) en presencia de una base para dar el compuesto (VIII–1), y luego reduciendo el grupo nitro del compuesto (VIII–1). El compuesto (VI–2) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–6). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–6). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–2) se puede conseguir en comercios, o se puede producir por un método en sí conocido. El compuesto obtenido (VIII–1) se puede usar en forma de una mezcla de reacción o un producto crudo para la siguiente reacción. Se puede usar para la siguiente reacción después del aislamiento y la purificación de la mezcla de reacción de acuerdo con un método convencional. El grupo nitro se puede reducir de acuerdo con un método en sí conocido, por ejemplo, el método descrito en la cuarta serie de experimentos químicos, vol. 20, 279–280, y similares, o un método análogo.

En el método R, el compuesto (IX–1) se produce haciendo reaccionar el compuesto (V–6) con el compuesto (VI–3) en presencia de una base. El compuesto (VI–3) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–6). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–6). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–3) se puede conseguir en comercios, o se puede producir por un método en sí conocido.

En el método S, el compuesto (IX–2) se produce haciendo reaccionar el compuesto (IX–1) con un compuesto representado por la fórmula $R^{10}C(O)L^2$. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (IX–1). Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (IX–1). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos

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similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $R^{10}C(O)L^2$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método T, el compuesto (IX–2) se produce haciendo reaccionar el compuesto (IX–1) con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (IX–1) se hace reaccionar con ácido carboxílico ($R^{10}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{10}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (IX–1). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con

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preferencia, 1 a 5 equivalentes, respecto del compuesto (IX–1). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (IX–1). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto de compuesto (IX–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El ácido carboxílico ($R^{10}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método U, el compuesto (IX–3) se produce al tratar el compuesto (IX–2) con una base o un ácido. Como base, se pueden mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, hidróxido de cesio, hidróxido de bario, y similares. Una base se usa

en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (IX–2). Como ácido, se pueden usar, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido trifluoroacético, y similares. Un ácido se usa en 0.1 a 20 equivalentes, con preferencia, 0.3 a 10 equivalentes, respecto del compuesto (IX–2). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1.

En el método V, el compuesto (II–7) se produce haciendo reaccionar el compuesto (IX–3) con azida de difenilfosforilo en presencia de una base. Se usa azida de difenilfosforilo en 0.1 a 10 equivalentes, con preferencia, 0.3 a 5 equivalentes, respecto del compuesto (IX–3). Como base, se pueden usar aquellas similares a las bases ejemplificadas en el Esquema 1. Como la base para este método, se prefieren, por ejemplo, trietilamina, N–etildiisopropilamina, N–metilmorfolina, piridina, y similares. Como solvente para esta reacción, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. Por ejemplo, se prefieren alcoholes tales como metanol, etanol, 2–propanol, 2–metil–2–propanol, y similares. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C.

En el método W, el compuesto (II–8) se produce al tratar el

compuesto (II–7) con una base o un ácido. Como base, se pueden mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, hidróxido de cesio, hidróxido de bario, y similares. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–7). Como ácido, se pueden usar, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido trifluoroacético, y similares. Un ácido se usa en 0.1 a 20 equivalentes, con preferencia, 0.3 a 10 equivalentes, respecto del compuesto (II–7). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1.

En el método X, el compuesto (II–9) se produce haciendo reaccionar el compuesto (II–8) con un compuesto representado por la fórmula $R^{15}C(O)L^2$. El compuesto representado por la fórmula $R^{15}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–8). La base se puede usar en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–8). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C,

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con preferencia, de –78 °C a 200 °C. El compuesto representado por la fórmula $R^{15}C(O)L^2$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método Y, el compuesto (II–9) se produce haciendo reaccionar el compuesto (II–8) con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (II–8) se hace reaccionar con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{15}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–8). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con preferencia, 1 a 5 equivalentes, respecto del compuesto (II–8). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10

equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–8). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. La base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–8). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El ácido carboxílico ($R^{15}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método Z, el compuesto (II–10) se produce haciendo reaccionar el compuesto (II–8) con un compuesto representado por la fórmula $R^{16}L^1$ en presencia de una base. El compuesto representado por la fórmula $R^{16}L^1$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–8). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como

solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, –78 °C a 200 °C. El compuesto representado por la fórmula $R^{16}L^1$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, el método descrito en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares, o un método análogo.

En el método Aa, el compuesto (II–12) se produce al tratar el compuesto (II–11) con una base o un ácido. Como base, se pueden mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, hidróxido de cesio, hidróxido de bario, y similares. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–11). Como ácido, se pueden usar, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido trifluoroacético, y similares. Un ácido se usa en 0.1 a 20 equivalentes, con preferencia, 0.3 a 10 equivalentes, respecto del compuesto (II–11). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1.

En el método Ab, el compuesto (II–13) se produce haciendo reaccionar el compuesto (II–12) con un compuesto representado por

la fórmula $R^{15}C(O)L^2$. El compuesto representado por la fórmula $R^{15}C(O)L^2$ se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–12). Se puede usar una base en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–12). Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. un compuesto representado por la fórmula $R^{15}C(O)L^2$ se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

En el método Ac, (II–13) se produce haciendo reaccionar el compuesto (II–12) con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación. Cuando el compuesto (II–12) se hace reaccionar con ácido carboxílico ($R^{15}CO_2H$) en presencia de un agente de condensación, se usa ácido carboxílico ($R^{15}CO_2H$) en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–12). Como agente de condensación, se pueden

usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con preferencia, 1 a 5 equivalentes, respecto del compuesto (II–12). De ser necesario, se puede usar un promotor de la condensación apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–12). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. La base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–12). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, –78 °C a 200 °C. El ácido carboxílico ($R^{15}CO_2H$) se puede conseguir en comercios, o se puede producir de acuerdo con

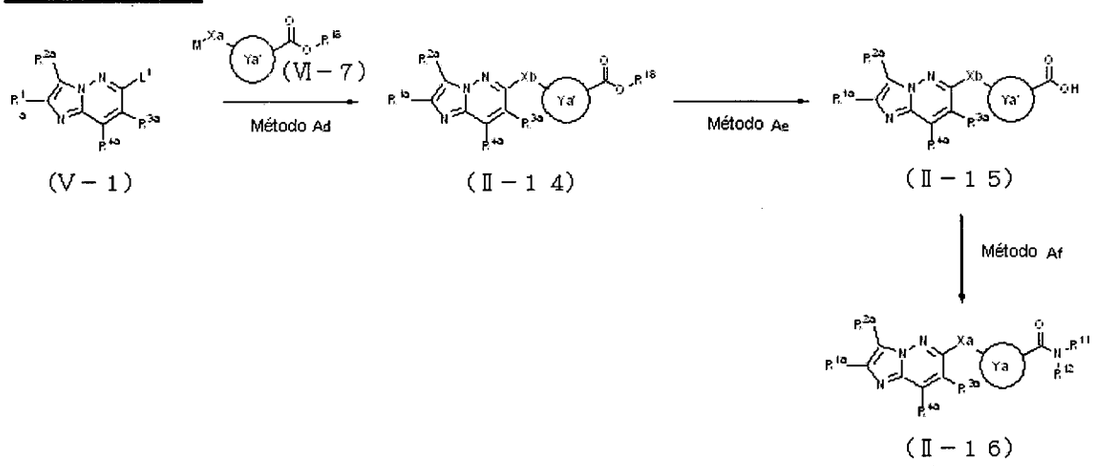
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un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 12

El compuesto (II) en donde Ya es sustituido con un aminocarbonilo sustituido opcionalmente, y está sustituido opcionalmente también se puede producir, por ejemplo, por medio del método indicado en el Esquema 12. Los compuestos (II–14), (II–15) y (II–16) están incluidos en el compuesto (II).

Esquema 12



en donde R^{18} es un grupo alquilo, y los otros símbolos son como se definieron con anterioridad.

Como el alquilo para R^{18}, se pueden mencionar, por ejemplo, metilo, etilo, propilo, isopropilo, tert-butilo, y similares.

En el método Ad, el compuesto (II–14) se puede producir haciendo reaccionar el compuesto (V–1) con el compuesto (VI–7). El compuesto (VI–7) se usa en 0.1 a 10 equivalentes, con preferencia,

0.3 a 3 equivalentes, respecto del compuesto (V–1). De ser necesario, se puede añadir una base. Como base, se pueden usar base inorgánica o base orgánica, y similares. Específicamente, se pueden usar, por ejemplo, carbonato de sodio, carbonato de potasio, carbonato de cesio, bicarbonato de sodio, trietilamina, N–etildiisopropilamina, N–metilmorfolina, 1,8–diazabiciclo[5,4,0]undec–7–eno, piridina, 4–(dimetilamino)piridina, N,N–dimetilanilina, metóxido de sodio, etóxido de sodio, tert-butóxido de potasio, hidruro de sodio, amida de sodio, diisopropilamida de litio, y similares. Estas bases se usan en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, –78 °C a 200 °C. El compuesto (VI–7) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo. La reacción se puede llevar a cabo usando un sintetizador de microondas.

En el método Ae, el compuesto (II–15) se produce al tratar el compuesto (II–14) con una base o un ácido. Como base, se pueden

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mencionar, por ejemplo, hidróxido de sodio, hidróxido de potasio, hidróxido de cesio, hidróxido de bario, y similares. Una base se usa en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–14). Como ácido, se pueden usar, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido trifluoroacético, y similares. Un ácido se usa en 0.1 a 20 equivalentes, con preferencia, 0.3 a 10 equivalentes, respecto del compuesto (II–14). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los ejemplificados en el Esquema 1.

En el método Af, el compuesto (II–16) se produce haciendo reaccionar el compuesto (II–15) con un derivado de amina ($R^{11}R^{12}NH$) con un agente de condensación. El derivado de amina ($R^{11}R^{12}NH$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–15). Como agente de condensación, se pueden usar, por ejemplo, clorhidrato de 1–etil–1–(3–dimetilaminopropil)carbodiimida, 1,3–diciclohexilcarbodiimida, cianofosfato de dietilo, azida de difenilfosforilo, 1,1'–carbonildiimidazol, hexafluorofosfato de benzotriazol–1–iloxitripirrolidinofosfonio, hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio, hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio, y similares. Estos agentes de condensación se usan en 1 a 10 equivalentes, con preferencia, 1 a 5 equivalentes, respecto del compuesto (II–15). De ser necesario, se puede usar un promotor de la condensación

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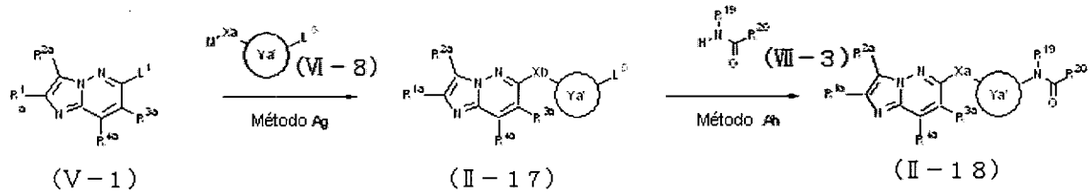
apropiado (por ejemplo, 1–hidroxibenzotriazol, N–hidroxisuccinimida, etc.). Estos promotores de la condensación se usan en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (II–15). Esta reacción puede proseguir más suavemente cuando se añade una base. Como base, se pueden usar aquellas similares a la base ejemplificada en el Esquema 1. Estas bases se usan en 0.01 a 10 equivalentes, con preferencia, 0.03 a 5 equivalentes, respecto del compuesto (II–15). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de amina ($R^{11}R^{12}NH$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 13

El compuesto (II) en donde Ya es sustituido con amida opcionalmente sustituida, y también está sustituido opcionalmente, también se puede producir por medio del método indicado en el Método de producción 2, así como, por ejemplo, en el Esquema 13. Los compuestos (II–17) y (II–18) están incluidos en el compuesto (II).

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Esquema 13



(V-1) (II-17) (II-18)

en donde L^5 es un grupo saliente, R^{19} y R^{20} son, como $-NR^{19}C(O)R^{20}$, cada uno un grupo amino sustituido como tal con el "alquil C_{1-8}–carbonilo, alquenil C_{2-8}–carbonilo, alquinil C_{2-8}–carbonilo, cicloalquil C_{3-8}–carbonilo, cicloalquenil C_{3-8}–carbonilo, aril C_{6-18}–carbonilo, aril C_{6-18}–alquil C_{1-4}–carbonilo o heterociclil–carbonilo, cada uno de los cuales está sustituido opcionalmente" como el sustituyente en el anillo Y antes mencionado, y los otros símbolos son como se definieron con anterioridad.

Como el grupo saliente para L^5, se puede usar un átomo de halógeno.

En el método Ag, el compuesto (II–17) se puede producir haciendo reaccionar el compuesto (V–1) con el compuesto (VI–8). El compuesto (VI–8) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (V–1). De ser necesario, se puede añadir una base. Como base, se pueden usar base inorgánica o base orgánica, y similares. Específicamente, se pueden mencionar, por ejemplo, carbonato de sodio, carbonato de potasio, carbonato de cesio, bicarbonato de sodio, trietilamina, N–etildiisopropilamina, N–metilmorfolina, 1,8–diazabiciclo[5,4,0]undec–7–eno, piridina, 4–(dimetilamino)piridina, N,N–dimetilanilina, metóxido de sodio, etóxido de sodio, tert-butóxido de potasio, hidruro

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de sodio, amida de sodio, diisopropilamida de litio, y similares. Estas bases se usan en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (V–1). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VI–8) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, el método descrito en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo. La reacción se puede llevar a cabo usando un sintetizador de microondas.

En el método Ah, el compuesto (II–18) se puede producir haciendo reaccionar el compuesto (II–17) con el compuesto (VII–3) bajo un catalizador de cobre. El compuesto (II–3) se usa en 0.1 a 10 equivalentes, con preferencia, 0.3 a 3 equivalentes, respecto del compuesto (VII–17). Como el catalizador de cobre, se pueden usar, por ejemplo, yoduro de cobre y trifluorometansulfonato de cobre (II). De ser necesario, se puede añadir una base. Como base, se pueden usar, por ejemplo, carbonato de sodio, carbonato de potasio, carbonato de cesio, bicarbonato de sodio, metóxido de sodio, etóxido de sodio, tert-butóxido de potasio, tert-butóxido de sodio, fosfato de

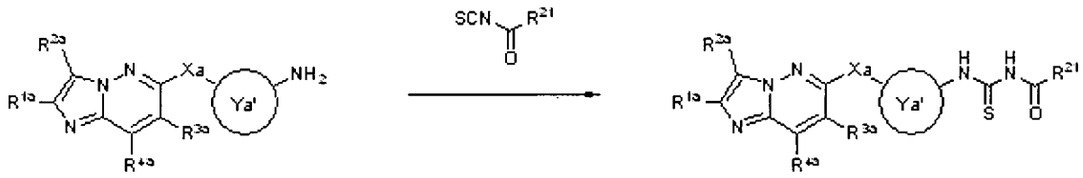
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potasio tribásico, trans–1,2–ciclohexandiamina, 1,10–fenantrolina, N,N–dimetiletilendiamina, y similares. Estas bases se usan en 1 a 30 equivalentes, con preferencia, 1 a 10 equivalentes, respecto del compuesto (II–17). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El compuesto (VII–3) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido, por ejemplo, los métodos descritos en "Advanced Organic Chemistry, 4a. Ed." (Jerry March), "Comprehensive Organic Transformations, 2a. Ed." (Richard C. Larock), y similares o un método análogo.

Método de producción 14

El compuesto (II) en donde Ya es sustituido con aciltioureído sustituido opcionalmente y está sustituido opcionalmente también se puede producir, por ejemplo, por medio del método indicado en el Esquema 14. El compuesto (II–19) está comprendido en el compuesto (II).

Esquema 14



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en donde R^{21} es, como $-C(S)NHC(O)R^{21}$, un grupo que se vuelve el "amino sustituido con sustituido opcionalmente aminotiocarbonilo" como el sustituyente en el anillo Y antes mencionado, y los otros símbolos son como se definieron con anterioridad.

El compuesto (II–19) se puede producir haciendo reaccionar el compuesto (II–2) con un derivado de aciltiocianato ($R^{21}C(O)NCS$). El derivado de aciltiocianato ($R^{21}C(O)NCS$) se usa en 0.1 a 10 equivalentes, con preferencia, 0.5 a 5 equivalentes, respecto del compuesto (II–19). Esta reacción se lleva a cabo ventajosamente usando un solvente inerte a la reacción. Como solvente, se pueden usar aquellos similares a los solventes ejemplificados en el Esquema 1. El tiempo de reacción varía generalmente de 1 min a 200 h, con preferencia, de 10 min a 100 h. La temperatura de reacción varía, en general, de –100 °C a 250 °C, con preferencia, de –78 °C a 200 °C. El derivado de aciltiocianato ($R^{21}C(O)NCS$) se puede conseguir en comercios, o se puede producir de acuerdo con un método en sí conocido.

También es posible producir un compuesto comprendido en el alcance de la presente invención sometiendo los compuestos (I) – (IV) (por ejemplo, el compuesto (II) y el compuesto (III) obtenidos por medio del método antes mencionado) por introducción de sustituyentes y conversión del grupo funcional por un medio en sí conocido. Para la conversión del sustituyente, se puede usar un método convencional conocido. Por ejemplo, se pueden mencionar

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conversión en carboxi por hidrólisis del éster, conversión en carbamoílo por amidación de carboxi, conversión en hidroximetilo por reducción de carboxi, conversión en compuesto alcohólico por reducción o alquilación de carbonilo, aminación reductiva de carbonilo, oximación de carbonilo, acilación, ureación, sulfonilación o alquilación de amino, sustitución y aminación de halógeno activo por amina, aminación por reducción de nitro, alquilación de hidroxi, sustitución y aminación de hidroxi, y similares. Cuando está presente un sustituyente reactivo que causa una reacción no objetivo durante la introducción de sustituyentes y la conversión de grupos funcionales, se introduce un grupo protector con anterioridad en el sustituyente reactivo a través de un medio conocido en sí, y el grupo protector se elimina con un medio conocido en sí después de la reacción objetivo, tras lo cual también se puede producir un compuesto dentro del alcance de la presente invención.

Los compuestos (I) – (IV) (por ejemplo, el compuesto (II) y el compuesto (III) obtenidos en el método antes mencionado) se pueden aislar y purificar por un medio en sí conocido, como transferencia de fases, concentración, extracción del solvente, fraccionamiento, conversión de líquidos, cristalización, recristalización, cromatografía, y similares. Cuando los compuestos (I) – (IV) se obtienen como compuestos libres, se pueden convertir en las sales deseadas por un método en sí conocido o una de sus modificaciones; por el contrario, cuando los compuestos se obtienen como sales, se pueden convertir en formas libres u otras sales

deseadas por un método en sí conocido o una de sus modificaciones.

Los compuestos (I) – (IV) (en lo sucesivo mencionados como compuesto (I) y similares) se pueden usar como profármacos. Un profármaco del compuesto (I), y similares significa un compuesto que se convierte en el compuesto (I), y similares por reacción debida a una enzima, un ácido gástrico, etc. en la condición fisiológica en el organismo viviente, es decir, un compuesto que se convierte en el compuesto (I) y similares con oxidación, reducción, hidrólisis, etc. debido a una enzima; un compuesto que se convierte en el compuesto (I), y similares por hidrólisis, etc. debido a ácido gástrico, y similares.

Un profármaco del compuesto (I), y similares puede ser un compuesto obtenido al someter un grupo amino en el compuesto (I), y similares a una acilación, alquilación o fosforilación (por ejemplo, un compuesto obtenido al someter un grupo amino en el compuesto (I), y similares a una eicosanoilación, alanilación, pentilaminocarbonilación, (5–metil–2–oxo–1,3–dioxolen–4–il)metoxicarbonilación, tetrahidrofuranoilación, pirrolidilmetilación, pivaloiloximetilación o tert-butilación); un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) y similares a una acilación, alquilación, fosforilación o boración (por ejemplo, un compuesto obtenido al someter un grupo hidroxi en el compuesto (I) y similares a una acetilación, palmitoilación, propanoilación, pivaloilación, succinilación, fumarilación, alanilación o dimetilaminometilcarbonilación); un compuesto obtenido al someter

un carboxi en el compuesto (I), y similares a una esterificación o amidación (por ejemplo, un compuesto obtenido al someter un carboxi en el compuesto (I), y similares a una etilesterificación, fenilesterificación, carboximetilesterificación, dimetilaminometilesterificación, pivaloiloximetilesterificación, etoxicarboniloxietilesterificación, ftalidilesterificación, (5–metil–2–oxo–1,3–dioxolen–4–il)metilesterificación, ciclohexiloxicarboniletilesterificación o metilamidación), y similares. Cualquiera de estos compuestos se puede producir a partir del compuesto (I), y similares por un método en sí conocido.

Un profármaco del compuesto (I) y similares también puede ser uno que se convierte en el compuesto (I) en una condición fisiológica, por ejemplo las descritas en *IYAKUHIN no KAIHATSU* (Development of Pharmaceuticals), Vol. 7, Design of Molecules, p, 163–198, publicado por HIROKAWA SHOTEN (1990).

Cuando el compuesto (I), y similares tienen isómeros tales como un isómero óptico, estereoisómero, isómero, posicional, isómero rotacional, y similares, cualquier isómero y sus mezclas están incluidos en el compuesto (I), y similares. Por ejemplo, cuando el compuesto (I), y similares tienen un isómero óptico, un isómero óptico separado de un racemato también está comprendido en el compuesto (I), y similares. Estos isómeros se pueden obtener como productos independientes por medio de un medio de síntesis o un medio de separación (concentración, extracción del solvente, cromatografía en columna, recristalización, y similares) conocidos

per se.

El compuesto (I), y similares pueden ser un cristal, y tanto un cristal individual como mezclas cristalinas están incluidos en el compuesto (I), y similares. Los cristales se pueden producir por cristalización de acuerdo con métodos de cristalización conocidos *per se*.

El compuesto (I), y similares pueden ser un cocristal.

El compuesto (I), y similares pueden ser un solvato (por ejemplo, hidrato, etc.) o un no solvato, los cuales están incluidos ambos en el compuesto (I), y similares.

Un compuesto marcado con un isótopo (por ejemplo, ^{3}H, ^{14}C, ^{35}S, ^{125}I etc.) también está incluido en el compuesto (I), y similares.

Los compuestos (I) – (IV) de la presente invención, una de sus sales y uno de sus profármacos (en lo sucesivo, abreviados a veces como el compuesto de la presente invención) tienen, por ejemplo, actividad inhibidora de la fosforilación contra una quinasa que tiene esta acción de fosforilación. Tal como se usa en la presente, la quinasa comprende no sólo una sustancia que tiene una acción de fosforilación en sí mismo como un todo, sino también una sustancia una de cuyas partes tiene una acción de fosforilación. La acción de fosforilación que tienen las quinasas comprende tanto una acción de fosforilación en sí misma como en otras sustancias.

Los ejemplos de quinasas incluyen receptor del factor de crecimiento endotelial vascular (VEGFR), receptor del factor de crecimiento derivado de plaquetas (PDGFR), Raf, y similares. Los

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ejemplos del receptor del factor de crecimiento endotelial vascular (VEGFR) incluyen receptor del factor de crecimiento endotelial vascular 1 (VEGFR1, Flt–1), receptor del factor de crecimiento endotelial vascular 2 (VEGFR2, KDR, Flk–1), receptor del factor de crecimiento endotelial vascular 3 (VEGFR3, Flt–4), y similares. De ellos, es preferible receptor del factor de crecimiento endotelial vascular 2 (VEGFR2). Los ejemplos del receptor del factor de crecimiento derivado de plaquetas (PDGFR) incluyen receptor del factor de crecimiento derivado de plaquetas α (PDGFRα), receptor del factor de crecimiento derivado de plaquetas β (PDGFRβ), y similares. Los ejemplos del Raf incluyen A–Raf, B–Raf, C–Raf, y similares. En particular, como quinasa, se prefieren receptor del factor de crecimiento endotelial vascular 2 (VEGFR2), receptor del factor de crecimiento derivado de plaquetas (PDGFR) y Raf.

Además de ellos, se prefieren como quinasas la tirosina quinasa con dominios de homología Ig y EGF 2 (TIE2), receptor del factor de crecimiento de fibroblastos 1 (FGFR1), receptor del factor de crecimiento de fibroblastos 2 (FGFR2), receptor del factor de crecimiento de fibroblastos 3 (FGFR3), receptor del factor de crecimiento de fibroblastos 4 (FGFR4), receptor del factor de células madre (c–Kit), Aurora A, Aurora B, CDK, MEK1, MEK2, Akt, ERK, MAPK, Src, MET, receptor del factor de crecimiento epitelial (EGFR), receptor del factor de crecimiento epitelial humano 2 (HER2), receptor del factor de crecimiento epitelial humano 4 (HER4), Abl, Fgr, Fms, y similares.

Por ejemplo, la actividad inhibidora del receptor del factor de crecimiento endotelial vascular 2 del compuesto de la presente invención se puede determinar de acuerdo con el Ejemplo de ensayo 1, la actividad inhibidora del crecimiento de células endoteliales vasculares se puede determinar de acuerdo con el Ejemplo de ensayo 2, la actividad antitumoral se puede determinar de acuerdo con el Ejemplo de ensayo 3, la actividad inhibidora del receptor del factor de crecimiento derivado de plaquetas α se puede determinar de acuerdo con el Ejemplo de ensayo 4, la actividad inhibidora del receptor del factor de crecimiento derivado de plaquetas β se puede determinar de acuerdo con el Ejemplo de ensayo 5, y la actividad inhibidora de B–Raf se puede determinar de acuerdo con el Ejemplo de ensayo 6.

El compuesto de la presente invención muestra particularmente una potente actividad inhibidora del receptor del factor de crecimiento endotelial vascular (VEGFR), y específicamente una alta selectividad por el receptor del factor de crecimiento endotelial vascular 2 (VEGFR2, KDR, Flk–1) y una potente actividad inhibidora de quinasas por VEGFR1, PDGFR, y Raf. Además, como el compuesto de la presente invención también es superior en eficacia, propiedades farmacocinéticas (absorción, distribución, metabolismo, excreción, etc.), solubilidad (hidrosolubilidad, etc.), interacción con otros productos farmacéuticos, seguridad (toxicidad aguda, toxicidad crónica, toxicidad genética, toxicidad reproductiva, cardiotoxicidad, carcinogenicidad, etc.) y estabilidad (estabilidad química, estabilidad

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enzimática, etc.), es de utilidad como agente farmacéutico.

Conforme a ello, el compuesto de la presente invención es de utilidad como un inhibidor de quinasa, con preferencia, un inhibidor del receptor del factor de crecimiento endotelial vascular (VEGFR), un inhibidor del receptor del factor de crecimiento derivado de plaquetas (PDGFR), un inhibidor de Raf, con mayor preferencia, un inhibidor del receptor del factor de crecimiento endotelial vascular 2 (VEGFR2, KDR, Flk–1) para un mamífero (por ejemplo, ratón, rata, hámster, conejo, gato, perro, bovino, oveja, mono, ser humano, etc.). Además, el compuesto de la presente invención es de utilidad como un inhibidor de angiogénesis o un inhibidor del crecimiento celular endotelial vascular. El compuesto de la presente invención se usa como un agente farmacéutico como un agente para la prevención o el tratamiento de enfermedades posiblemente afectadas por un factor del crecimiento endotelial vascular, por ejemplo, cáncer [por ejemplo, cáncer colorrectal (por ejemplo, cáncer colorrectal familiar, cáncer colorrectal sin poliposis hereditario, tumor del estroma gastrointestinal, etc.), cáncer de pulmón (por ejemplo, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, mesotelioma maligno, etc.), mesotelioma, cáncer pancreático (por ejemplo, cáncer del tubo pancreático, etc.), cáncer gástrico (por ejemplo, adenocarcinoma papilar, adenocarcinoma mucino, cáncer adenoescamoso, etc.), cáncer de mama (por ejemplo, carcinoma ductal invasivo, cáncer ductal in situ, cáncer de mama inflamatorio, etc.), cáncer de ovario (por ejemplo, cáncer ovárico

epitelial, tumor de células germinales extragonadales, tumor de células germinales ováricas, tumor potencial ovárico de baja malignidad, etc.), cáncer de próstata (por ejemplo, cáncer de próstata dependiente de hormonas, cáncer de próstata no dependiente de hormonas, etc.), cáncer de hígado (por ejemplo, cáncer de hígado primario, cáncer del conducto biliar extrahepático, etc.), cáncer tiroides (por ejemplo, cáncer de tiroides medular, etc.), cáncer de riñón (por ejemplo, carcinoma de células renales, cáncer de células pélvicas renales y transicionales de uréter, etc.), cáncer uterino, tumor cerebral (por ejemplo, astrocitoma pineal, astrocitoma policítico, astrocitoma difuso, astrocitoma anaplásico, etc.), melanoma, sarcoma, cáncer de vejiga, cáncer sanguíneo incluso mieloma múltiple, etc.], retinopatía diabética, artritis reumatoidea, psoriasis, aterosclerosis, sarcoma de Kaposi, EPOC, dolor, asma, endometriosis, nefritis, inflamación tales como osteoartritis, y similares e hipertensión, un inhibidor del crecimiento del cáncer, un supresor de la metástasis cancerosa, un promotor de la apoptosis, y similares. De ellos, es efectivo, por ejemplo, para cáncer colorrectal, cáncer de pulmón, cáncer pancreático, cáncer gástrico, cáncer de mama, cáncer de ovario, cáncer de próstata, cáncer de hígado, cáncer de tiroides, cáncer de riñón, tumor cerebral, melanoma, cáncer de vejiga y cáncer de la sangre. En particular, el compuesto de la presente invención es efectivo para pacientes con cáncer de pulmón, cáncer colorrectal, cáncer de ovario, cáncer de próstata o cáncer de riñón.

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El compuesto de la presente invención se puede administrar por vía oral o parenteral como tal o en una mezcla con un portador farmacológicamente aceptable.

La forma de dosificación del compuesto de la presente invención para la administración oral es, por ejemplo, comprimido (incluso comprimido recubierto con azúcar, comprimido recubierto con película), píldora, gránulo, polvo, cápsula (incluso cápsula blanda, microcápsula), jarabe, emulsión, suspensión, y similares, y la forma de dosificación para la administración parenteral es, por ejemplo, inyección, agente inyectable, instilación, supositorio, y similares. Además, es efectivo para producir una preparación de liberación prolongada al combinar el compuesto con una base apropiada (por ejemplo, polímero de ácido butírico, polímero de ácido glicólico, copolímero de ácido butírico–ácido glicólico, una mezcla de un polímero de ácido butírico y un polímero de ácido glicólico, éster de ácido graso de poliglicerol, etc.).

Como método para producir el compuesto de la presente invención en la forma de dosificación antes mencionada, se puede usar un método de producción conocido generalmente empleado en el campo pertinente. Cuando se produce la forma de dosificación antes mencionada, se añaden apropiadamente cantidades adecuadas de aditivos tales como excipiente, aglutinante, desintegrante, lubricante, endulzante, tensoactivo, agente de suspensión, emulsionante, y similares, generalmente usados en el campo pertinente, como necesarios para la producción.

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Cuando el compuesto de la presente invención se prepara en un comprimido, por ejemplo, se puede producir añadiendo un excipiente, un aglutinante, un desintegrante, un lubricante, y similares, y cuando se debe preparar una píldora o un gránulo, se pueden producir añadiendo un excipiente, un aglutinante, un desintegrante, y similares. Cuando se deben preparar un polvo o una cápsula, se pueden producir añadiendo un excipiente, y similares, cuando se debe preparar un jarabe, se puede producir añadiendo un endulzante, y similares, y cuando se debe preparar una emulsión o una suspensión, se puede producir añadiendo un agente de suspensión, un tensoactivo, un emulsionante, y similares.

Los ejemplos de excipiente incluyen lactosa, sacarosa, glucosa, almidón, sacarosa, celulosa microcristalina, glicirriza en polvo, manitol, hidrógeno–carbonato de sodio, fosfato de calcio, sulfato de calcio, y similares.

Los ejemplos de aglutinante incluyen 5 – 10% en peso de pasta de almidón líquida, 10 – 20% en peso de solución de goma arábiga o solución de gelatina, 1 – 5% en peso de solución de tragacanto, solución de carboximetilcelulosa, solución de alginato de sodio, glicerina, y similares.

Los ejemplos del desintegrante incluyen almidón, carbonato de calcio, y similares.

Los ejemplos del lubricante incluyen estearato de magnesio, ácido esteárico, estearato de calcio, talco purificado, y similares.

Los ejemplos del endulzante incluyen glucosa, fructosa, azúcar

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invertida, sorbitol, xilitol, glicerina, jarabe simple, y similares.

Los ejemplos del agente tensoactivo incluyen laurilsulfato sódico, polisorbato 80, éster de ácido monograso de sorbitano, estearato de polioxilo 40, y similares.

Los ejemplos del agente de suspensión incluyen goma arábiga, alginato de sodio, carboximetilcelulosa sódica, metilcelulosa, bentonita, y similares.

Los ejemplos del emulsionante incluyen goma arábiga, tragacanto, gelatina, polisorbato 80, y similares.

Por otra parte, cuando el compuesto de la presente invención se produce en la forma de dosificación antes mencionada, se puede añadir a demanda una cantidad apropiada de un agente colorante, un conservante, una sustancia aromática, un correctivo, un estabilizante, un espesante y similares, típicamente usados en el campo de la preparación.

Como inyección, se mencionan inyección intravenosa, así como inyección subcutánea, inyección intracutánea, inyección intramuscular, instilación, y similares, y como preparación de liberación prolongada, se mencionan un agente transdérmico de iontoforesis, y similares.

Estas inyecciones se preparan por medio de métodos conocidos en sí, o por disolución, suspensión o emulsión del compuesto de la presente invención en un líquido acuoso u oleoso esterilizado. Como un líquido acuoso para inyección, se pueden mencionar solución fisiológica, soluciones isotónicas que contienen

glucosa u otros fármacos auxiliares (por ejemplo, D–sorbitol, D–manitol, cloruro de sodio, y similares), y otros, y se pueden usar en combinación con auxiliares de disolución apropiados, tales como alcoholes (por ejemplo, etanol), polialcoholes (por ejemplo, propilenglicol, polietilenglicol), tensoactivos no iónicos (por ejemplo, polisorbato 80, HCO–50), y similares. Como un líquido oleoso, se pueden mencionar aceite de sésamo, aceite de frijol de soya, y similares, que se pueden usar en combinación con auxiliares de disolución tales como benzoato de bencilo, alcohol bencílico, y similares. Además, se pueden mencionar buffers (por ejemplo, buffer de fosfato, buffer de acetato de sodio), agentes suavizantes (por ejemplo, cloruro de benzalconio, clorhidrato de procaína, y similares), estabilizantes (por ejemplo, albúmina de suero humano, polietilenglicol, y similares), conservantes (por ejemplo, alcohol bencílico, fenol, y similares), y otros. Una inyección preparada está envasada generalmente en una ampolla.

Si bien el contenido del compuesto de la presente invención en el agente farmacéutico de la presente invención varía de acuerdo con la forma de la preparación farmacéutica, generalmente es de aproximadamente el 0.01 al 100% en peso, con preferencia, de aproximadamente el 2 al 85% en peso, con mayor preferencia, de aproximadamente el 5 al 70% en peso, respecto de toda la preparación.

Si bien el contenido del aditivo en el agente farmacéutico de la presente invención varía según la forma de la preparación

farmacéutica, generalmente es de aproximadamente el 1 al 99.9% en peso, con preferencia, de aproximadamente el 10 al 90% en peso, respecto de toda la preparación.

El compuesto de la presente invención es estable y de baja toxicidad, y se puede usar de manera segura. Como la dosis diaria varía según la condición y el peso corporal de los pacientes, el tipo de compuesto, la vía de administración, y similares, en el caso de, por ejemplo, una administración oral a pacientes para el tratamiento del cáncer, la dosis diaria para un adulto (peso corporal de aproximadamente 60 kg) es de aproximadamente 1 a 1000 mg, con preferencia, de aproximadamente 3 a 300 mg, con mayor preferencia, de aproximadamente 10 a 200 mg, como ingrediente activo (el compuesto de la presente invención), que se puede dar en una sola administración o administrado en 2 ó 3 porciones por día.

Cuando el compuesto de la presente invención se administra por vía parenteral, varía en general administrado en forma de un líquido (por ejemplo, inyección). Como la dosis varía según el sujeto de administración, el órgano blanco, el síntoma, el método de administración, y similares, varía, por ejemplo, de aproximadamente 0,01 mg a aproximadamente 100 mg, con preferencia, de aproximadamente 0.01 a aproximadamente 50 mg, con mayor preferencia, de aproximadamente 0.01 a aproximadamente 20 mg, en forma de una inyección, respecto de 1 kg de peso corporal, que se administra con preferencia por inyección intravenosa.

El compuesto de la presente invención se puede usar

concurrentemente con otros fármacos. Para ser específicos, el compuesto de la presente invención se puede usar junto con medicamentos tales como agentes terapéuticos hormonales, agentes quimioterapéuticos, agentes inmunoterapéuticos, agentes farmacéuticos que inhiben la acción de los factores de crecimiento celular o los receptores del factor de crecimiento celular, y similares. A continuación, los fármacos que se pueden usar en combinación con el compuesto de la presente invención se abrevian como fármacos concomitantes.

Los ejemplos de "agentes terapéuticos hormonales" incluyen fosfoestrol, dietilestilbestrol, clorotrianiseno, acetato de medroxiprogesterona, acetato de megestrol, acetato de clormadinona, acetato de ciproterona, danazol, alilestrenol, gestrinona, mepartricina, raloxifeno, ormeloxifeno, levormeloxifeno, antiestrógenos (por ejemplo, citrato de tamoxifeno, citrato de toremifeno, y similares), preparaciones en píldora, mepitiostano, testrolactona, aminoglutetimida, agonistas de LH–RH (por ejemplo, acetato de goserelina, buserelina, leuprorelina, y similares), droloxifeno, epitiostanol, sulfonato de etinilestradiol, inhibidores de aromatasa (por ejemplo, clorhidrato de fadrozol, anastrozol, retrozol, exemestano, vorozol, formestano, y similares), antiandrógenos (por ejemplo, flutamida, bicartamida, nilutamida, y similares), inhibidores de 5α–reductasa (por ejemplo, finasterida, epristerida, y similares), fármacos hormonales de la corteza suprarrenal (por ejemplo, dexametasona, prednisolona, betametasona, triamcinolona, y

similares), inhibidores de la síntesis de andrógenos (por ejemplo, abiraterona, y similares), retinoides y fármacos que retardan el metabolismo de los retinoides (por ejemplo, liarozol, y similares), y similares.

Los ejemplos de "agentes quimioterapéuticos" incluyen agentes de alquilación, antimetabolitos, antibióticos anticancerosos, agentes anticancerígenos derivados de plantas, y similares.

Los ejemplos de "agentes de alquilación" incluyen mostaza nitrogenada, clorhidrato de N–óxido de mostaza nitrogenada, clorambutilo, ciclofosfamida, ifosfamida, tiotepa, carbocuona, tosilato de improsulfano, busulfano, clorhidrato de nimustina, mitobronitol, melfalano, dacarbazina, ranimustina, fosfato de estramustina sódica, trietilenemelamina, carmustina, lomustina, estreptozocina, pipobromano, etoglúcido, carboplatino, cisplatino, miboplatino, nedaplatino, oxaliplatino, altretamina, ambamustina, clorhidrato de dibrospidio, fotemustina, prednimustina, pumitepa, ribomustina, temozolomida, treosulfano, trofosfamida, estimalámero de zinostatina, adozelesina, cistemustina, bizelesina, preparaciones DDS de ellos, y similares.

Los ejemplos de "antimetabolitos" incluyen mercaptopurina, ribósido de 6–mercaptopurina, tioinosina, metotrexato, pemetrexed, enocitabina, citarabina, octofosfato de citarabina, clorhidrato de ancitabina, fármacos 5–FU (por ejemplo, fluorouracilo, tegafur, UFT, doxifluridina, carmofur, galocitabina, emitefur, capecitabina, y similares), aminopterina, nelzarabina, leucovorina cálcica, tabloide,

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butocina, folinato cálcico, levofolinato cálcico, cladribina, emitefur, fludarabina, gemcitabina, hidroxicarbamida, pentostatina, piritrexima, idoxuridina, mitoguazona, tiazofrina, ambamustina, bendamustina, sus preparaciones de DDS y similares.

Los ejemplos del "antibióticos anticancerosos" incluyen actinomicina–D, actinomicina–C, mitomicina–C, cromomicina–A3, clorhidrato de bleomicina, sulfato de bleomicina, sulfato de peplomicina, clorhidrato de daunorrubicina, clorhidrato de doxorrubicina, clorhidrato de aclarrubicina, clorhidrato de pirarrubicina, clorhidrato de epirrubicina, neocarzinostatina, mitramicina, sarcomicina, carzinofilina, mitotano, clorhidrato de zorrubicina, clorhidrato de mitoxantrono, clorhidrato de idarrubicina, sus preparaciones de DDS, y similares.

Los ejemplos de "agentes anticancerígenos derivados de plantas" incluyen etopósido, fosfato de etopósido, sulfato de vinblastina, sulfato de vincristina, sulfato de vindesina, tenipósido, paclitaxel, docetaxel, vinorelbina, sus preparaciones de DDS, y similares.

Los ejemplos de "agentes inmunoterapéuticos (BRM)" incluyen picibanilo, crestina, sizofirano, lentinano, ubenimex, interferones, interleuquinas, factor estimulantes de colonias de macrófagos, factor estimulante de colonias de granulocitos, eritropoyetina, linfotoxina, vacuna BCG, *Corinebacterium parvum*, levamisol, polisacárido K, procodazol, anticuerpo anti–CTLA4, y similares.

Los ejemplos del "factor de crecimiento celular" en los "agentes

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farmacéuticos que inhiben la acción de factores de crecimiento celular o receptores de factores de crecimiento celular" incluyen cualquier sustancia que favorece la proliferación celular, que normalmente son péptidos con peso molecular de más de 20.000, capaces de exhibir su actividad con bajas concentraciones al unirse a un receptor, incluso (1) EGF (factor de crecimiento epidérmico) o sustancias que poseen sustancialmente la misma actividad que EGF [por ejemplo, TGFα, y similares], (2) insulina o sustancias que poseen sustancialmente la misma actividad [por ejemplo, insulina, IGF (factor de crecimiento similar a insulina)–1, IGF–2, y similares], (3) FGF (factor de crecimiento de fibroblastos) o sustancias que poseen sustancialmente la misma actividad que FGF [por ejemplo, FGF ácido, FGF básico, KGF (factor de crecimiento de queratinocitos), FGF–10, y similares], (4) otros factores de crecimiento celular [por ejemplo, CSF (factor estimulante de colonias), EPO (eritropoyetina), IL–2 (interleuquina–2), NGF (factor de crecimiento nervioso), PDGF (factor de crecimiento derivado de plaquetas), TGFβ (factor de crecimiento de transformación β), HGF (factor de crecimiento de hepatocitos), VEGF (factor de crecimiento de endotelio vascular), heregulina, angiopoyetina, y similares] y similares].

Los ejemplos de los "receptores de factor de crecimiento" incluyen cualquier receptor capaz de fijarse a los antes mencionados factores de crecimiento, incluso receptor de EGF, receptor de herregulina (HER3, etc.), receptor de insulina, receptor de IGF 1,

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receptor de IGF 2, receptor de FGF–1 o receptor de FGF–2, receptor de VEGF, receptor de angiopoyetina (Tie2, etc.), receptor de PDGF, y similares.

Como los "agentes farmacéuticos que inhiben la acción de los factores de crecimiento celular o los receptores de los factores de crecimiento celular", se usan inhibidor de EGF, inhibidor de TGFα, inhibidor de harregulina, inhibidor de insulina, inhibidor de IGF, inhibidor de FGF, inhibidor de KGF, inhibidor de CSF, inhibidor de EPO, inhibidor de IL–2, inhibidor de NGF, inhibidor de PDGF, inhibidor de TGFβ, inhibidor de HGF, inhibidor de VEGF, inhibidor de angiopoyetina, inhibidor del receptor de EGF, inhibidor de HER2, inhibidor de HER4, inhibidor de insulina, inhibidor del receptor de IGF–1, inhibidor del receptor de IGF–2, inhibidor del receptor 1 de FGF, inhibidor del receptor 2 de FGF, inhibidor del receptor 3 de FGF, inhibidor del receptor 4 de FGF, inhibidor del receptor de VEGF, inhibidor de Tie–2, inhibidor del receptor de PDGF, inhibidor de Abl, inhibidor de Raf, inhibidor de FLT3, inhibidor de c–Kit, inhibidor de Src, inhibidor de PKC, inhibidor de Trk, inhibidor de Ret, inhibidor de mTOR, inhibidor de Aurora, inhibidor de PLK, inhibidor de MEK(MEK1/2), inhibidor de MET, inhibidor de CDK, inhibidor de Akt, inhibidor de ERK, y similares. Más específicamente, se usan anticuerpos anti–VEGF (Bevacizumab etc.), anticuerpo anti–HER2 (Trastuzumab, Pertuzumab etc.), anticuerpo anti–EGFR (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab etc.), anticuerpos anti–VEGFR, Imatinib, Erlotinib, Gefitinib, Sorafenib, Sunitinib, Dasatinib,

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Lapatinib, Vatalanib, 4–(4–fluoro–2–metil–1H–indol–5–iloxi)–6–metoxi–7–[3–(1–pirrolidinil)propoxi]quinazolina (AZD–2171), Lestaurtinib, Pazopanib, Canertinib, Tandutinib, 3–(4–bromo–2,6–difluorobenciloxi)–5–[3–[4–(1–pirrolidinil)butil]ureido]isotiazol–4–carboxamida (CP–547632), Axitinib, N–(3,3–dimetil–2,3–dihidro–1H–indol–6–il)–2–(piridin–4–ilmetilamino)piridin–3–carboxamida (AMG–706), Nilotinib, 6–[4–(4–etilpiperazin–1–ilmetil)fenil]–N–[1(R)–feniletil]–7H–pirrolo[2,3–d]pirimidin–4–amina (AEE–788), Vandetanib, Temsirolimus, Everolimus, Enzastaurina, N–[4–[4–(4–metilpiperazin–1–il)–6–(3–metil–1H–pirazol–5–ilamino)pirimidin–2–ilsulfanil]fenil]ciclopropancarboxamida (VX–680), éster 2–[N–[3–[4–[5–[N–(3–fluorofenil)carbamoilmetil]–1H–pirazol–3–ilamino]quinazolin–7–iloxi]propil]–N–etilamino]etílico del ácido fosfórico (AZD–1152), ácido 4–[9–cloro–7–(2,6–difluorofenil)–5H–pirimido[5,4–d][2]benzazepin–2–ilamino]benzoico (MLN–8054), sal sódica de N–[2–metoxi–5–[(E)–2–(2,4,6–trimetoxifenil)vinilsulfonilmetil]fenil]glicina (ON–1910Na), 4–[8–ciclopentil–7(R)–etil–5–metil–6–oxo–5,6,7,8–tetrahidropteridin–2–ilamino]–3–metoxi–N–(1–metilpiperidin–4–il)benzamida (BI–2536), éster 2–hidroxietílico del ácido 5–(4–bromo–2–clorofenilamino)–4–fluoro–1–metil–1H–bencimidazol–6–carbohidroxámico (AZD–6244), N–[2(R),3–dihidroxipropoxi]–3,4–difluoro–2–(2–fluoro–4–yodofenilamino)benzamida (PD–0325901), y similares.

Además de los fármacos antes mencionados, se pueden usar L–asparaginasa, aceglatona, clorhidrato de procarbazina, sal de

complejo de protoporfirina–cobalto, hematoporfirina de mercurio y sodio, inhibidores de la topoisomerasa I (por ejemplo, irinotecano, topotecano, y similares), inhibidores de la topoisomerasa II (por ejemplo, sobuzoxano, y similares), inductores de la diferenciación (por ejemplo, retinoide, vitamina D, y similares), otros inhibidores de la angiogénesis (por ejemplo, humagilina, extracto de tiburón, inhibidor de COX–2, y similares), α–bloqueantes (por ejemplo, clorhidrato de tamsulosina, y similares), ácidos bisfosfónicos (pamidronato, zoledronato, y similares), talidomida, 5 azacitidina, decitabina, bortezomib, anticuerpo antitumoral tal como anticuerpo anti–CD20, y similares, anticuerpo marcado con toxina, y similares.

Al combinar el compuesto de la presente invención y un fármaco concomitante, se puede lograr un efecto superior, tal como:

(1) la dosis se puede reducir en comparación con una única administración del compuesto de la presente invención o un fármaco concomitante,

(2) el fármaco por combinar con el compuesto de la presente invención se puede seleccionar de acuerdo con la condición patológica de los pacientes (caso moderado, caso grave, y similares),

(3) el período del tratamiento puede ser más prolongado,

(4) se puede diseñar un efecto de tratamiento prolongado,

(5) se puede lograr un efecto sinérgico por medio del uso combinado del compuesto de la presente invención y un fármaco concomitante, y similares.

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En la presente memoria descriptiva, el compuesto de la presente invención y un fármaco concomitante usado en combinación se denominan "agente de combinación de la presente invención".

Para usar el agente de combinación de la presente invención, el tiempo de administración del compuesto de la presente invención y el fármaco concomitante no están restringidos, y el compuesto de la presente invención y el fármaco concomitante se pueden administrar a un sujeto simultáneamente, o se pueden administrar en momentos diferentes. La dosificación del fármaco concomitante puede ser determinada de acuerdo con la cantidad de administración clínicamente fijada y se puede seleccionar apropiadamente según el sujeto de administración, la vía de administración, la enfermedad, la combinación, y similares.

Los ejemplos del modo de administración del uso combinado del compuesto de la presente invención y el fármaco concomitante incluyen los siguientes métodos:

(1) El compuesto de la presente invención y el fármaco concomitante se producen simultáneamente para dar una única preparación administrada. (2) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran simultáneamente por la misma vía de administración. (3) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran por la misma vía de administración, pero en distintos momentos. (4) El compuesto de

la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran simultáneamente por distintas vías de administración. (5) El compuesto de la presente invención y el fármaco concomitante se producen por separado para dar dos tipos de preparaciones que se administran por distintas vías de administración, en distintos momentos (por ejemplo, el compuesto de la presente invención y el fármaco concomitante se administran en ese orden, o en orden inverso). La dosis del fármaco concomitante se determina de acuerdo con su dosis clínica. Y la relación del compuesto de la presente invención y el fármaco concomitante se determina de acuerdo con el sujeto, la vía de administración, la enfermedad, el síntoma, la combinación, y similares. Por ejemplo, cuando el sujeto es un ser humano, el fármaco concomitante se usa en 0.01 a 100 (p/p), respecto del compuesto de la presente invención.

El agente de combinación de la presente invención tiene baja toxicidad y, por ejemplo, el compuesto de la presente invención y/o el fármaco concomitante antes mencionado se pueden mezclar, de acuerdo con un método en sí conocido, con un portador farmacológicamente aceptable para dar composiciones farmacéuticas tales como comprimidos (incluso comprimido recubierto con azúcar, comprimido entérico), polvos, gránulos, cápsulas (incluso cápsula blanda), soluciones, inyecciones, supositorios, agentes de liberación prolongada, y similares, que se pueden administrar de modo seguro por vía oral o parenteral (por ejemplo, local, rectal, venosa, y

similares). Una inyección se puede administrar directamente a la lesión por administración intravenosa, intramuscular, subcutánea o intratisular.

Como un portador farmacológicamente aceptable que se puede usar para producir una preparación del agente de combinación de la presente invención, se pueden mencionar aquellos similares a los portadores farmacológicamente aceptables antes mencionados, que se pueden usar para la producción del agente farmacéutico de la presente invención. De ser necesario, se pueden emplear también los aditivos antes citados que se pueden usar para la producción del agente farmacéutico de la presente invención, tales como conservantes, antioxidantes, agentes colorantes, endulzantes, adsorbentes, agentes humectantes, y similares en cantidades apropiadas.

La relación de composición del compuesto de la presente invención al fármaco concomitante en el agente de combinación de la presente invención se puede fijar apropiadamente según el sujeto de administración, la vía de administración, las enfermedades, y similares.

Por ejemplo, el contenido del compuesto de la presente invención en el agente de combinación de la presente invención varía según la forma de dosificación, y usualmente varía de aproximadamente el 0.01 al 100% en peso, con preferencia, de aproximadamente el 0.1 al 50% en peso, con mayor preferencia, de aproximadamente el 0.5 al 20% en peso, en base a la preparación.

El contenido del fármaco concomitante en el agente de combinación de la presente invención varía según la forma de dosificación, y y usualmente varía de aproximadamente el 0.01 al 90% en peso, con preferencia, de aproximadamente el 0.1 al 50% en peso, con mayor preferencia, de aproximadamente el 0.5 al 20% en peso, en base a la preparación.

El contenido de aditivos en el agente de combinación de la presente invención varía según la forma de dosificación, y usualmente varía de aproximadamente el 1 al 99,99% en peso, con preferencia, de aproximadamente el 10 al 90% en peso, en base a la preparación.

Cuando el compuesto de la presente invención y el fármaco concomitante se preparan por separado, se puede adoptar el mismo contenido.

Estas preparaciones se pueden producir por un método en sí conocido, que generalmente se emplea en el proceso de preparación.

Por ejemplo, el compuesto de la presente invención y el fármaco concomitante se puede preparar en una inyección acuosa junto con un dispersante (por ejemplo, Tween 80 (fabricado por Atlas Powder, US), HCO 60 (fabricado por Nikko Chemicals), polietilenglicol, carboximetilcelulosa, alginato de sodio, hidroxipropilmetilcelulosa, dextrina, y similares), un estabilizante (por ejemplo, ácido ascórbico, pirosulfito de sodio, y similares), un tensoactivo (por ejemplo, Polisorbato 80, macrogol, y similares), un solubilizante (por ejemplo, glicerina, etanol, y similares), un buffer

(por ejemplo, ácido fosfórico y su sal de metal alcalino, ácido cítrico y su sal de metal alcalino, y similares), un agente isotónico (por ejemplo, cloruro de sodio, cloruro de potasio, manitol, sorbitol, glucosa, y similares), un agente de ajuste del pH (por ejemplo, ácido clorhídrico, hidróxido de sodio, y similares), un conservante (por ejemplo, p–oxibenzoato de etilo, ácido benzoico, metilparabeno, propilparabeno, alcohol bencílico, y similares), un agente de disolución (por ejemplo, glicerina concentrada, meglumina, y similares), un auxiliar de disolución (por ejemplo, propilenglicol, sacarosa, y similares), un agente suavizante (por ejemplo, glucosa, alcohol bencílico, y similares), y otros, o se pueden disolver, suspender o emulsionar en un aceite vegetal tales como aceite de oliva, aceite de sésamo, aceite de semillas de algodón, aceite de maíz, y similares o un auxiliar de disolución tales como propilenglicol, y similares y se pueden preparar en una inyección oleosa, logrando una inyección.

Además, se pueden añadir un excipiente (por ejemplo, lactosa, sacarosa, almidón, y similares), un agente desintegrante (por ejemplo, almidón, calcio carbonato, y similares), un aglutinante (por ejemplo, almidón, goma arábiga, carboximetilcelulosa, polivinilpirrolidona, hidroxipropilcelulosa, y similares), un lubricante (por ejemplo, talco, estearato de magnesio, polietilenglicol 6000, y similares), y otros al compuesto de la presente invención o el fármaco concomitante de acuerdo con un método en sí conocido, y la mezcla se puede moldear por compresión, luego si se desea, el

producto moldeado se puede recubrir por medio de un método en sí conocido a los fines de enmascarar el sabor, la propiedad entérica o la durabilidad, para dar una preparación para administración oral. Como agente de recubrimiento, se puede usar, por ejemplo, hidroxipropilmetilcelulosa, etilcelulosa, hidroximetilcelulosa, hidroxipropilcelulosa, polioxietilenglicol, Tween 80, Pluronic F68, acetato–ftalato de celulosa, ftalato de hidroxipropilmetilcelulosa, acetato–succinato de hidroximetilcelulosa, Eudoragit (copolímero de ácido metacrílico–ácido acrílico, fabricado por Rohm, DE), pigmento (por ejemplo, óxido de hierro rojo, dióxido de titanio, etc.), y similares. La preparación para administración oral puede ser cualquier preparación de liberación inmediata y una preparación de liberación prolongada.

Más aún, el compuesto de la presente invención y el fármaco concomitante se pueden preparar en un supositorio sólido, semisólido o líquido oleoso o acuoso de acuerdo con un método en sí conocido, mezclándolo con un sustrato oleoso, un sustrato acuoso o un sustrato en gel acuoso. Como el sustrato oleoso antes mencionado, se pueden mencionar, por ejemplo, glicéridos de ácidos grasos superiores [por ejemplo, manteca de cacao, Witepsols (fabricado por Dynamit Nobel, Alemania), etc.], glicéridos de ácido graso de cadena media [por ejemplo, Migliols (fabricado por Dynamit Nobel, Alemania), etc.], o aceites vegetales (por ejemplo, aceite de sésamo, aceite de frijol de soya, aceite de semillas de algodón, y otros), y similares. Por otra parte, como sustrato acuoso, se pueden

mencionar, por ejemplo, polietilenglicol, propilenglicol, y similares, y como sustrato en gel acuoso, se pueden mencionar, por ejemplo, gomas naturales, derivados de celulosa, polímeros venílicos, polímeros de ácido acrílico, y similares.

Como la preparación de liberación prolongada antes mencionada, se mencionan microcápsulas de liberación prolongada, y similares. La microcápsula de liberación prolongada se puede producir por un método en sí conocido, como el método indicado en el siguiente punto [2].

El compuesto de la presente invención se moldea, con preferencia, en una preparación para administración oral como una preparación sólida (por ejemplo, polvo, gránulo, comprimido, cápsula), y similares, o se moldea en una preparación para administración rectal como un supositorio, y similares. En particular, es preferible una preparación para administración oral.

El fármaco concomitante se puede incorporar en la forma de fármaco antes mencionada según el tipo de fármaco.

[1] Una inyección del compuesto de la presente invención o el fármaco concomitante, y su preparación, [2] una preparación de liberación prolongada o preparación de liberación inmediata del compuesto de la presente invención o el fármaco concomitante, y su preparación, [3] un agente integrador rápido sublingual, bucal o intraoral del compuesto de la presente invención o el fármaco concomitante, y su preparación, se describen específicamente a continuación.

ff2

[1] Inyección y su preparación

Se prefiere una inyección preparada al disolver el compuesto de la presente invención o el fármaco concomitante en agua. Esta inyección puede contener un benzoato y/o salicilato.

La inyección se obtiene al disolver el compuesto de la presente invención o el fármaco concomitante, y si se desea, un benzoato y/o salicilato, en agua.

Como las sales antes mencionadas de ácido benzoico y salicílico, se mencionan por ejemplo, sales de metales alcalinos tales como sodio, potasio, y similares, sales de metales alcalinotérreos tales como calcio, magnesio, y similares, sales de amonio, sales de meglumina, sales con base orgánicas tales como trometamol, y similares, etc.

La concentración del compuesto de la presente invención o el fármaco concomitante en una inyección es de 0.5 a 50 p/v%, con preferencia, de aproximadamente 3 a 20 p/v%. La concentración de un benzoato y/o salicilato es de 0.5 a 50 p/v%, con preferencia, de aproximadamente 3 a 20 p/v%.

La inyección de la presente invención se puede mezclar adecuadamente con un aditivo usado convencionalmente para la inyección, tal como un estabilizante (por ejemplo, ácido ascórbico, pirosulfito de sodio y similares), un agente tensoactivo (por ejemplo, Polisorbate 80, macrogol, y similares), un solubilizante (por ejemplo, glicerina, etanol y similares), un buffer (por ejemplo, ácido fosfórico y su sal de metal alcalino, ácido cítrico y su sal de metal alcalino, y

similares), un agente isotonizante (por ejemplo, cloruro de sodio, cloruro de potasio y similares), un agente dispersante (por ejemplo, hidroxipropilmetilcelulosa, dextrina), un agente de ajuste de pH (por ejemplo, ácido clorhídrico, hidróxido de sodio, y similares), un conservador (por ejemplo, p–oxibenzoato de etilo, ácido benzoico, y similares), un agente disolvente (por ejemplo, glicerina conc., megluminas, y similares), un auxiliar de disolución (por ejemplo, propilenglicol, sacarosa, y similares), un agente suavizante (por ejemplo, glucosa, alcohol bencílico, y similares), y similares. Estos aditivos generalmente se mezclan en una proporción generalmente usada para inyecciones.

El pH de una inyección se ajusta ventajosamente a pH 2 a 12, con preferencia, pH 2,5 a 8,0, por adición de un agente de ajuste de pH.

Se obtiene una inyección al disolver en agua el compuesto de la presente invención o el fármaco concomitante y, si se desea, un benzoato y/o salicilato, y de ser necesario, los aditivos antes mencionados. Se pueden disolver en cualquier orden, y se pueden disolver adecuadamente de la misma manera que en un método de producción convencional de una inyección.

Una solución acuosa para inyección se puede calentar ventajosamente, alternativamente, por ejemplo, se puede someter a esterilización por filtrado, esterilización por calor a alta presión, y similares para dar una inyección, de la misma manera que para las inyecciones habituales.

Una solución acuosa para inyección se puede someter ventajosamente a esterilización por calor a alta presión a 100 °C a 121 °C durante 5 a 30 min.

Por otra parte, también se puede producir una preparación con propiedades antibacterianas de una solución para permitir administraciones múltiples en porciones.

[2] Preparación de liberación prolongada o preparación de liberación inmediata, y su preparación

Se prefiere una preparación de liberación prolongada que se obtiene, si se desea, al recubrir un núcleo que contiene el compuesto de la presente invención o el fármaco concomitante con un agente de película tal como una sustancia insoluble en agua, un polímero que aumenta de tamaño, y similares. Por ejemplo, se prefiere una preparación de liberación prolongada para administración oral de un tipo de administración una vez por día.

Como la sustancia insoluble en agua usada en un agente de película se enumeran, por ejemplo, éteres de celulosa tales como etilcelulosa, butilcelulosa, y similares, ésteres de celulosa tales como acetato de celulosa, propionato de celulosa, y similares, ésteres de polivinilo tales como acetato de polivinilo, butirato de polivinilo, y similares, copolímeros de ácido acrílico/ácido metacrílico, copolímeros de metacrilato de metilo, copolímeros de etoxietilmetacrilato/cinnamoetilmetacrilato/aminoalquilmetacrilato, ácido poliacrílico, ácido polimetacrílico, copolímeros de alquilamina de ácido metacrílico, poli(metacrilato de metilo), polimetacrilato,

polimetacrilamida, copolímeros de aminoalquilmetacrilato, poli(anhídrido metacrílico), copolímero de glicidilmetacrilato, en particular, polímeros basados en ácido acrílico tales como Eudoragit (Rohm Pharma) tales como Eudoragit RS–100, RL–100, RS–30D, RL–30D, RL–PO, RS–PO (copolímero de acrilato de etiloe/metacrilato de metilo/cloruro de trimetilmetacriloílo/metilamonio), Eudoragit NE–30D (copolímero de metacrilato de metilo/acrilato de etilo), y similares, aceites hidrogenados tales como aceite de ricino hidrogenado (por ejemplo, Lubri wax (Freund Corporation), y similares), ceras tales como cera carnauba, éster de ácido graso de glicerina, parafina y similares, ésteres de ácidos grasos de poliglicerina y similares.

Como polímero que aumenta de tamaño se prefieren polímeros con un grupo ácido disociante y que aumenta de tamaño dependiente del pH, y polímeros con un grupo ácido disociante, que manifiesta pequeño aumento de tamaño en regiones ácidas tales como el estómago y gran aumento de tamaño en regiones neutras tales como el intestino delgado y el intestino grueso.

Como tal polímero con grupo ácido disociante y que muestra aumento de tamaño con dependencia de pH se puede usar copolímeros de ácido poliacrílico que forman enlaces cruzados tales como Carbomero 934P, 940, 941, 974P, 980, 1342, y similares, policarbofilo, policarbofilo de calcio (todos fabricados por BF Goodrich), Hiviswako 103, 104, 105, 304 (todos fabricados por Wako Pure Chemical Industries, Ltd.), y similares.

El agente de película usado en la preparación de liberación prolongada también puede contener una sustancia hidrofílica.

Como sustancia hidrofílica se pueden mencionar, por ejemplo, polisacáridos que pueden contener un grupo sulfato tal como pululano, dextrina, alginato de metal alcalino, y similares, polisacáridos con hidroxialquilo o carboxialquilo tales como hidroxipropilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa sódica, y similares, metilcelulosa, polivinilpirrolidona, alcoholpolivinílico, polietilenglicol, y similares.

El contenido de una sustancia insoluble en agua en el agente de película de una preparación de liberación prolongada es de aproximadamente 30 a aproximadamente 90% (p/p), con preferencia, de aproximadamente 35 a aproximadamente 80% (p/p), con mayor preferencia, de aproximadamente 40 a aproximadamente 75% (p/p), el contenido de un polímero que aumenta de tamaño es de aproximadamente 3 a aproximadamente 30% (p/p), con preferencia, de aproximadamente 3 a aproximadamente 15% (p/p). El agente de película además puede contener una sustancia hidrofílica, y en cuyo caso, el contenido de una sustancia hidrofílica en el agente de película es de aproximadamente 50% (p/p) o menos, con preferencia, aproximadamente 5 a 40% (p/p), con mayor preferencia, de aproximadamente 5 a 35% (p/p). Este % (p/p) indica % en peso sobre la base de una composición de agente de película que se obtiene al extraer un solvente (por ejemplo, agua, alcoholes inferiores tales como metanol, etanol, y similares) de una solución de agente de

película.

La preparación de liberación prolongada se produce al preparar un núcleo que contiene fármacos tal como se ejemplifica a continuación, y luego recubrir el núcleo obtenido con una solución de agente de película preparada al disolver en caliente una sustancia insoluble en agua, un polímero que aumenta de tamaño, y similares o al disolverlo o dispersarlo en un solvente.

I. Preparación del núcleo que contiene fármaco

La forma del núcleo que contiene un fármaco para ser recubierto con un agente formador de película (en adelante, en ocasiones referido simplemente como núcleo) no está particularmente restringido, y de preferencia, se forma el núcleo en partículas tales como un gránulo o partícula fina.

Cuando el núcleo se compone de gránulos o partículas finas, su tamaño de partícula promedio es con preferencia, de aproximadamente 150 a aproximadamente 2000 μm, con mayor preferencia de aproximadamente 500aa aproximadamente 1400 μm.

La preparación del núcleo se puede llevar a cabo por el método de producción habitual. Por ejemplo, un excipiente adecuado, agente enlazante, agente desintegrante, lubricante, estabilizante, y similares se mezclan con un fármaco, y la mezcla se somete a un método de granulación por extrusión húmeda, método de granulación de lecho fluido o similares, para preparar un núcleo.

El contenido de fármacos en un núcleo es de aproximadamente 0.5 a aproximadamente 95% (p/p), con preferencia, de

aproximadamente 5.0 a aproximadamente 80% (p/p), con mayor preferencia, de aproximadamente 30 a aproximadamente 70% (p/p).

Como excipiente contenido en el núcleo, por ejemplo, se usan sacáridos tales como sacarosa, lactosa, manitol, glucosa y similares, almidón, celulosa cristalina, fosfato de calcio, almidón de maíz y similares. Entre ellos se prefieren celulosa cristalina, y almidón de maíz.

Como agente enlazante se usa, por ejemplo, alcohol polivinílico, hidroxipropilcelulosa, polietilenglicol, polivinilpirrolidona, Pluronic F68, goma arábiga, gelatina, almidón y similares. Como agente desintegrante se usa, por ejemplo, carboximetilcelulosa de calcio (ECG505), croscarmelosa de sodio (Ac–Di–Sol), polivinilpirrolidona con enlaces cruzados (Crospovidona), hidroxipropilcelulosa poco sustituida (L–HPC) y similares. De ellos se prefiere hidroxipropilcelulosa, polivinilpirrolidona, hidroxipropilcelulosa poco sustituida. Como lubricante e inhibidor de coagulación se usa por ejemplo, talco, estearato de magnesio y sus sales inorgánicas, y como lubricante, se usa polietilenglicol, y similares. Como estabilizante se usan ácidos tales como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico y similares.

También se puede preparar un núcleo, además del antes mencionado, por ejemplo, por un método de granulación en rodillo en el cual el fármaco o una mezcla de fármaco con un excipiente, lubricante y similares se añade en porciones sobre una partícula

portadora inerte que es el centro del núcleo, mientras se rocía un enlazante disuelto en un solvente adecuado tal como agua, alcohol inferior (por ejemplo, metanol, etanol y similares), y similares, un método de recubrimiento en bandeja, un método de recubrimiento de lecho fluido o un método de granulación fundida. Como partícula portadora inerte se pueden usar, por ejemplo, los preparados de sacarosa, lactosa, almidón, celulosa cristalina o ceras, y su tamaño promedio de partícula es con preferencia, de aproximadamente 100 μm a aproximadamente 1500 μm.

Para separar un fármaco contenido en un núcleo y un agente formador de película se puede cubrir el núcleo con un agente protector. Como agente protector se usan, por ejemplo, las sustancias hidrofílicas antes mencionadas, sustancias insolubles en agua, y similares. Como agente protector, con preferencia, se usa polietilenglicol, y polisacáridos con hidroxialquilo o carboxialquilo, con mayor preferencia se usa hidroxipropilmetilcelulosa e hidroxipropilcelulosa. El agente protector puede contener, como estabilizante, ácidos tales como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico y similares, y lubricantes tales como talco y similares. Cuando se usa el agente protector, la cantidad de recubrimiento es de aproximadamente 1 a aproximadamente 15% (p/p), con preferencia, de aproximadamente 1 a aproximadamente 10% (p/p), con mayor preferencia, de aproximadamente 2 a aproximadamente 8% (p/p), sobre la base del núcleo.

El agente protector se puede recubrir por un método de recubrimiento usual, y específicamente, el agente protector se puede recubrir por recubrimiento por aspersión del núcleo, por ejemplo, mediante un método de recubrimiento de lecho fluido, método de recubrimiento en bandeja y similares.

II. Recubrimiento del núcleo con agente formador de película

Un núcleo obtenido en la antes mencionada etapa I se recubre con una solución de agente formador de película obtenido al disolver en caliente la antes mencionada sustancia insoluble en agua y el polímero que aumenta de tamaño con dependencia del pH, y una sustancia hidrofílica, o al disolver o dispersarlos en un solvente, para dar una preparación de liberación prolongada.

Como método para recubrir un núcleo con una solución de agente formador de película, por ejemplo, se enumera un método de recubrimiento por aspersión y similares.

La relación de composición de una sustancia insoluble en agua, polímero que aumenta de tamaño o sustancia hidrofílica en solución de agente formador de película se selecciona apropiadamente de manera tal que el contenido de estos componentes en una película de recubrimiento son los contenidos antes mencionados, respectivamente.

La cantidad de recubrimiento de agente formador de película es de aproximadamente 1 a aproximadamente 90% (p/p), con preferencia, de aproximadamente 5 a aproximadamente 50% (p/p), con mayor preferencia, de aproximadamente 5 a aproximadamente

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35% (p/p), sobre la base de un núcleo (no incluye la cantidad de recubrimiento del agente protector).

Como solvente en solución de un agente formador de película, se puede usar agua o un solvente orgánico solo o como mezcla. En el caso de uso en mezcla, la relación de mezcla de agua con solvente orgánico (agua/solvente orgánico : en peso) se puede variar en el rango de 1 a 100%, y con preferencia, de 1 a aproximadamente 30%. El solvente orgánico no está particularmente restringido siempre que disuelva una sustancia insoluble en agua, y por ejemplo, se usan alcoholes inferiores tales como alcohol metílico, alcohol etílico, alcohol isopropílico, alcohol n–butílico, y similares, alcanonas inferiores tales como acetona, y similares, acetonitrilo, cloroformo, cloruro de metileno y similares. Entre ellos se prefieren los alcoholes inferiores, y alcohol etílico y alcohol isopropílico tienen particular preferencia. Se usa gua y una mezcla de agua con un solvente orgánico preferible,emte como solvente para un agente formador de película. En este caso, de ser necesario, también se puede agregar un ácido tal como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, ácido maleico, y similares a la solución de agente formador de película para estabilizar la solución de agente formador de película.

Una operación de cobertura por recubrimiento por aspersión se puede llevar a cabo por un método de recubrimiento usual, y específicamente, se puede efectuar por recubrimiento por aspersión de una solución de agente formador de película sobre un núcleo

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mediante un método de recubrimiento por lecho fluido, método de recubrimiento en bandeja, y similares. En este caso, de ser necesario, también se puede agregar talco, óxido de titanio, estearato de magnesio, estearato de calcio, ácido silícico levemente anhidro, y similares como lubricante, y también se puede agregar éster de ácido graso de glicerina, aceite de ricino hidrogenado, citrato de trietilo, alcohol cetílico, alcohol estearílico, y similares como plastificante.

Después de recubrir con un agente formador de película, de ser necesario se puede mezclar un agente antiestático tal como talco y similares.

La preparación de liberación inmediata puede ser líquida (solución, suspensión, emulsión, y similares) o sólida (partícula, píldora, comprimido, y similares). Como preparación de liberación inmediata, se usan agentes orales y agentes parenterales tales como una inyección, y similares, y se prefieren agentes orales.

La preparación de liberación inmediata, usualmente puede contener, además de un fármaco de componente activo, también portadores, aditivos y excipientes convencionalmente usados en el campo de la producción (en lo sucesivo,, abreviados a veces como excipiente). El excipiente usado no está particularmente restringido, con la condición de que sea un excipiente ordinariamente usado como un excipiente de preparación. Por ejemplo, como excipiente para una preparación sólida oral, se enumeran lactosa, almidón, almidón de maíz, celulosa cristalina (Avicel PH101, fabricado por

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Asahi Kasei Corporation, y similares), azúcar en polvo, azúcar granulado, manitol, ácido silícico ligeramente anhidro, carbonato de magnesio, carbonato de calcio, L–cisteína, y similares, y con preferencia, almidón de maíz y manitol, y similares. Estos excipientes se pueden usar solos o en combinación de dos o más. El contenido del excipiente va, por ejemplo, de aproximadamente el 4.5 a aproximadamente el 99,4 % p/p, con preferencia, de aproximadamente el 20 a aproximadamente el 98,5 % p/p, con mayor preferencia, de aproximadamente el 30 a aproximadamente el 97 % p/p, en base a la cantidad total de la preparación de liberación inmediata.

El contenido de un fármaco en la preparación de liberación inmediata se puede seleccionar apropiadamente en el rango de aproximadamente el 0.5 a aproximadamente el 95%, con preferencia, de aproximadamente el 1 a aproximadamente el 60% en base a la cantidad total de la preparación de liberación inmediata.

Cuando la preparación de liberación inmediata es una preparación sólida oral, usualmente contiene, además de los componentes antes mencionados, también un agente integrante. Como este agente integrante, se usan, por ejemplo, carboximetilcelulosa cálcica (ECG–505, fabricada por Gotoku Yakuhin), croscarmelosa sódica (por ejemplo, Actisol, fabricada por Asahi Kasei Corporation), crospovidona (por ejemplo, Kollidon CL, fabricada por BASF), hidroxipropilcelulosa de baja sustitución (fabricada por Shin–Etsu Chemical Co., Ltd.), carboximetilalmidón

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(fabricado por Matsutani Kagaku K.K.), carboximetilalmidón sódico (Exprotab, fabricado por Kimura Sangio), almidón parcialmente pregelatinizado (PCS, fabricado por Asahi Kasei Corporation), y similares, y por ejemplo, se pueden usar aquellos que desintegran un gránulo por adsorción de agua en contacto con agua, causando hinchamiento o formando un canal entre un ingrediente efectivo que constituye el núcleo y un excipiente. Estos agentes desintegrantes se pueden usar solos o en combinación de dos o más. La cantidad de agente desintegrante usada se selecciona apropiadamente según el tipo y la cantidad de mezcla de un fármaco usado, diseño de la propiedad de liberación, y similares, y por ejemplo, va de aproximadamente el 0.05 a aproximadamente el 30 % p/p, con preferencia, de aproximadamente el 0.5 a aproximadamente el 15 % p/p, en base a la cantidad total del agente de liberación rápida.

Cuando la preparación de liberación inmediata es una preparación sólida oral, también puede contener, además de la composición antes mencionada, si se desea, aditivos convencionales en preparaciones sólidas. Como tal aditivo, se usan, por ejemplo, un aglutinante (por ejemplo, sacarosa, gelatina, goma arábiga en polvo, metilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa, polivinilpirrolidona, pululano, dextrina, y similares), un lubricante (por ejemplo, polietilenglicol, estearato de magnesio, talco, ácido silícico ligeramente anhidro (por ejemplo, Aerosil (Nippon Aerosil)), un tensoactivo (por ejemplo, tensoactivos aniónicos tales como alquilsulfato de sidui, y similares, tensoactivos

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no iónicos tales como éster de ácido gras de polioxietileno y éster de ácido graso de polioxietilensorbitano, derivados de aceite de ricino y polioxietileno, y similares), un agente colorante (por ejemplo, una materia colorante de brea, caramelo, óxido de hierro rojo, óxido de titanio, riboflavinas), de ser necesario, un agente para el apetito (por ejemplo, endulzante, saborizante, y similares), un adsorbente, conservante, agente humectante, agente antiestática, y similares. Adicionalmente, como el estabilizante, también se pueden añadir un ácido orgánico como ácido tartárico, ácido cítrico, ácido succínico, ácido fumárico, y similares.

Como el aglutinante antes mencionado, hidroxipropilcelulosa, se usan con preferencia polietilenglicol y polivinilpirrolidona, y similares.

La preparación de liberación inmediata se puede preparar, en base a la tecnología usual para producir preparaciones, mezclando los componentes antes mencionados y, de ser necesario, amasando la mezcla y moldeándola. La mezcla antes mencionada se lleva a cabo generalmente usando métodos, por ejemplo, mezcla, amasado, y similares. Específicamente, se pueden preparar, cuando se forma la preparación de liberación inmediata, por ejemplo, en una partícula, se puede preparar de acuerdo con el mismo medio que en el método antes mencionado para preparar un núcleo de una preparación de liberación prolongada, mezclando los componentes usando un granulador vertical, una amasadora universal (fabricada por Hata Tekkosho), granulador en lecho fluido FD–5S (fabricado por Powrex

Corporation), y similares, y luego, granulando la mezcla por medio de un método de granulación por extrusión húmeda, método de granulación en lecho fluido, y similares.

La preparación de liberación inmediata así obtenida y la preparación de liberación prolongada se pueden convertir en sí en productos o en productos apropiadamente junto con excipientes de preparación, y similares, por separado, por medio de un método ordinario, luego se pueden administrar de modo simultáneo o se pueden administrar en combinación en cualquier intervalo de administración o se pueden preparar en sí en una preparación oral (por ejemplo, gránulo, partícula fina, comprimido, cápsula, y similares) o se pueden preparar en una preparación oral apropiadamente junto con excipientes de preparación, y similares. Se puede permitir que se preparen en gránulos o finas partículas y se envasen en la misma cápsula para usar como una preparación para la administración oral.

[3] Agente de desintegración rápida sublingual, bucal o intraoral y su preparación

Los agentes de desintegración rápida sublingual, bucal o intraoral pueden ser una preparación sólida como un comprimido, y similares, o pueden ser un parche de membrana mucosa oral (película).

Como agente de desintegración rápida sublingual, bucal o intraoral, se prefiere una preparación que contiene el compuesto de la presente invención o el fármaco concomitante y un excipiente.

También pueden contener agentes auxiliares tales como un lubricante, agente isotónico, portador hidrofílico, polímero dispersable en agua, estabilizante, y similares. Además, para una mayor absorción y mayor eficacia del uso *in vivo*, pueden estar contenidos derivados de β–ciclodextrina o β–ciclodextrina (por ejemplo, hidroxipropil–β–ciclodextrina, y otros), y similares.

Como el excipiente antes mencionado, se enumeran lactosa, sacarosa, D–manitol, almidón, celulosa cristalina, ácido silícico ligeramente anhidro, y similares. Como el lubricante, se enumeran estearato de magnesio, estearato de calcio, talco, sílice coloidal, y similares, y en particular, se prefieren estearato de magnesio y sílice coloidal. Como agente isotonizante, se enumeran cloruro de sodio, glucosa, fructosa, manitol, sorbitol, lactosa, sacarosa, glicerina, urea, y similares, y en particular, se prefiere manitol. Como portador hidrofílico, se enumeran portadores hidrofílicos hinchables tales como celulosa cristalina, etilcelulosa, polivinilpirrolidona con enlaces cruzados, ácido silícico ligeramente anhidro, ácido silícico, difosfato de calcio, carbonato de calcio, y similares, y en particular, se prefiere celulosa cristalina (por ejemplo, celulosa microcristalina, y similares). Como polímero dispersable en agua, se enumeran gomas (por ejemplo, goma tragacanto, goma acacia, goma ciamoposis), alginatos (por ejemplo, alginato de sodio), derivados celulósicos (por ejemplo, metilcelulosa, carboximetilcelulosa, hidroximetilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa), gelatina, almidón hidrosoluble, ácidos poliacrílicos (por ejemplo, carbómero), ácido

polimetacílico, alcohol polivinílico, polietilenglicol, polivinilpirrolidona, policarbófilo, ácido ascórbico, palmitatos, y similares, y se prefieren hidroxipropilmetilcelulosa, ácido poliacrílico, alginatos, gelatina, carboximetilcelulosa, polivinilpirrolidona, polietilenglicol, y similares. En particular, se prefiere la hidroxipropilmetilcelulosa. Como el estabilizante, se enumeran cisteína, tiosorbitol, ácido tartárico, ácido cítrico, carbonato de sodio, ácido ascórbico, glicina, sulfito de sodio, y similares, y en particular, se prefieren ácido cítrico y ácido ascórbico.

El agente de desintegración rápida sublingual, bucal o intraoral se puede producir mezclando el compuesto de la presente invención o el fármaco concomitante y un excipiente por un método en sí conocido. Además, si se desea, se pueden mezclar agentes auxiliares tales como un lubricante, un agente isotónico, un portador hidrofílico, un polímero dispersable en agua, un estabilizante, un colorante, un endulzante, un conservante, y similares. El agente de desintegración rápida sublingual, bucal o intraoral se obtiene mezclando los componentes antes mencionados de forma simultánea o a intervalos, luego sometiendo la mezcla a moldeo para formar comprimidos bajo presión. Para obtener una dureza apropiada, también se puede permitir que los materiales se humecten con un solvente como agua, alcohol, y similares, si se desea, y después del proceso de formación de comprimidos, y después del moldeo, los materiales se secan para obtener un producto.

En el caso del moldeo en un parche de membrana mucosa

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(película), el compuesto de la presente invención o el fármaco concomitante y el polímero dispersable en agua antes mencionado (preferentemente, hidroxipropilcelulosa, hidroxipropilmetilcelulosa), excipiente, y similares se disuelven en un solvente como agua, y similares, y la solución resultante se moldea para dar una película. Por otra parte, también se pueden añadir aditivos tales como un plastificante, estabilizante, antioxidante, conservante, colorante, buffer, endulzante, y similares. Para impartir una elasticidad apropiada a la película, pueden estar contenidos glicoles tales como polietilenglicol, propilenglicol, y similares, o para mejorar la adición de la película a una línea de membrana mucosa intraoral, también puede estar contenido un polímero bioadhesivo (por ejemplo, policarbófilo, carbopol). En el moldeo, se vierte una solución sobre la superficie no adhesiva, se distribuye hasta un espesor uniforme (con preferencia, aproximadamente 10 a 1000 micras) por medio de una herramienta de aplicación como una hoja, y similares, luego, la solución se seca para formar una película. Puede ser ventajoso que la película así formada se seque a temperatura ambiente o bajo calor y se corte en el área deseada.

Como agente de desintegración rápida intraoral preferido, se enumeran agentes de dosificación de separación rápida compuesto por un cuerpo reticulado que comprende el compuesto de la presente invención o el fármaco concomitante, y un portador hidrosoluble o hidrodifusible que es inerte al compuesto de la presente invención o al fármaco concomitante. Este cuerpo reticulado se obtiene

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sublimando un solvente de la composición sólida constituida por una solución preparada por disolución del compuesto de la presente invención o el fármaco concomitante en un solvente apropiado.

Es preferible que la composición de un agente de desintegración rápida intraoral contenga un agente formador de matriz y un componente secundario, además del compuesto de la presente invención o el fármaco concomitante.

Los ejemplos del agente formador de matriz incluyen gelatinas, dextrinas, proteínas animales o vegetales tales como frijol de soya, trigo y proteína de semillas de psyllium, y similares; sustancias gomosas tales como goma arábiga, goma guar, agar, goma xantán, y similares; polisacáridos; ácidos algínicos; carboximetilcelulosas; carragenanos; dextranos; pectinas; polímeros sintéticos tales como polivinilpirrolidona, y similares; sustancias derivadas de un complejo de gelatina–goma arábiga, y similares. Además pueden estar contenidos sacáridos tales como manitol, dextrosa, lactosa, galactosa, trehalosa, y similares; sacáridos cíclicos tales como ciclodextrina, y similares; sales inorgánicas tales como fosfato de sodio, cloruro de sodio y silicato de magnesio, y similares; aminoácidos que tienen 2 a 12 átomos de carbono tales como glicina, L–alanina, ácido L–aspártico, ácido L–glutámico, L–hidroxiprolina, L–isoleucina, L–leucina, L–fenilalanina, y similares.

Uno o varios de los agentes formadores de matriz se pueden introducir en una solución o suspensión antes de solidificar. Un agente formador de matriz de este tipo puede estar presente además

de un tensoactivo, o puede estar presente mientras se excluye a un tensoactivo. Los agentes formadores de matriz ayudan a mantener el compuesto de la presente invención o el fármaco concomitante en la solución o suspensión en condición difusa, además de la formación de la matriz.

La composición puede contener componentes secundarios tales como un conservante, antioxidante, tensoactivo, espesante, colorante, agente de control del pH, agente saborizante, endulzante, agente enmascarador del sabor, y similares. Como agente colorante apropiado, se enumeran óxidos de hierro rojo, negro y amarillo, y tinturas FD & C tales como Azul 2 FD & C, Rojo 40 FD & C, y similares fabricado por Ellis y Everard. Los ejemplos del agente colorante apropiado incluyen menta, frambuesas, regaliz, naranja, limón, pomelo, caramelo, vainilla, cereza, sabor uva y sus combinaciones. Los ejemplos del agente de control del pH apropiado incluyen ácido cítrico, ácido tartárico, ácido fosfórico, ácido clorhídrico y ácido maleico. Los ejemplos del endulzante apropiado incluyen aspartamo, acesulfamo K y taumatina, y similares. Los ejemplos del agente enmascarador del sabor apropiado incluyen bicarbonato de sodio, resina de intercambio iónico, compuestos de inclusión de ciclodextrina, sustancias adsorbentes y apomorfina microcapsulada.

La preparación contiene el compuesto de la presente invención o el fármaco concomitante en una cantidad usualmente de aproximadamente el 0.1 al aproximadamente 50% en peso, con

preferencia, de aproximadamente el 0.1 al aproximadamente 30% en peso, y con preferencia son preparaciones (tales como el agente sublingual, bucal, antes mencionado, y similares) que pueden disolver el 90% o más del compuesto de la presente invención o el fármaco concomitante (en agua) dentro el rango de tiempo de aproximadamente 1 a aproximadamente 60 min, con preferencia, de aproximadamente 1 a aproximadamente 15 min, con mayor preferencia, de aproximadamente 2 a aproximadamente 5 min, y preparaciones de desintegración rápida intraoral que se desintegran dentro del rango de 1 a 60 seg, con preferencia, de 1 a 30 seg, con mayor preferencia, de 1 a 10 seg, después de ser colocados en una cavidad oral.

El contenido del excipiente antes mencionado en toda la preparación va de aproximadamente 10 a aproximadamente 99% en peso, con preferencia, de aproximadamente 30 a aproximadamente 90% en peso. El contenido del derivado de β–ciclodextrina o β–ciclodextrina en toda la preparación va de 0 al aproximadamente 30% en peso. El contenido del lubricante en toda la preparación va de aproximadamente el 0.01 a aproximadamente el 10% en peso, con preferencia, de aproximadamente el 1 a aproximadamente el 5% en peso. El contenido del agente isotónico en toda la preparación va de aproximadamente el 0.1 a aproximadamente el 90% en peso, con preferencia, de aproximadamente el 10 al aproximadamente 70% en peso. El contenido del portador hidrofílico en toda la preparación va de aproximadamente el 0.1 a aproximadamente el 50% en peso, con

preferencia, de aproximadamente el 10 a aproximadamente el 30% en peso. El contenido del polímero dispersable en agua en toda la preparación va de aproximadamente el 0.1 a aproximadamente el 30% en peso, con preferencia, de aproximadamente el 10 a aproximadamente el 25% en peso. El contenido del estabilizante en toda la preparación va de aproximadamente el 0.1 a aproximadamente el 10% en peso, con preferencia, de aproximadamente el 1 al 5% en peso. La preparación antes mencionada también puede contener aditivos tales como un agente colorante, endulzante, conservante, y similares, de ser necesario.

La dosificación del agente de combinación de la presente invención difiere según el tipo de compuesto de la presente invención, edad, peso corporal, condición patológica, forma farmacológica, método de administración, período de administración, y similares, y por ejemplo, se administra a un paciente con cáncer (adulto, peso corporal: aproximadamente 60 kg), un agente de combinación por vía intravenosa, en una dosis de aproximadamente 0.01 a aproximadamente 1000 mg/kg/día, con preferencia, aproximadamente de 0.01 a aproximadamente 100 mg/kg/día, con mayor preferencia, de aproximadamente 0.1 a aproximadamente 100 mg/kg/día, en particular de aproximadamente 0.1 a aproximadamente 50 mg/kg/día, en especial de aproximadamente 1.5 a aproximadamente 30 mg/kg/día, en términos del compuesto de la presente invención o el fármaco concomitante, respectivamente, una o varias veces divididas en el día, De hecho, como la dosis tal como

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se describió con anterioridad varía según diversas condiciones, a veces pueden ser suficientes menores cantidades que las antes mencionadas, además, a veces se deben administrar cantidades fuera de ese rango.

La cantidad del fármaco concomitante se puede fijar en cualquier valor salvo que los efectos secundarios sean problemáticos. La dosificación diaria en términos del fármaco concomitante difiere según la gravedad del síntoma, la edad, el peso corporal, la diferencia de sensibilidad del sujeto, el período de administración, el intervalo, y la naturaleza, farmacia, tipo de preparación farmacéutica, tipo de ingrediente efectivo, y similares, y no estar not particularmente restringida, y la cantidad de fármaco es, en el caso de una administración oral, por ejemplo, usualmente de aproximadamente 0.001 a 2000 mg, con preferencia, de aproximadamente 0.01 a 500 mg, con mayor preferencia, de aproximadamente 0.1 a 100 mg, por 1 kg de un mamífero y esta se administra usualmente una a 4 veces divididas en el día.

Al administrar un agente de combinación de la presente invención, el compuesto de la presente invención se puede administrar después de la administración del fármaco concomitante o el fármaco concomitante se puede administrar después de la administración del compuesto de la presente invención, a pesar de que se pueden administrar de forma simultánea. Cuando se administran en un intervalo, el intervalo difiere según el ingrediente efectivo por administrar, la forma farmacológica y el método de

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administración, y por ejemplo, cuando el fármaco concomitante se administra primero, se ejemplifica un método en el que el compuesto de la presente invención se administra dentro de un rango de tiempo de 1 min a 3 días, con preferencia, de 10 min a 1 día, con mayor preferencia, de 15 min a 1 h después de la administración del fármaco concomitante. Cuando el compuesto de la presente invención se administra primero, se ejemplifica un método en el que el fármaco concomitante se administra dentro de un rango de tiempo de 1 min a 1 día, con preferencia, de 10 min a 6 h, con mayor preferencia, de 15 min a 1 h después de la administración del compuesto de la presente invención.

En un método de administración preferible, por ejemplo, el fármaco concomitante que se moldeó en una preparación para administración oral se administra por vía oral en una dosis diaria de aproximadamente 0.001 a 200 mg/kg, y aproximadamente 15 min más tarde, se administra el compuesto de la presente invención que se moldeó en una preparación para administración oral en una dosis diaria de aproximadamente 0.005 a 100 mg/kg.

Por otra parte, el compuesto de la presente invención o el agente de combinación de la presente invención se puede usar concurrentemente con una terapia no farmacológica. Para ser precisos, el compuesto de la presente invención y el agente de combinación de la presente invención se pueden combinar con una terapia no farmacológica tales como (1) cirugía, (2) quimioterapia hipertensiva usando angiotensina II, etc., (3) terapia génica, (4)

termoterapia, (5) crioterapia, (6) cauterización con láser, (7) radioterapia, y similares.

Por ejemplo, al usar el compuesto de la presente invención o el agente de combinación de la presente invención antes o después de una cirugía, y similares, o antes o después de un tratamiento combinados de dos o tres tipos de ellos, se pueden lograr efectos tales como prevención de la emergencia de una resistencia, prolongación de la supervivencia sin enfermedad, supresión de la metástasis o la recurrencia del cáncer, la prolongación de la vida, y similares.

Además, es posible combinar un tratamiento con el compuesto de la presente invención o el agente de combinación de la presente invención con un terapia de apoyo [(i) administración de antibióticos (por ejemplo, tipo β–lactama como pansporina, y similares, de tipo macrólidos como claritromicina, y similares etc.) para la complicación con diversas enfermedades infecciosas, (ii) administración de nutrición parenteral total, preparación de aminoácidos o preparación de vitaminas generales para mejorar la desnutrición, (iii) administración de morfina para mitigar el dolor, (iv) administración de un agente farmacéutico para mejorar los efectos secundarios como náuseas, vómitos, anorexia, diarrea, leucopenia, trombocitopenia, reducida concentración de hemoglobina, pérdida de cabello, hepatopatía, renopatía, DIC, fiebre, y similares y (v) administración de un agente farmacéutico para suprimir la resistencia a múltiples fármacos del cáncer, y similares].

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Con preferencia, el compuesto de la presente invención o el agente de combinación de la presente invención se administra por vía oral (incluso preparaciones de liberación prolongada), intravenosa (incluso bolos, infusiones y clatratos), subcutánea e intramuscular (incluso bolos, infusiones y preparaciones de liberación prolongada), transdérmica, intratumoral o proximal antes o después de realizar el tratamiento antes descrito.

Como un período para administrar el compuesto de la presente invención o el agente de combinación de la presente invención antes de la cirugía, etc., por ejemplo, se puede administrar una vez aproximadamente 30 min a 24 h antes de la cirugía, etc., o en 1 a 3 ciclos aproximadamente 3 meses a 6 meses antes de la cirugía, etc. De este modo, la cirugía, etc. se puede realizar fácilmente porque, por ejemplo, un tejido canceroso se reduciría al administrar el compuesto de la presente invención o el agente de combinación de la presente invención antes de la cirugía, y similares.

Como un período para administrar el compuesto de la presente invención o el agente de combinación de la presente invención después de la cirugía, etc., por ejemplo, se puede administrar repetidamente unas pocas semanas a 3 meses, aproximadamente 30 min a 24 h después de la cirugía, y similares. De este modo, mejora el efecto de la cirugía, etc. al administrar el compuesto de la presente invención o el agente de combinación de la presente invención después de la cirugía, y similares.

Ejemplos

La presente invención se explica específicamente a continuación por medio de los Ejemplos de referencia, los Ejemplos, los Ejemplos de formulación, los Ejemplos experimentales y los Ejemplos de ensayo, que no deben ser interpretados como limitativos.

El análisis de LC/MS en los ejemplos se realizó en las siguientes condiciones.

Herramienta de medición: Waters Corporation ZQ

Columna: fabricada por Shiseido Co., Ltd. CAPCELL PAK C18 UG120 S–3 3 μm, 35 X 1,5 mm

Solvente: SOLUCIÓN A; 5 mM de acetato de amonio acuoso / acetonitrilo = 98/2

SOLUCIÓN B; 100 mM de acetato de amonio acuoso / acetonitrilo = 5/95

Ciclo de gradiente: 0,00 min (SOLUCIÓN A/SOLUCIÓN B = 100/0), 2,00 min (SOLUCIÓN A/SOLUCIÓN B = 0/100), 3,00 min (SOLUCIÓN A/SOLUCIÓN B = 0/100), 3,01 min (SOLUCIÓN A/SOLUCIÓN B = 100/0), 3,80 min (SOLUCIÓN A/SOLUCIÓN B = 100/0)

Caudal: 0,5 mL/min, la temperatura de la columna era la temperatura ambiente sin temperatura de control.

Método de ionización: ionización con electronebulización, se detectaron picos de iones positivos y negativos ESI.

El porcentaje del área de los picos detectado el UV: 220 nm del pico del producto resultante se tomó como la pureza del compuesto.

En los ejemplos, la HPLC preparativa se realizó como sigue.

Herramientas de HPLC preparativa: Gilson, Inc. Sistema de purificación de alto rendimiento

Columna: YMC Combiprep Hidrosphere C18 S–5 5 μm, 12 nM. 50 X 20 mm

Solvente: SOLUCIÓN A; agua

SOLUCIÓN B; acetonitrilo

Ciclo de gradiente: 0,00 min (SOLUCIÓN A/SOLUCIÓN B = 98/2), 1,10 min (SOLUCIÓN A/SOLUCIÓN B = 98/2), 5,00 min (SOLUCIÓN A/SOLUCIÓN B = 0/100), 6,40 min (SOLUCIÓN A/SOLUCIÓN B = 0/100), 6,50 min (SOLUCIÓN A/SOLUCIÓN B = 2/98), 6,52 min (SOLUCIÓN A/SOLUCIÓN B = 2/98)

Caudal: 25 mL/min, método de detección: UV 220 nm

Salvo que se especifique otra cosa, la elución por cromatografía en columna se realizó bajo observación de TLC (cromatografía en capa fina) en los Ejemplos de referencia y los Ejemplos. Para la observación por TLC, se usó 60F254 fabricado por Merck, o placa NH TLC fabricada por Fuji Silysia Chemical Ltd. como placa de TLC, y el solvente usado como un solvente de elución en cromatografía en columna se usó como solvente de desarrollo. Para la detección, se empleó también un detector de UV. Como cromatografía en columna de gel de sílice, se usaron gel de sílice gel 60 (malla 70–230) fabricada por Merck, gel de sílice NH (malla 100–200) fabricada por Fuji Silysia Chemical Ltd., y similares. Le temperatura ambiente generalmente significa de aproximadamente

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10 °C a 35 °C. Para secar el extracto, se usó sulfato de sodio anhidro o sulfato de magnesio anhidro.

En los Ejemplos de formulación, se usan los productos compatibles con Japanese Pharmacopoeia 14a. Edición o Japanese Pharmaceutical Excipients 2003 como aditivos de preparación (por ejemplo, lactosa, almidón de maíz, estearato de magnesio, celulosa microcristalina).

Las abreviaturas en los Ejemplos y Ejemplos de referencia significan lo siguiente.

LC: cromatografía líquida

MS: espectrometría de masas

ESI: ionización por electronebulización

FAB: rayo atómico rápido

M: pico iónico molecular

RMN: espectros de resonancia magnética nuclear

Hz: hertz

J: constante de acoplamiento

m: multiplete

q: cuarteto

t: triplete

d: doblete

s: singulete

br: amplio

dt: doble triplete

brs: singulete amplio

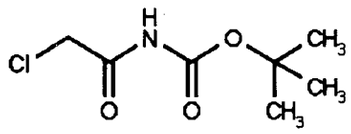
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% en p: porcentaje en peso

DMSO: dimetilsulfóxido

Ejemplo de referencia 1

Producción de (cloroacetil)carbamato de tert-butilo



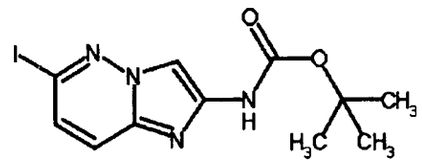
A una suspensión de 2–cloroacetamida (25 g, 267 mmol) en 1,2–dicloroetano (125 mL) se añadió gota a gota cloruro de oxalilo (28 mL, 321 mmol) a 0 °C. Tras calentar a reflujo durante 3 h, la mezcla se enfrió hasta 0 °C, se añadió alcohol tert-butílico/1,2–dicloroetano (75 mL, 1/1) a la mezcla, y la mezcla se agitó durante 20 min. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con 1,2–dicloroetano. Tras lavar con solución acuosa saturada de hidrógeno–carbonato de sodio y agua, el extracto se secó sobre sulfato de magnesio anhidro y se filtró. El solvente se evaporó a presión reducida, y el residuo se recristalizó en ciclohexano para dar el compuesto del título (25,6 g, 49%) en forma de cristales blancos.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,58 (9H, s), 4,46 (2H, s), 7,59 (1H, br).

Ejemplo de referencia 2

Producción de tert-butilo (6–yodoimidazo[1,2–b]piridazin–2–il)carbamato de tert-butilo

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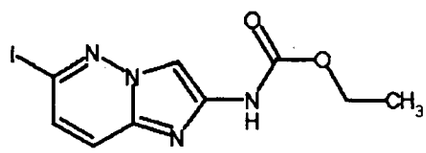


A una solución de 3–amino–6–yodopiridazina (10,0 g, 45,2 mmol) en N,N–dimetilacetamida (100 mL) se añadieron (cloroacetil)carbamato de tert-butilo (14,0 g, 72,4 mmol) e hidrógeno–fosfato disódico (16,1 g, 113 mmol), y la mezcla se agitó a 120 °C durante 3 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua (400 mL) a la mezcla, y los cristales precipitados se filtraron y se lavaron con acetonitrilo y éter de petróleo para dar el compuesto del título (10,2 g, 63%) en forma de un polvo verde.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,49 (9H, s), 7,45 (1H, d, J = 9,5 Hz), 7,69 (1H, d, J = 9,5 Hz), 8,01 (1H, brs), 10,20 (1H, brs).

Ejemplo de referencia 3

Producción de (6–yodoimidazo[1,2–b]piridazin–2–il)carbamato de etilo



A una solución de 3–amino–6–yodopiridazina (27,0 g, 122 mmol) en N,N–dimetilacetamida (270 mL) se añadieron (cloroacetil)carbamato de etilo (32,4 g, 195 mmol) e hidrógeno–fosfato disódico (43,4 g, 305 mmol), y la mezcla se agitó a 110 °C

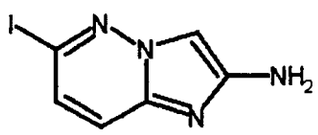
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durante 3 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua (810 mL), y los cristales precipitados se filtraron y se lavaron con acetonitrilo y éter para dar el compuesto del título (33,0 g, 81%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,26 (3H, t, J = 7,1 Hz), 4,17 (2H, q, J = 7,1 Hz), 7,47 (1H, d, J = 9,2 Hz), 7,70 (1H, d, J = 9,2 Hz), 8,06 (1H, s), 10,51 (1H, brs).

Ejemplo de referencia 4–1

Producción de 6–yodoimidazo[1,2–b]piridazin–2–amina



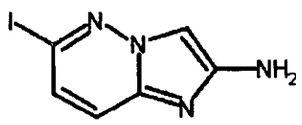
A una suspensión de (6–yodoimidazo[1,2–b]piridazin–2–il)carbamato de tert-butilo (10,2 g, 28,3 mmol) en se añadió acetato de etilo (50 mL) ácido clorhídrico 4 N/acetato de etilo (75 mL), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió éter dietílico (200 mL) a la mezcla de reacción, y el precipitado se filtró. Tras lavar con solución acuosa saturada de hidrógeno–carbonato de sodio, el filtrado se lavó con agua, acetonitrilo y éter dietílico para dar el compuesto del título (4,9 g, 67%) en forma de un polvo verde.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,61 (2H, s), 7,22 (1H, d, J = 8,7 Hz), 7,36 (1H, s), 7,39 (1H, d, J = 8,7 Hz).

Ejemplo de referencia 4–2

Producción de 6–yodoimidazo[1,2–b]piridazin–2–amina

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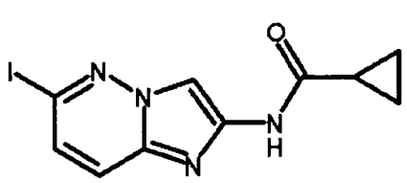


A hidróxido de bario octahidratado (14,5 g, 46,1 mmol) se añadió agua (240 mL), y la mezcla se agitó a 80 °C durante 15 min. Una solución de (6–yodoimidazo[1,2–b]piridazin–2–il)carbamato de etilo (10,2 g, 30,7 mmol) en N–metilpirrolidona (80 mL) se añadió a la mezcla, y la mezcla se agitó a 120 °C durante 8 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua (480 mL) a la mezcla, y la mezcla se agitó durante 1 h. La mezcla se extrajo dos veces con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, se añadió éter diisopropílico al residuo, y los cristales precipitados se recogieron por filtración para dar el compuesto del título (6,1 g, 76%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,61 (2H, s), 7,22 (1H, d, J = 8,7 Hz), 7,36 (1H, s), 7,39 (1H, d, J = 8,7 Hz).

Ejemplo de referencia 5

Producción de N–(6–yodoimidazo[1,2–b]piridazin–2–il) ciclopropancarboxamida



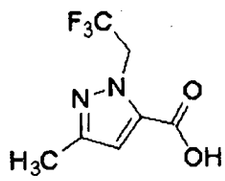
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A una solución (10 mL) de 6–yodoimidazo[1,2–b]piridazin–2–amina (1,0 g, 3,85 mmol) en N,N–dimetilacetamida se añadió cloruro de ciclopropilcarbonilo (0,38 mL, 4,23 mmol), y la mezcla se agitó a temperatura ambiente durante 4 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con hexano/acetato de etilo (4/1) para dar el compuesto del título (1,01 g, 80%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,82 – 0,86 (4H, m), 1,90 – 2,00 (1H, m), 7,49 (1H, d, J = 9,3 Hz), 7,73 (1H, d, J = 9,3 Hz), 8,23 (1H, s), 11,20 (1H, s).

Ejemplo de referencia 7

Producción de ácido 3–metil–1–(2,2,2–trifluoroetil)–1H–pirazol–5–carboxílico



A una suspensión de hidruro de sodio (1,62 g, 40,4 mmol) en N,N–dimetilformamida (250 mL) se añadió gota a gota una solución de 3–metil–1H–pirazol–5–carboxilato de etilo (5660 mg, 36,8 mmol) en N,N–dimetilformamida (50 mL) durante 10 min bajo enfriamiento con hielo. Después de completar la adición gota a gota, la mezcla de reacción se agitó a 0 °C durante 10 min y a temperatura ambiente

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durante 40 min. A la mezcla se añadió trifluorometansulfonato de 2,2,2–trifluoroetilo (9,87 g, 40,4 mmol), y la mezcla se agitó a temperatura ambiente durante 3 h. Bajo enfriamiento con hielo, se añadió ácido clorhídrico 1 N (36 mL) a la mezcla, y el solvente se evaporó a presión reducida. Se añadieron acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno-carbonato de sodio al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→60/40), y se recristalizó en acetato de etilo/hexano para dar 3–metil–1–(2,2,2–trifluoroetil)–1H–pirazol–5–carboxilato de etilo (1,98 g, 23%) en forma de cristales blancos.

A una solución de 3–metil–1–(2,2,2–trifluoroetil)–1H–pirazol–5–carboxilato de etilo (1,74 g, 7,36 mmol) en tetrahidrofurano (5,0 mL) se añadió hidróxido de sodio 8 N (4,6 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió ácido clorhídrico 6 N (6,0 mL) a la mezcla (pH = 3), y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se filtró, y se lavó con acetato de etilo/hexano para dar el compuesto del título (1,28 g, 84%) en forma de un polvo blanco.

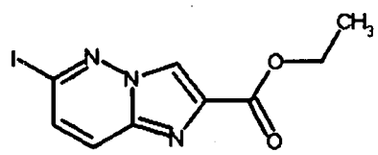
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 5,36 (2H, q, J =

807

9,0 Hz), 6,76 (1H, s), 13,66 (1H, brs).

Ejemplo de referencia 8

Producción de 6–yodoimidazo[1,2–b]piridazin–2–carboxilato de etilo

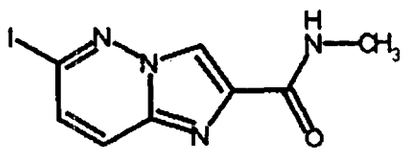


Usando 3–amino–6–yodopiridazina (2,0 g, 9,05 mmol), N,N–dimetilacetamida (20 mL), 3–bromo–2–oxopropanato de etilo (1,82 mL, 14,5 mmol) e hidrógeno–fosfato disódico (3,21 g, 22,6 mmol), y de la misma manera que en el Ejemplo de referencia 3, se obtuvo el compuesto del título (1,2 g, 44%) en forma de un polvo verde.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,33 (3H, t, J = 7,1 Hz), 4,33 (2H, q, J = 7,1 Hz), 7,65 (1H, d, J = 9,5 Hz), 7,96 (1H, d, J = 9,5 Hz), 8,88 (1H, s).

Ejemplo de referencia 9

Producción de 6–yodo–N–metilimidazo[1,2–b]piridazin–2–carboxamida



A una suspensión de 6–yodoimidazo[1,2–b]piridazin–2–carboxilato de etilo (4,5 g, 14,8 mmol) en metanol (13,5 mL) se añadió gota a gota una solución de metilamina/tetrahidrofurano (2

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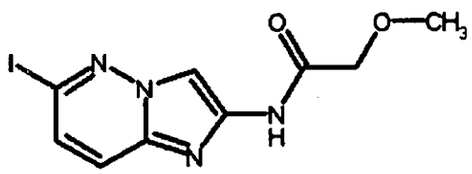
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808

mol/L, 37,1 mL, 74,2 mmol), y la mezcla se agitó a temperatura ambiente durante 96 h. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo, salmuera saturada y agua para dar el compuesto del título (3,2 g, 71%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,79 (3H, d, J = 4,8 Hz), 7,62 (1H, d, J = 9,6 Hz), 7,90 (1H, d, J = 9,6 Hz), 8,46 – 8,55 (1H, m), 8,65 (1H, s).

Ejemplo de referencia 10

Producción de N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metoxiacetamida



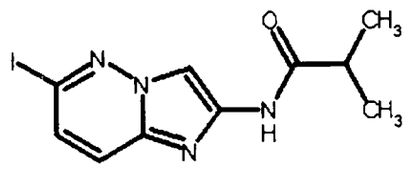
Usando 6–yodoimidazo[1,2–b]piridazin–2–amina (1,0 g, 3,85 mmol), N,N–dimetilacetamida (10 mL) y cloruro de metoxiacetilo (0,46 g, 4,23 mmol) como materiales de partida y de la misma manera que en el Ejemplo de referencia 5, se obtuvo el compuesto del título (1,01 g, 79%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,36 (3H, s), 4,09 (2H, s), 7,51 (1H, d, J = 9,6 Hz), 7,75 (1H, d, J = 9,6 Hz), 8,30 (1H, s), 10,73 (1H, s).

Ejemplo de referencia 11

Producción de N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilpropanamida

809

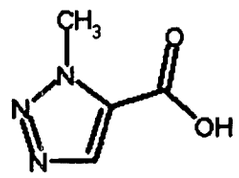


Usando 6–yodoimidazo[1,2–b]piridazin–2–amina (1,0 g, 3,85 mmol), N,N–dimetilacetamida (8,0 mL) y cloruro de isobutirilo (0,44 mL, 4,23 mmol) como materiales de partida y de la misma manera que en el Ejemplo de referencia 5, se obtuvo el compuesto del título (0,93 g, 73%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,10 (6H, d, J = 6,6 Hz), 2,67 – 2,74 (1H, m), 7,49 (1H, d, J = 9,3 Hz), 7,73 (1H, d, J = 9,3 Hz), 8,27 (1H, s), 10,87 (1H, s).

Ejemplo de referencia 12

Producción de ácido 1–metil–1H–1,2,3–triazol–5–carboxílico



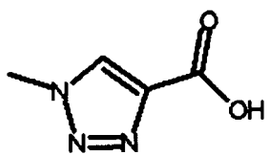
A una solución de 1–metil–1H–1,2,3–triazol–5–carboxilato de etilo (1,15 g, 7,41 mmol) en metanol (17 mL) se añadió hidróxido de sodio 1 N (11,5 mL), y la mezcla se agitó a temperatura ambiente durante 1 h. El metanol se evaporó a presión reducida, se añadió ácido clorhídrico 1 N (12 mL) a la mezcla, los cristales precipitados se recogieron por filtración y se lavaron con agua. Los cristales se secaron al vacío a 90 °C para dar el compuesto del título (148 mg, 16%) en forma de un polvo blanco.

810

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,23 (3H, s), 8,20 (1H, s).

Ejemplo de referencia 13

Producción de ácido 1–metil–1H–1,2,3–triazol–4–carboxílico

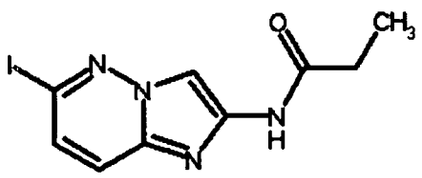


Usando 1–metil–1H–1,2,3–triazol–4–carboxilato de etilo (1,48 g, 9,54 mmol), metanol (22 mL), hidróxido de sodio 1 N (15 mL) y ácido clorhídrico 1 N (15 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 12, se obtuvo el compuesto del título (605 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,09 (3H, s), 8,62 (1H, s), 10,06 (1H, br).

Ejemplo de referencia 14

Producción de N–(6–yodoimidazo[1,2–b]piridazin–2–il)propanamida



Usando 6–yodoimidazo[1,2–b]piridazin–2–amina (1,0 g, 3,85 mmol), N,N–dimetilacetamida (10 mL) y cloruro de propionilo (0,37 mL, 4,23 mmol) como materiales de partida y de la misma manera que en el Ejemplo de referencia 5, se obtuvo el compuesto del título (0,88 g, 72%) en forma de un polvo color café oscuro.

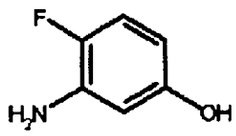
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,08 (3H, d, J = 7,5 Hz), 2,39

811

(2H, q, J = 7,5 Hz), 7,48 (1H, d, J = 9,3 Hz), 7,73 (1H, d, J = 9,3 Hz), 8,26 (1H, s), 10,86 (1H, s).

Ejemplo de referencia 15

Producción de 3–amino–4–fluorofenol



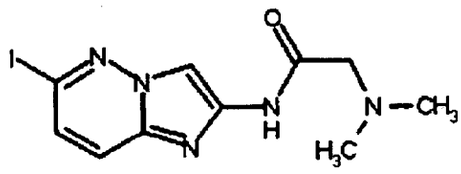
A una solución de 2–cloro–4–fluoro–5–nitrofenol (3,20 g, 16,7 mmol) en metanol (60 mL) se añadió 20% en peso de hidróxido de paladio sobre carbón (1,60 g) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 8 h bajo una atmósfera de hidrógeno. Después de reemplazar el nitrógeno, se añadió trietilamina (2,32 mL, 16,7 mmol) a la mezcla de reacción, y la mezcla se filtró a través de un embudo de Kiriyama. Se añadió salmuera saturada al filtrado, y la mezcla se extrajo dos veces con éter dietílico. El extracto se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se recristalizó en éter dietílico/hexano para dar el compuesto del título (1,40 g, 66%) en forma de cristales de color color café pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 3,70 (2H, brs), 4,50 (1H, s), 6,10 (1H, dt, J = 8,7, 3,0 Hz), 6,26 (1H, dd, J = 7,5, 3,0 Hz), 6,81 (1H, dd, J = 10,8, 8,7 Hz).

Ejemplo de referencia 16

Producción de N–(6–yodoimidazo[1,2–b]piridazin–2–il)–N^2,N^2–dimetilglicinamida

812

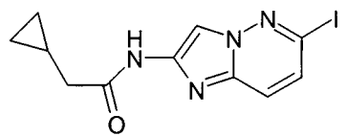


A una solución de 6–yodoimidazo[1,2–b]piridazin–2–amina (1040 mg, 4,0 mmol) en N–metilpirrolidona (5,0 mL) se añadió clorhidrato de cloruro de dimetilaminoacetilo (948 mg, 6,0 mmol), y la mezcla se agitó a temperatura ambiente durante 6 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30), y se precipitó en éter diisopropílico para dar el compuesto del título (1019 mg, 74%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,28 (6H, s), 3,16 (2H, s), 7,51 (1H, d, J = 9,2 Hz), 7,75 (1H, d, J = 9,2 Hz), 8,29 (1H, s), 10,50 (1H, s).

Ejemplo de referencia 17

Producción de 2–ciclopropil–N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida



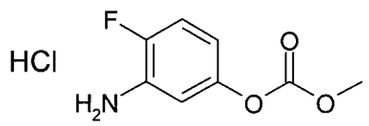
A una solución de ácido ciclopropilacético (441 mg, 4,4 mmol) en tetrahidrofurano (8,0 mL) se añadieron N,N–dimetilformamida (1 gota) y cloruro de tionilo (0,32 mL, 4,4 mmol), y la mezcla se agitó a

temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida, y se disolvió en N,N–dimetilacetamida (2,0 mL). A una solución de 6–yodoimidazo[1,2–b]piridazin–2–amina (1,04 g, 4,0 mmol) en N,N–dimetilacetamida (6,0 mL) se añadió gota a gota la solución antes mencionada bajo enfriamiento con hielo. La mezcla se agitó a temperatura ambiente durante 2 h. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice básica (acetato de etilo/hexano = 80/20→100/0), y se recristalizó en acetato de etilo para dar el compuesto del título (982 mg, 72%) en forma de cristales de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,10 – 0,25 (2H, m), 0,45 – 0,55 (2H, m), 1,00 – 1,15 (1H, m), 2,27 (2H, d, J = 6,9 Hz), 7,48 (1H, d, J = 9,4 Hz), 7,72 (1H, d, J = 9,4 Hz), 8,28 (1H, s), 10,82 (1H, s).

Ejemplo de referencia 18

Producción de clorhidrato de 3–amino–4–fluorofenilmetilcarbonato



A una solución (20 mL) de 2–cloro–4–fluoro–5–

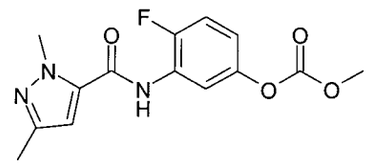
814

nitrofenilmetilcarbonato (1,00 g, 4,0 mmol) en metanol se añadió hidróxido de paladio sobre carbón al 20% (0,4 g) bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante 5 días. Después de reemplazar el nitrógeno, el catalizador se filtró. El solvente se evaporó del filtrado a presión reducida, y el residuo se recristalizó en éter dietílico para dar el compuesto del título (759 mg, 86%) en forma de un polvo de color verde pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 3,89 (3H, s), 6,75–6,85 (1H, m), 7,05–7,15 (2H, m).

Ejemplo de referencia 19

Producción de 3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–fluorofenilmetilcarbonato



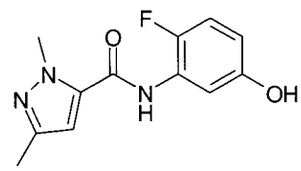
Usando una solución de clorhidrato de 3–amino–4–fluorofenilmetilcarbonato (740 mg, 3,34 mmol) y cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (556 mg, 3,51 mmol) en N,N–dimetilacetamida (10 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (895 mg, 87%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,30 (3H, s), 3,91 (3H, s), 4,14 (3H, s), 6,45 (1H, s), 6,85 – 6,95 (1H, m), 7,13 (1H, dd, J = 9,0 Hz, 10,5 Hz), 7,83 (1H, br s), 8,33 (1H, dd, J = 2,7 Hz, 6,6 Hz).

815.

Ejemplo de referencia 20

Producción de N–(2–fluoro–5–hidroxifenil)–1,3–dimetil–1H–pirazol–5–carboxamida

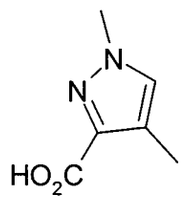


A una solución de 3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–fluorofenilmetilcarbonato (448 mg, 1,46 mmol) en metanol (10 mL) se añadió solución acuosa 1 N de hidróxido de sodio (2 mL, 2 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 40 min. Bajo enfriamiento con hielo, se añadió ácido clorhídrico 1 N a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se recristalizó en éter dietílico/hexano para dar el compuesto del título (305 mg, 84%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,98 (3H, s), 6,56 (1H, m), 6,82 (1H, s), 6,97 – 7,10 (2H, m), 9,47 (1H, s), 9,85 (1H, s).

Ejemplo de referencia 21

Producción de ácido 1,4–dimetil–1H–pirazol–3–carboxílico



Usando 1,4–dimetil–1H–pirazol–3–carboxilato de etilo (440 mg,

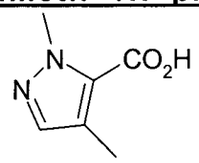
816

2,62 mmol), solución acuosa 1 N de hidróxido de sodio (3 mL, 3 mmol) y etanol (3 mL), y por reacción de la misma manera que en el Ejemplo de referencia 20, se obtuvo el compuesto del título (152 mg, 41%) en forma de cristales de color amarillo pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,30 (3H, s), 3,92 (3H, s), 7,21 (1H, s).

Ejemplo de referencia 22

Producción de ácido 1,4–dimetil–1H–pirazol–5–carboxílico

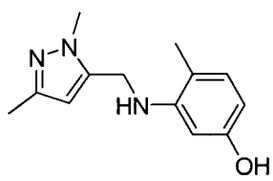


Usando 1,4–dimetil–1H–pirazol–5–carboxilato de etilo (565 mg, 3,36 mmol), solución acuosa 1 N de hidróxido de sodio (4 mL, 4 mmol) y etanol (4 mL), y por reacción de la misma manera que en el Ejemplo de referencia 20, se obtuvo el compuesto del título (261 mg, 55%) en forma de cristales incoloros.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,31 (3H, s), 4,16 (3H, s), 7,34 (1H, s).

Ejemplo de referencia 23

Producción de 3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}–4–metilfenol



A una solución de 3–amino–4–metilfenol (930 mg, 7,5 mmol) en N,N–dimetilacetamida (10 mL) se le añadió una solución de cloruro

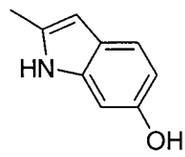
de 1,3–dimetil–1H–pirazol–5–carbonilo (1370 mg, 8,7 mmol) en N, N–dimetilacetamida (5 mL), y la mezcla se agitó a 0 °C durante 20 min. A la mezcla se añadieron acetato de etilo/tetrahidrofurano, solución acuosa saturada de hidrógeno–carbonato de sodio, y la capa acuosa se extrajo 4 veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar N–(5–hidroxi–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida (1170 mg, 63%) en forma de un sólido blanco. A una suspensión de hidruro de litio y aluminio (1130 mg, 24 mmol) en tetrahidrofurano (35 mL) se añadió lentamente gota a gota una solución de N–(5–hidroxi–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida (1170 mg, 4,8 mmol) en tetrahidrofurano (10 mL) bajo enfriamiento con hielo. Después de la adición gota a gota, la mezcla de reacción se calentó a reflujo durante 5 h. Se añadió una solución acuosa saturada de sulfato de sodio a la mezcla bajo enfriamiento, se añadió sulfato de magnesio y el material insoluble se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (570 mg, 52%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,98 (3H, s), 2,06 (3H, s), 3,72 (3H, s), 4,21 (2H, d, J = 5,7 Hz), 5,23 (1H, t, J = 5,7 Hz), 5,89 (1H, s), 5,93 (1H, dd, J = 8,0, 2,3 Hz), 5,97 (1H, d, J = 2,3 Hz), 6,71 (1H, d, J = 8,3 Hz), 8,73 (1H, s).

818

Ejemplo de referencia 24

Producción de 2–metil–1H–indol–6–ol



A una suspensión de hidruro de litio y aluminio (3,7 g, 97 mmol) en 1,4–dioxano (97 mL) se le añadió lentamente gota a gota una solución de 6–metoxi–1H–indol–2–carboxilato de metilo (2,0 g, 9,8 mmol) en 1,4–dioxano (30 mL) bajo enfriamiento con hielo. Después de la adición gota a gota, la mezcla de reacción se calentó a reflujo durante 24 h. Se añadió una solución acuosa saturada de sulfato de sodio a la mezcla bajo enfriamiento, se añadió sulfato de magnesio y el material insoluble se filtró. El filtrado se concentró a presión reducida, y el residuo se recristalizó en hexano para dar 6–metoxi–2–metil–1H–indol (1,0 g, 6,5 mmol) en forma de un sólido amarillo. A una solución de 6–metoxi–2–metil–1H–indol (1,0 g, 6,2 mmol) en ácido acético (15 mL) se añadió bromuro de hidrógeno acuoso al 48% (31 mL) a temperatura ambiente, y la mezcla de reacción se calentó a reflujo durante 3 h. El solvente se evaporó a presión reducida, acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno–carbonato de sodio se añadieron al residuo. La capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano

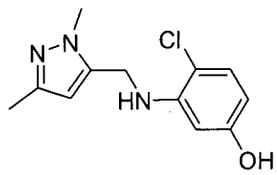
819

para dar el compuesto del título (600 mg, 65%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,29 (3H, d, J = 0,8 Hz), 5,88 – 5,95 (1H, m), 6,43 (1H, dd, J = 8,3, 2,3 Hz), 6,63 (1H, d, J = 2,3 Hz), 7,12 (1H, d, J = 8,3 Hz), 8,70 (1H, s), 10,45 (1H, br, s).

Ejemplo de referencia 25

Producción de 4–cloro–3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}fenol



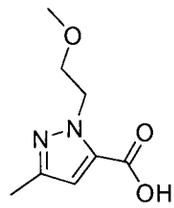
De la misma manera que en el Ejemplo de referencia 23 y usando 3–amino–4–clorofenol (920 mg, 6,4 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (1170 mg, 7,4 mmol) y N, N–dimetilacetamida (13 mL) como materiales de partida, se obtuvo N–(2–cloro–5–hidroxifenil)–1,3–dimetil–1H–pirazol–5–carboxamida (1190 mg, 4,5 mmol). Usando hidruro de litio y aluminio (1060 mg, 22 mmol), N–(2–cloro–5–hidroxifenil)–1,3–dimetil–1H–pirazol–5–carboxamida (1190 mg, 4,5 mmol) y tetrahidrofurano (40 mL) como materiales de partida, se obtuvo el compuesto del título (810 mg, 72%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,06 (3H, s), 3,72 (3H, s), 4,29 (2H, d, J = 5,7 Hz), 5,73 (1H, t, J = 5,7 Hz), 5,87 (1H, s), 6,02 (1H, dd, J = 8,3, 2,7 Hz), 6,11 (1H, d, J = 2,7 Hz), 6,99 (1H, d, J = 8,3 Hz), 9,27 (1H, s).

820

Ejemplo de referencia 26

Producción de ácido 1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxílico



A una suspensión de hidruro de sodio (310 mg, 7,8 mmol) en N,N–dimetilformamida (10 mL) se añadió lentamente una solución de 3–metil–1H–pirazol–5–carboxilato de etilo (1000 mg, 6,5 mmol) en N,N–dimetilformamida (5 mL) bajo enfriamiento con hielo, y la mezcla se agitó a 0 °C durante 10 min, luego a temperatura ambiente durante 20 min. A la mezcla de reacción se añadió una solución de 1–bromo–2–metoxietano (1090 mg, 7,8 mmol) en N,N–dimetilformamida (4 mL), y la mezcla se agitó a temperatura ambiente durante 7 h. El solvente se evaporó a presión reducida, y Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo. La capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→70/30) para dar 1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxilato de etilo (430 mg, 2,0 mmol) en forma de un líquido incoloro. A una solución del 1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxilato de etilo obtenida (430 mg, 2,0 mmol) en tetrahidrofurano (6 mL) se le añadió

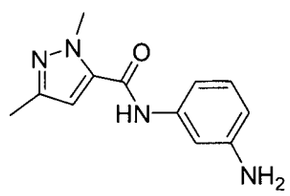
821

solución acuosa 8 N de hidróxido de sodio (1,3 mL), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadieron ácido clorhídrico 1 N (13 mL) y acetato de etilo a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (310 mg, 83%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,15 (3H, s), 3,17 (3H, s), 3,61 (2H, t, J = 5,8 Hz), 4,55 (2H, t, J = 5,8 Hz), 6,56 (1H, s), 13,19 (1H, br. s).

Ejemplo de referencia 27

Producción de N–(3–aminofenil)–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de 3–nitroanilina (1,0 g, 7,2 mmol) en N, N–dimetilacetamida (6 mL) se añadió una solución de cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (1260 mg, 8,0 mmol) en N,N–dimetilacetamida (2 mL), y la mezcla se agitó a temperatura ambiente durante 30 min. Se agregó agua (200 mL) a la mezcla bajo enfriamiento con hielo, y la mezcla se filtró. El sólido obtenido se lavó con agua y éter dietílico para dar 1,3–dimetil–N–(3–nitrofenil)–1H–pirazol–5–carboxamida (1850 mg, 7,1 mmol). A una solución de

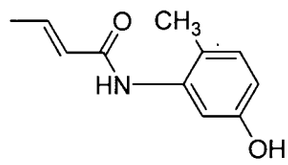
822

la 1,3–dimetil–N–(3–nitrofenil)–1H–pirazol–5–carboxamida obtenida (1850 mg, 7,1 mmol) en etanol (50 mL) se le añadió paladio / carbón al 10% (190 mg). Se le agregó monohidrato de hidrazina (1090 mg, 22 mmol) lentamente a la mezcla a temperatura ambiente y la mezcla se agitó a 60 °C durante 1 h. La mezcla de reacción se filtró, y el filtrado se evaporó a presión reducida. Al residuo se le añadieron acetato de etilo y agua, y la capa acuosa se extrajo con acetato de etilo (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (1650 mg, 99%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,98 (3H, s), 5,09 (2H, s), 6,31 (1H, d, J = 9,1 Hz), 6,76 – 6,83 (2H, m), 6,95 (1H, t, J = 8,0 Hz), 7,03 – 7,08 (1H, m), 9,81 (1H, s).

Ejemplo de referencia 28

Producción de (2E)–N–(5–hidroxi–2–metilfenil)but–2–enamida



De la misma manera que en el Ejemplo 259 y usando ácido (2E)–but–2–enoico (1680 mg, 19 mmol), tetrahidrofurano (5 mL), N, N–dimetilformamida (1 gota), cloruro de oxalilo (1670 μL, 19 mmol), 3–amino–4–metilfenol (2000 mg, 16 mmol) y N, N–dimetilacetamida (35 mL) como materiales de partida, se obtuvo el compuesto del

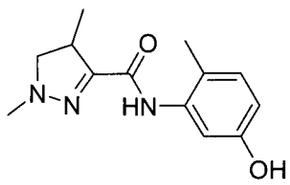
823

título (1830 mg, 59%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,85 (3H, dd, J = 7,0, 1,7 Hz), 2,07 (3H, s), 6,22 (1H, d, J = 15,5 Hz), 6,47 (1H, dd, J = 8,3, 2,5 Hz), 6,68 – 6,83 (1H, m), 6,95 (1H, d, J = 8,3 Hz), 7,02 (1H, s), 9,05 (1H, s), 9,16 (1H, s).

Ejemplo de referencia 29

Producción de N–(5–hidroxi–2–metilfenil)–1,4–dimetil–4,5–dihidro–1H–pirazol–3–carboxamida

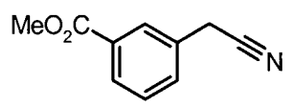


Una mezcla de (2E)–N–(5–hidroxi–2–metilfenil)but–2–enamida (1830 mg, 9,6 mmol) y 3–metil–1,2,3–oxadiazol–3–ium–5–olato (4 mL) se agitó a 150 °C durante 2 días. La mezcla de reacción se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→60/40) para dar el compuesto del título (351 mg, 15%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,15 (3H, d, J = 6,4 Hz), 2,07 (3H, s), 2,91 (3H, s), 3,04 – 3,11 (1H, m), 3,23 – 3,33 (2H, m), 6,47 (1H, dd, J = 8,3, 2,7 Hz), 6,97 (1H, d, J = 8,3 Hz), 7,13 (1H, d, J = 2,7 Hz), 8,94 (1H, s), 9,22 (1H, s).

Ejemplo de referencia 30

Producción de 3–(cianometil)benzoato de metilo



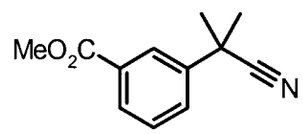
824

A una solución de 3–(bromometil)benzoato de metilo (10,0 g, 44 mmol) en acetonitrilo (100 mL) se añadieron cianuro de potasio (5,7 g, 87 mmol) y 18–corona–6 (1,0 g), y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se filtró, el solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→30/70). La solución combinada se concentró a presión reducida para dar el compuesto del título (7,0 g, 91%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,88 (3H, s), 4,17 (2H, s), 7,57 (1H, t, J = 7,6 Hz), 7,61 – 7,69 (1H, m), 7,88 – 7,95 (1H, m), 7,97 (1H, br s).

Ejemplo de referencia 31

Producción de 3–(1–ciano–1–metiletil)benzoato de metilo



A una solución de 3–(cianometil)benzoato de metilo (7,0 g, 40 mmol) en dimetilsulfóxido (80 mL) se añadió lentamente hidruro de sodio (60% en aceite, 4,8 g, 120 mmol) bajo enfriamiento a no más de 25 °C. La mezcla de reacción se agitó a temperatura ambiente durante 20 min. A la mezcla se añadió yoduro de metilo (7,5 mL, 120 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Bajo enfriamiento con hielo, la mezcla de reacción se diluyó con agua. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de

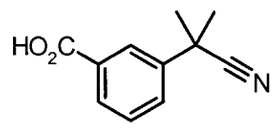
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sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→50/50). La solución combinada se concentró a presión reducida para dar el compuesto del título (6,4 g, 79%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,72 (6 H, s), 3,89 (3 H, s), 7,61 (1 H, t, J = 7,8 Hz), 7,84 (1 H, ddd, J = 7,8, 2,1, 1,2 Hz), 7,95 (1 H, dt, J = 7,8, 1,2 Hz), 8,08 (1 H, t, J = 1,5 Hz).

Ejemplo de referencia 32

Producción de ácido 3–(1–ciano–1–metiletil)benzoico



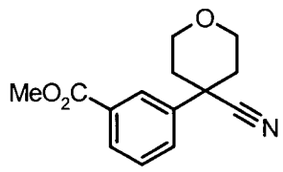
A una solución de 3–(1–ciano–1–metiletil)benzoato de metilo (2,8 g, 14 mmol) en tetrahidrofurano (30 mL) se añadieron hidróxido de litio monohidratado (0,98 g, 24 mmol), metanol (10 mL) y agua (10 mL), y la mezcla se agitó a temperatura ambiente durante 18 h. El solvente se evaporó a presión reducida, y el residuo se diluyó con agua (15 mL). La mezcla se ajustó a pH 3 agregando lentamente ácido clorhídrico 1 N. El precipitado blanco se recogió por filtración, se lavó con agua, y se secó al aire para dar el compuesto del título (2,5 g, 98%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,72 (6H, s), 7,57 (1H, t, J = 7,8 Hz), 7,78 (1H, dq, J = 7,8, 1,5 Hz), 7,92 (1H, dt, J = 7,8, 1,5 Hz), 8,08 (1H, t, J = 1,5 Hz) , 13,19 (1H, s).

826

Ejemplo de referencia 33

Producción de 3–(4–cianotetrahidro–2H–piran–4–il)benzoato de metilo

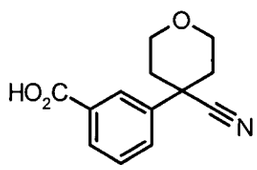


Usando 3–(cianometil)benzoato de metilo (1,0 g, 5,7 mmol), hidruro de sodio (60% en aceite, 0,69 g, 17 mmol), bis(2–bromoetil)éter (1,8 g, 6,9 mmol) y dimetilsulfóxido (12 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 31, se obtuvo el compuesto del título (650 mg, 46%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,02 – 2,21 (4H, m), 3,61 – 3,75 (2H, m), 3,89 (3H, s), 3,98 – 4,09 (2H, m), 7,64 (1H, t, J = 7,8 Hz), 7,83 – 7,91 (1H, m), 7,93 – 8,01 (1H, m), 8,10 (1H, t, J = 1,7 Hz).

Ejemplo de referencia 34

Producción de ácido 3–(4–cianotetrahidro–2H–piran–4–il)benzoico



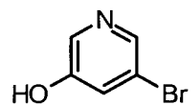
A una solución de 3–(4–cianotetrahidro–2H–piran–4–il)benzoato de metilo (0,62 g, 2,5 mmol) en tetrahidrofurano (6,0 mL) se añadieron hidróxido de litio monohidratado (0,18 g, 4,3 mmol),

metanol (2,0 mL) y agua (2,0 mL), y la mezcla se agitó a temperatura ambiente durante 12 h. El solvente se evaporó a presión reducida, y el residuo se diluyó con agua (5,0 mL). La mezcla se ajustó a pH 3 agregando lentamente ácido clorhídrico 1 N. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida para dar el compuesto del título (0,48 g, 83%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,00 – 2,23 (4H, m), 3,57 – 3,77 (2H, m), 3,94 – 4,10 (2H, m), 7,61 (1H, t, J = 7,8 Hz), 7,77 – 7,87 (1H, m), 7,90 – 8,00 (1H, m), 8,05 – 8,12 (1H, m), 13,20 (1H, br s).

Ejemplo de referencia 35

Producción de 5–bromopiridin–3–ol



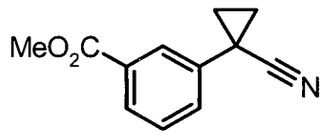
A una solución de 3–bromo–5–metoxipiridina (5,0 g, 27 mmol) en ácido acético (15 mL) se añadió ácido bromhídrico al 48% (23 mL), y la mezcla de reacción se calentó a reflujo durante 16 h. La mezcla se dejó enfriar hasta temperatura ambiente, y el solvente se evaporó a presión reducida. El residuo se ajustó a pH9 – 10 por adición de solución acuosa 8 N de hidróxido de sodio. La solución acuosa obtenida se lavó con éter dietílico, y el pH se ajustó a 5 – 6 por adición de ácido clorhídrico 6 N. El precipitado obtenido se

recogió por filtración, y se lavó con éter diisopropílico para dar el compuesto del título (2,8 g, 61%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,40 (1H, t, J = 2,1 Hz), 8,12 – 8,15 (2H, m), 10,47 (1H, br. s).

Ejemplo de referencia 36

Producción de 3–(1–cianociclopropil)benzoato de metilo

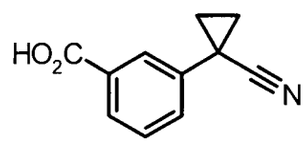


Usando 3–(cianometil)benzoato de metilo (1,5 g, 8,6 mmol), hidruro de sodio (60% en aceite, 1,0 g, 26 mmol), 1,2–dibromoetano (2,4 g, 13 mmol) y dimetilsulfóxido (30 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 31, se obtuvo el compuesto del título (1,3 g, 76%) en forma de un aceite incoloro.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,38 – 1,56 (2H, m), 1,74 – 1,82 (2H, m), 3,93 (3H, s), 7,40 – 7,49 (1H, m), 7,55 – 7,62 (1H, m), 7,88 (1H, t, J = 1,5 Hz), 7,96 (1H, dt, J = 7,8, 1,5 Hz).

Ejemplo de referencia 37

Producción de ácido 3–(1–cianociclopropil)benzoico



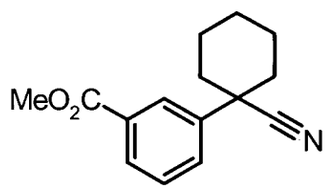
A una solución de 3–(1–cianociclopropil)benzoato de metilo

(1,3 g, 6,4 mmol) en tetrahidrofurano (12 mL) se le añadieron hidróxido de litio monohidratado (0,44 g, 11 mmol), metanol (4,0 mL) y agua (6,0 mL), y la mezcla se agitó a temperatura ambiente durante 14 h. El solvente se evaporó a presión reducida, y el residuo se diluyó con agua (5,0 mL). La mezcla se ajustó a pH 5 agregando lentamente ácido clorhídrico 1 N. El precipitado blanco se recogió por filtración, se lavó con agua, y se secó al aire para dar el compuesto del título (0,73 g, 61%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,50 – 1,62 (2 H, m), 1,76 – 1,86 (2 H, m), 7,41 – 7,59 (2 H, m), 7,82 – 7,97 (2 H, m), 13,19 (1 H, br. s.).

Ejemplo de referencia 38

Producción de 3–(1–cianociclohexil)benzoato de metilo

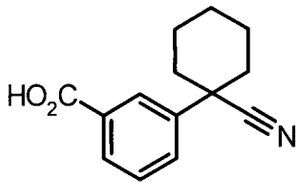


Usando 3–(cianometil)benzoato de metilo (1,5 g, 8,6 mmol), hidruro de sodio (60% en aceite, 1,0 g, 26 mmol), 1,5–dibromopentano (3,0 g, 13 mmol) y dimetilsulfóxido (30 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 31, se obtuvo el compuesto del título (1,4 g, 68%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,23 – 1,46 (1H, m), 1,53 – 2,17 (9H, m), 3,88 (3 H, s), 7,61 (1H, t, J = 7,8 Hz), 7,80 – 7,88 (1H, m), 7,95 (1H, dt, J = 7,8, 1,2 Hz), 8,10 (1H, t, J = 1,8 Hz).

Ejemplo de referencia 39

Producción de ácido 3–(1–cianociclohexil)benzoico

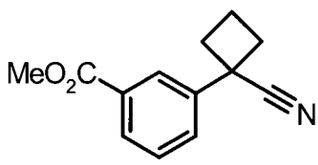


Usando 3–(1–cianociclohexil)benzoato de metilo (1,3 g, 5,3 mmol), hidróxido de litio monohidratado (0,52 g, 13 mmol), tetrahidrofurano (18 mL), metanol (6,0 mL) y agua (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 37, se obtuvo el compuesto del título (1,1 g, 88%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,21 – 1,43 (1H, m), 1,52 – 2,17 (9H, m), 7,58 (1H, t, J = 7,8 Hz), 7,80 (1H, dq, J = 7,8, 1,2 Hz), 7,92 (1H, dt, J = 7,8, 1,2 Hz), 8,09 (1H, t, J = 1,8 Hz).

Ejemplo de referencia 40

Producción de 3–(1–cianociclobutil)benzoato de metilo



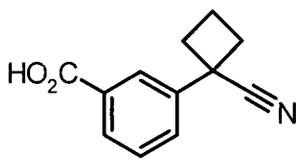
Usando 3–(cianometil)benzoato de metilo (1,8 g, 10 mmol), hidruro de sodio (60% en aceite, 1,2 g, 30 mmol), 1,3–dibromopropano (3,0 g, 15 mmol) y dimetilsulfóxido (30 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 31, se obtuvo el compuesto del título (0,91 g, 42%) en forma de un aceite incoloro.

831

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,92 – 2,12 (1H, m), 2,18 – 2,41 (1H, m), 2,56 – 2,91 (4H, m), 3,88 (3H, s), 7,59 – 7,66 (1H, m), 7,75 – 7,83 (1H, m), 7,91 – 8,02 (2H, m).

Ejemplo de referencia 41

Producción de ácido 3–(1–cianociclobutil)benzoico

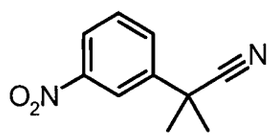


Usando 3–(1–cianociclobutil)benzoato de metilo (0,9 g, 4,2 mmol), hidróxido de litio monohidratado (0,26 g, 6,3 mmol), tetrahidrofurano (9,0 mL), metanol (3,0 mL) y agua (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo de referencia 37, se obtuvo el compuesto del título (0,73 g, 86%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,93 – 2,13 (1H, m), 2,20 – 2,42 (H, m), 2,56 – 2,90 (4H, m), 7,59 (1H, t, J = 7,8 Hz), 7,68 – 7,81 (1H, m), 7,85 – 8,01 (2H, m).

Ejemplo de referencia 42

Producción de 2–metil–2–(3–nitrofenil)propanonitrilo



A una solución bifásica de (3–nitrofenil)acetonitrilo (5,0 g, 31 mmol) y bromuro de tetraetilamonio (600 mg) en hidróxido de sodio acuoso 2 N (47 mL, 93 mmol) y cloruro de metileno (50 mL) se le

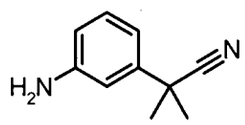
832

añadió yoduro de metilo (8,0 mL, 130 mmol), y la mezcla se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 2/98→10/90) para dar el compuesto del título (0,38 g, 6,5%) en forma de aceite amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,76 (6H, s), 7,76 (1H, t, J = 8,0 Hz), 8,04 (1H, dd, J = 7,8, 0,8 Hz), 8,24 (1H, d, J = 8,3 Hz), 8,32 (1H, s).

Ejemplo de referencia 43

Producción de 2–(3–aminofenil)–2–metilpropanonitrilo

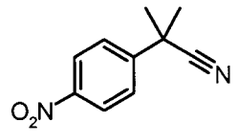


A una solución de 2–metil–2–(3–nitrofenil)propanonitrilo (0,35 g, 1,8 mmol) en acetato de etilo (10 mL) se añadió paladio / carbón al 10% (35 mg), y la mezcla se agitó durante 10 h bajo una atmósfera de hidrógeno. El catalizador residual se filtró a través de celite, y se lavó con acetato de etilo. El filtrado se concentró a presión reducida para dar el compuesto del título (0,35 g, 1,8 mmol) en forma de un aceite amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,61 (6H, s), 5,21 (2H, br. s), 6,46 – 6,55 (1H, m), 6,56 – 6,63 (1H, m), 6,71 (1H, t, J = 2,1 Hz), 7,04 (1H, t, J = 7,8 Hz).

Ejemplo de referencia 44

Producción de 2–metil–2–(4–nitrofenil)propanonitrilo

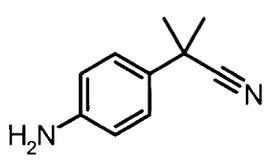


A una solución bifásica de (4–nitrofenil)acetonitrilo (5,0 g, 31 mmol) y bromuro de tetraetilamonio (2,0 g) en hidróxido de sodio acuoso 2 N (75 mL, 150 mmol) y cloruro de metileno (50 mL) se añadió yoduro de metilo (9,6 mL, 150 mmol), y la mezcla se agitó a temperatura ambiente durante 4 h. A la mezcla de reacción se añadieron solución acuosa 2 N de hidróxido de sodio (10 mL, 20 mmol) y yoduro de metilo (1,5 mL, 24 mmol), y la mezcla se agitó luego durante 2 h. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→10/90) para dar el compuesto del título (3,8 g, 65%) en forma de un aceite amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,75 (6H, s), 7,79 – 7,88 (2H, m), 8,25 – 8,34 (2H, m).

Ejemplo de referencia 45

2–(4–aminofenil)–2–metilpropanonitrilo

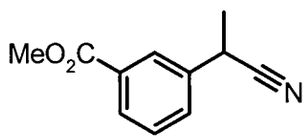


A una solución de 2–metil–2–(4–nitrofenil)propanonitrilo (0,95 g, 5,0 mmol) en acetato de etilo (10 mL) se le añadió paladio / carbón al 10% (100 mg), y la mezcla se agitó a temperatura ambiente durante 14 h bajo una atmósfera de hidrógeno. El catalizador residual se filtró a través de celite, y se lavó con acetato de etilo. El filtrado se concentró a presión reducida para dar el compuesto del título (0,81 g, 99%) en forma de un aceite amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,59 (6H, s), 5,14 (2H, br. s), 6,57 (2H, d, J = 8,7 Hz), 7,12 (2H, d, J = 8,7 Hz).

Ejemplo de referencia 46

Producción de 3–(1–cianoetil)benzoato de metilo



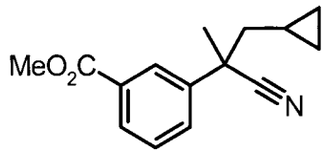
A una solución de ácido 3–(1–cianoetil)benzoico (2,0 g, 11 mmol) en metanol (20 mL) se añadió ácido sulfúrico concentrado (0,2 mL), y la mezcla se agitó a 60 °C durante 8 h. La mezcla de reacción se concentró a presión reducida, y se neutralizó con solución acuosa saturada de hidrógeno–carbonato de sodio. La mezcla se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida para dar el compuesto del título (1,9 g, 89%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,57 (3H, d, J = 7,2 Hz), 3,88 (3H, s), 4,46 (1H, q, J = 7,2 Hz), 7,59 (1H, t, J = 7,8 Hz), 7,68 – 7,76

(1H, m), 7,94 (1H, dt, J = 7,8, 1,5 Hz), 8,00 (1H, t, J = 1,8 Hz).

Ejemplo de referencia 47

Producción de 3–(1–ciano–2–ciclopropil–1–metiletil)benzoato de metilo



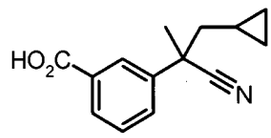
A una solución de 3–(1–cianoetil)benzoato de metilo (1,5 g, 7,9 mmol) en acetonitrilo (20 mL) se añadieron metóxido de sodio (0,95 g, 17 mmol) y (bromometil)ciclopropano (1,3 g, 9,5 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. A la mezcla de reacción se añadió hidruro de sodio (60% en aceite, 0,7 g, 17 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla se diluyó con éter dietílico, y se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada. La capa orgánica se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→40/60) para dar el compuesto del título (129 mg, 6,7%) en forma de un aceite incoloro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ –0,10 – 0,03 (1H, m), 0,21 (1H, dt, J = 4,9, 9,1 Hz), 0,26 – 0,39 (1H, m), 0,39 – 0,50 (1H, m), 0,51 – 0,66 (1H, m), 1,70 – 1,77 (3H, m), 1,77 – 1,89 (1H, m), 1,92 – 2,03 (1H, m), 3,88 (3H, s), 7,55 – 7,67 (1H, m), 7,77 – 7,86 (1H, m), 7,95 (1H, d, J = 7,7 Hz), 8,08 – 8,13 (1H, m).

836

Ejemplo de referencia 48

Producción de ácido 3–(1–ciano–2–ciclopropil–1–metiletil)benzoico

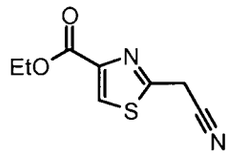


A una solución de 3–(1–ciano–2–ciclopropil–1–metiletil)benzoato de metilo (120 mg, 0,49 mmol) en tetrahidrofurano/metanol/agua (=3,0 mL/1,0 mL/1,0 mL) se añadió hidróxido de litio monohidratado (40 mg, 0,99 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 4 h. La mezcla se concentró a presión reducida, y la solución acuosa obtenida se ajustó a pH 5 por adición de ácido clorhídrico 1 N. La mezcla se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 50/50→100/0) para dar el compuesto del título (76 mg, 66%) en forma de un aceite incoloro.

^{1}H RMN (DMSO–d_6, 300 MHz) δ –0,04 – 0,09 (1 H, m), 0,18 – 0,31 (1 H, m), 0,36 – 0,49 (1H, m), 0,49 – 0,62 (1H, m), 0,64 – 0,82 (1H, m), 1,73 – 1,87 (2H, m), 1,91 – 2,03 (2H, m), 7,44 – 7,63 (1H, m), 7,79 – 7,86 (1H, m), 8,09 (1H, d, J = 7,9 Hz), 8,15 – 8,22 (1H, m), 11,25 – 12,45 (1H, br. s).

Ejemplo de referencia 49

Producción de 2–(cianometil)–1,3–tiazol–4–carboxilato de etilo

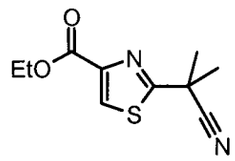


A una solución de 3–bromo–2–oxopropanato de etilo (21 g, 110 mmol) en N,N–dimetilformamida (50 mL) se añadió una solución de 2–cianoetantioamida (10 g, 100 mmol) en N,N–dimetilformamida (50 mL) bajo enfriamiento con hielo, y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. La mezcla se concentró a presión reducida, y el residuo obtenido se disolvió en acetato de etilo, y se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada. La capa orgánica se secó sobre sulfato de sodio anhidro y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→60/40) para dar el compuesto del título (5,1 g, 26%) en forma de un polvo amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,31 (3H, t, J = 7,2 Hz), 4,31 (2H, q, J = 7,2 Hz), 4,63 (2H, s), 8,53 (1H, s).

Ejemplo de referencia 50

Producción de 2–(1–ciano–1–metiletil)–1,3–tiazol–4–carboxilato de etilo



A una solución de 2–(cianometil)–1,3–tiazol–4–carboxilato de etilo (2,0 g, 10 mmol) en dimetilsulfóxido (20 mL) se añadió hidruro

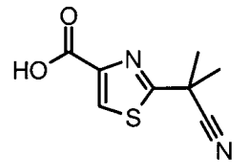
838

de sodio (60% en aceite, 1,6 g, 41 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. Bajo enfriamiento, se añadió una solución de yoduro de metilo (2,5 mL, 41 mmol) en dimetilsulfóxido (10 mL) gota a gota a la mezcla, y la mezcla se agitó a temperatura ambiente durante 6 h. Se añadió agua a la mezcla bajo enfriamiento, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 5/95→50/50) para dar el compuesto del título (0,90 g, 39%) en forma de un aceite amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,31 (3H, t, J = 7,2 Hz), 1,83 (6H, s), 4,33 (2H, q, J = 7,2 Hz), 8,59 (1H, s).

Ejemplo de referencia 51

Producción de ácido 2–(1–ciano–1–metiletil)–1,3–tiazol–4–carboxílico



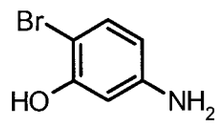
A una solución de 2–(1–ciano–1–metiletil)–1,3–tiazol–4–carboxilato de etilo (0,9 g, 4,0 mmol) en tetrahidrofurano/metanol/agua (=12 mL/4,0 mL/4,0 mL) se añadió hidróxido de litio monohidratado (330 mg, 8,0 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 10 h. La mezcla se

concentró a presión reducida, y la solución acuosa obtenida se ajustó a pH 5 por adición de ácido clorhídrico 1 N. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida para dar el compuesto del título (256 mg, 53%) en forma de un polvo blanco.

^{1}H RMN (DMSO–d, 300 MHz$_6$) δ 1,82 (6H, s), 8,43 (1H, s).

Ejemplo de referencia 52

Producción de 5–amino–2–bromofenol



Se añadió 4–bromo–3–metoxianilina (5,0 g, 25 mmol) a ácido bromhídrico al 48% (20 mL), y la mezcla de reacción se agitó a 80 °C durante 16 h. Después de completar la reacción, la mezcla se dejó enfriar hasta temperatura ambiente, y se ajustó a pH 7 – 8 por adición de solución acuosa 8 N de hidróxido de sodio. La mezcla se extrajo con acetato de etilo, y la capa orgánica obtenida se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 10/90→100/0) para dar el compuesto del título (2,0 g, 43%) en forma de un polvo blanco.

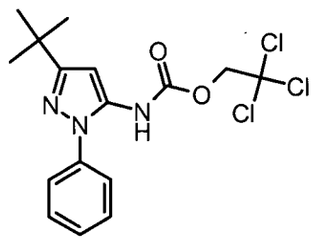
^{1}H–RMN (DMSO–d$_6$, 300 MHz) δ 5,10 (2H, s), 5,97 (1H, dd, J = 8,4, 2,4 Hz), 6,19 (1H, d, J = 2,4 Hz), 6,99 (1H, d, J = 8,4 Hz), 9,64

840

(1H, s).

Ejemplo de referencia 53

Producción de (3–tert-butil–1–fenil–1H–pirazol–5–il)carbamato de 2,2,2–tricloroetilo

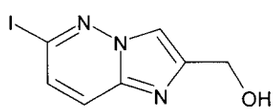


A una solución bifásica de 3–tert-butil–1–fenil–1H–pirazol–5–amina (5,0 g, 23 mmol) en acetato de etilo (45 mL)/hidróxido de sodio acuoso 3 N (20 mL) se añadió clorocarbonato de 2,2,2–tricloroetilo (4,5 mL, 33 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2 h. La capa orgánica obtenida se lavó con hidrógeno–carbonato de sodio acuoso al 5%, agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida para dar el compuesto del título (5,0 g, 55%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,28 (9H, s), 4,85 (2H, br. s), 6,30 (1H, s), 7,28 – 7,53 (5H, m).

Ejemplo de referencia 54

Producción de (6–yodoimidazo[1,2–b]piridazin–2–il)metanol



A una solución de 3–amino–6–yodopiridazina (2,0 g, 9,0 mmol)

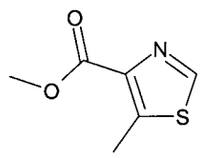
841

en etanol (40 mL) se añadió acetato de 3–cloro–2–oxopropilo (2,73 g, 18,1 mmol), y la mezcla se calentó a reflujo durante 24 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano. El extracto se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se recogió por filtración y se lavó con acetato de etilo/hexano para dar el compuesto del título (498 mg, 20%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,62 (2H, d, J = 5,6 Hz), 5,33 (1H, t, J = 5,6 Hz), 7,49 (1H, d, J = 9,3 Hz), 7,80 (1H, d, J = 9,3 Hz), 8,14 (1H, s).

Ejemplo de referencia 55

Producción de 5–metil–1,3–tiazol–4–carboxilato de metilo



A una solución de 2–amino–5–metil–1,3–tiazol–4–carboxilato de metilo (2,15 g, 12,5 mmol) en tetrahidrofurano (60 mL) se añadió lentamente nitrito de tert-butilo (2,23 mL, 18,7 mmol) con agitación a 50 °C, y la mezcla se agitó a 60 °C durante 2 h. La mezcla se diluyó con agua (100 mL), y se extrajo con acetato de etilo (100 mL×2). La capa orgánica se concentró a presión reducida, y el residuo se

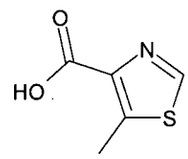
842

purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 80/20→0/100) para dar el compuesto del título (1,17 g, rendimiento 60%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,72 (3H, s), 3,82 (3H, s), 8,90 (1H, s).

Ejemplo de referencia 56

Producción de ácido 5–metil–1,3–tiazol–4–carboxílico



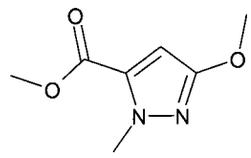
A una solución de 5–metil–1,3–tiazol–4–carboxilato de metilo (1,17 g, 7,4 mmol) en metanol (15 mL) se añadió solución acuosa 8 N de hidróxido de sodio (2,00 mL), y la mezcla se agitó a temperatura ambiente durante 18 h. Se le añadió ácido clorhídrico 6 N (2,67 mL) a la mezcla, y la mezcla se concentró a presión reducida. Se le añadió agua al residuo, y el precipitado se recogió por filtración, y se lavó con agua. El precipitado se suspendió en un solvente mixto de acetato de etilo (9 mL) y etanol (1 mL), y la mezcla se agitó a 80 °C durante 3 min. Tras dejar enfriar hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con acetato de etilo, y se secó a presión reducida para dar el compuesto del título (531 mg, rendimiento 50%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,71 (3H, s), 8,87 (1H, s), 12,88 (1H, br s).

843

Ejemplo de referencia 57

Producción de 3–metoxi–1–metil–1H–pirazol–5–carboxilato de metilo

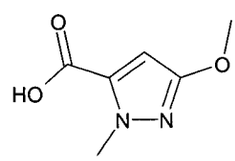


Una mezcla de 3–hidroxi–1–metil–1H–pirazol–5–carboxilato de metilo (2,34 g, 15,0 mmol), yodometano (3,19 g, 22,5 mmol), carbonato de potasio (4,15 g, 30,0 mmol) y N,N–dimetilformamida (15 mL) se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con agua (50 mL), y se extrajo con acetato de etilo (50 mL×3). La capa orgánica se lavó con agua (10 mL×2), y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 100/0→50/50) para dar el compuesto del título (2,01 g, rendimiento 79%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,78 (3H, s), 3,81 (3H, s), 3,94 (3H, s), 6,27 (1H, s).

Ejemplo de referencia 58

Producción de ácido 3–metoxi–1–metil–1H–pirazol–5–carboxílico



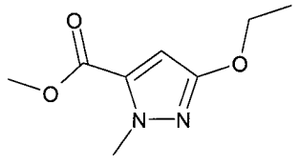
844

A una solución de 3–metoxi–1–metil–1H–pirazol–5–carboxilato de metilo (2,01 g, 11,8 mmol) en metanol (15 mL) se añadió solución acuosa 8 N de hidróxido de sodio (3,00 mL), y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió se añadió ácido clorhídrico 6 N (4,00 mL) a la mezcla, y la mezcla se concentró a presión reducida. Se añadió agua al residuo, y el precipitado se recogió por filtración, se lavó con agua y se secó al aire. El precipitado se suspendió en éter diisopropílico, y la mezcla se agitó a 80 °C durante 15 min. Tras dejar enfriar hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con éter diisopropílico, y se secó a presión reducida para dar el compuesto del título (746 mg, rendimiento 40%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,77 (3H, s), 3,93 (3H, s), 6,20 (1H, s), 13,37 (1H, br s).

Ejemplo de referencia 59

Producción de 3–etoxi–1–metil–1H–pirazol–5–carboxilato de metilo



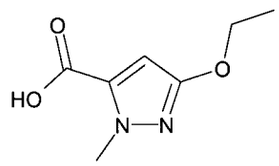
Usando 3–hidroxi–1–metil–1H–pirazol–5–carboxilato de metilo (2,34 g, 15,0 mmol), yodoetano (3,51 g, 22,5 mmol), carbonato de potasio (4,15 g, 30,0 mmol) y N,N–dimetilformamida (15 mL), y de la misma manera que en el Ejemplo de referencia 57, se obtuvo el compuesto del título (2,59 g, rendimiento 94%).

845

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,28 (3H, t, J = 7,0 Hz), 3,81 (3H, s), 3,93 (3H, s), 4,10 (2H, q, J = 7,0 Hz), 6,25 (1H, s).

Ejemplo de referencia 60

Producción de ácido 3–etoxi–1–metil–1H–pirazol–5–carboxílico

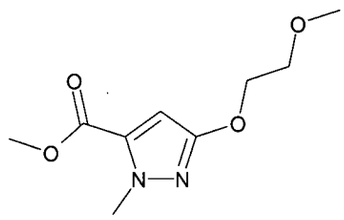


Usando 3–etoxi–1–metil–1H–pirazol–5–carboxilato de metilo (2,59 g, 14,1 mmol), metanol (15 mL) y solución acuosa 8 N de hidróxido de sodio (3,00 mL), y de la misma manera que en el Ejemplo de referencia 58, se obtuvo el compuesto del título (1,94 g, rendimiento 81%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,28 (3H, t, J = 7,0 Hz), 3,92 (3H, s), 4,09 (2H, q, J = 7,0 Hz), 6,19 (1H, s), 13,37 (1H, br s).

Ejemplo de referencia 61

Producción de 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carboxilato de metilo



Usando 3–hidroxi–1–metil–1H–pirazol–5–carboxilato de metilo (2,34 g, 15,0 mmol), 1–bromo–2–metoxietano (3,13 g, 22,5 mmol), carbonato de potasio (4,15 g, 30,0 mmol) y N,N–dimetilformamida (15 mL), y de la misma manera que en el Ejemplo de referencia 57,

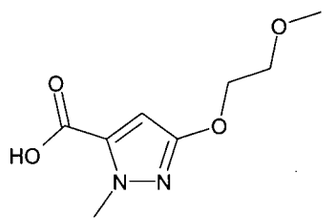
846

se obtuvo el compuesto del título (3,03 g, rendimiento 94%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,28 (3H, s), 3,57 – 3,64 (2H, m), 3,81 (3H, s), 3,93 (3H, s), 4,14 – 4,20 (2H, m), 6,28 (1H, s).

Ejemplo de referencia 62

Producción de ácido 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carboxílico

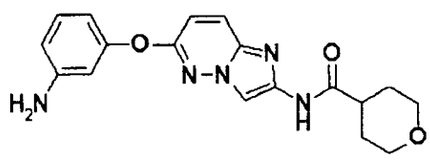


Usando 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carboxilato de metilo (3,03 g, 14,1 mmol), metanol (15 mL) y solución acuosa 8 N de hidróxido de sodio (3,00 mL), y de la misma manera que en el Ejemplo de referencia 58, se obtuvo el compuesto del título (2,72 g, rendimiento 96%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,28 (3H, s), 3,57 – 3,63 (2H, m), 3,92 (3H, s), 4,13 – 4,19 (2H, m), 6,21 (1H, s), 13,39 (1H, br s).

Ejemplo 1

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]tetrahidro–2H–piran–4–carboxamida



Una mezcla de 6–yodoimidazo[1,2–b]piridazin–2–amina (550

847

mg, 2,11 mmol), cloruro de tetrahidro–2H–piran–4–carbonilo (320 mg, 2,15 mmol) y N,N–dimetilacetamida (5,0 mL) se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se vertió en agua, y el sólido precipitado se recogió por filtración, se lavó con agua, y se secó al aire para dar N–(6–yodoimidazo[1,2–b]piridazin–2–il)tetrahidro–2H–piran–4–carboxamida en forma de un polvo blanco.

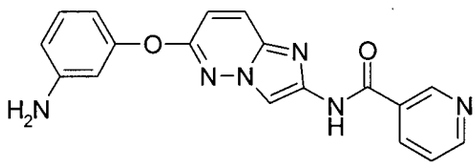
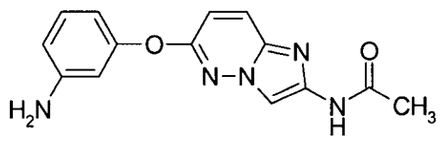
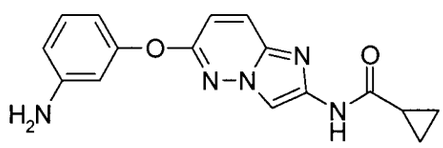
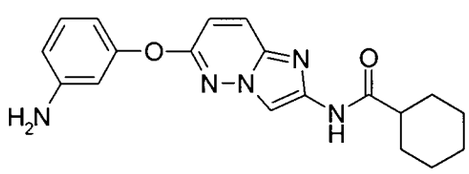
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)tetrahidro–2H–piran–4–carboxamida, 3–aminofenol (436 mg, 4,0 mmol), carbonato de potasio (552 mg, 4,0 mmol) y N,N–dimetilformamida (5,0 mL) se agitó con calentamiento a 180 °C durante 15 min usando un sintetizador de microondas. Después de enfriar, la mezcla de reacción se filtró, y el filtrado se purificó por HPLC preparativa para dar el compuesto del título (364 mg, 49%) en forma de un polvo color café oscuro.

^{1}H–RMN ($CDCl_3$, 400 MHz) δ 1,67 – 1,81 (4H, m), 2,34 – 2,44 (1H, m), 3,25 – 3,34 (2H, m), 3,78 (2H, s), 3,86 – 3,94 (2H, m), 6,33 – 6,37 (1H, m), 6,37 – 6,43 (2H, m), 6,67 (1H, d, J = 9,5 Hz), 7,02 (1H, t, J = 8,1 Hz), 7,54 (1H, d, J = 9,5 Hz), 7,89(1H, s), 8,06 (1H, s).

De la misma manera que en el Ejemplo 1, se sintetizaron los compuestos de los Ejemplos 2 a 5. Las estructuras de los compuestos de los Ejemplos 2 a 5 se indican en la Tabla 1.

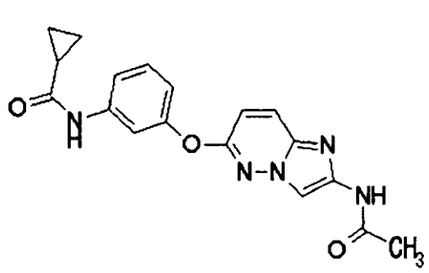
Tabla 1

848

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
2		347
3		284
4		310
5		352

Ejemplo 6

Producción de N-(3-{[2-(acetilamino)imidazo[1,2-b]piridazin-6-il]oxi}fenil)ciclopropancarboxamida



Una mezcla de N-[6-(3-aminofenoxi)imidazo[1,2-b]piridazin-

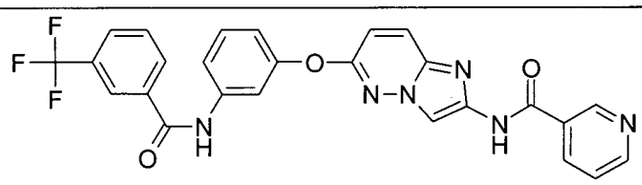
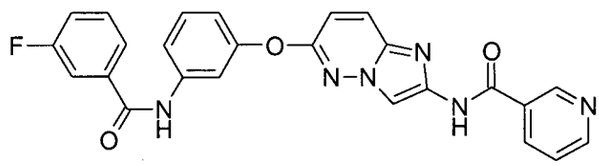
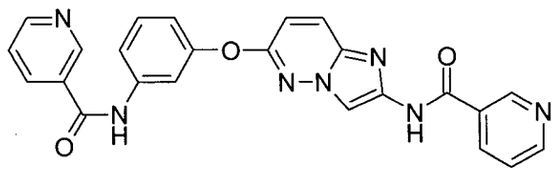
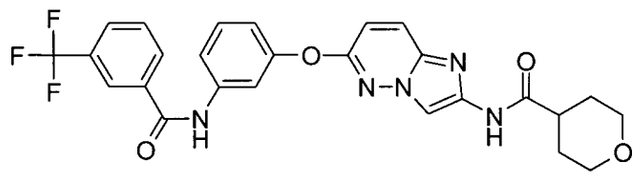
849

2–il]acetamida (17 mg, 0,06 mmol), cloruro de ciclopropancarbonilo (9,5 mg, 0,09 mmol) y N,N–dimetilacetamida (0,5 mL) se agitó a temperatura ambiente durante 14 h. La mezcla de reacción se purificó por HPLC preparativa para dar el compuesto del título (10,8 mg, 51%).

LC–MS 352(M+H).

De la misma manera que en el Ejemplo 6, se sintetizaron los compuestos de los Ejemplos 7 a 51. Las estructuras de los compuestos de los Ejemplos 7 a 51 se indican en las Tablas 2 a 7.

Tabla 2

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
7		519
8		469
9		452
10		526

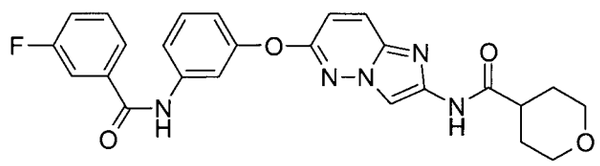
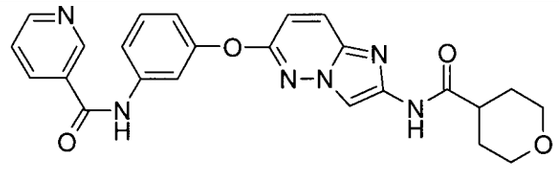
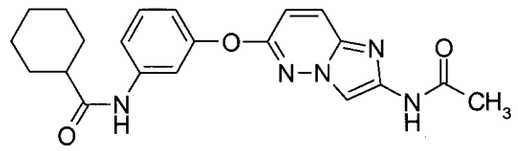
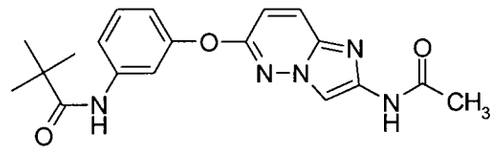
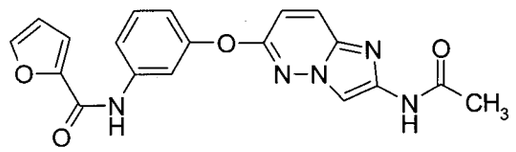
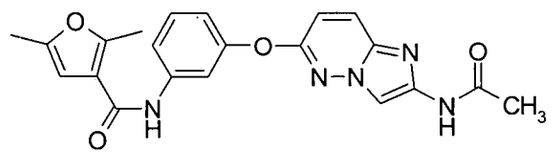
Ejemplo N.º	Fórmula química estructural	MS (m/Z)
11		476
12		459
13		394
14		368

Tabla 3

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
15		378
16		406

851

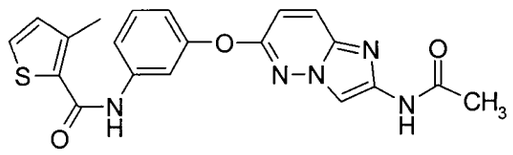
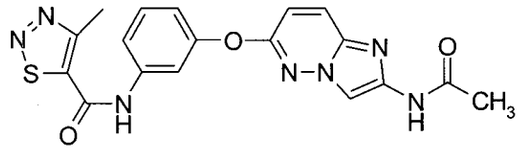
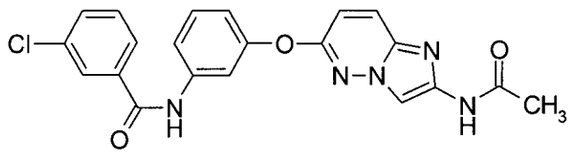
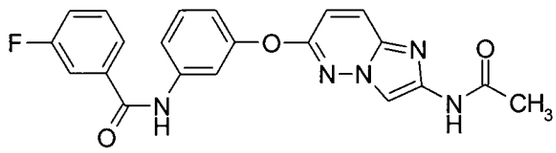
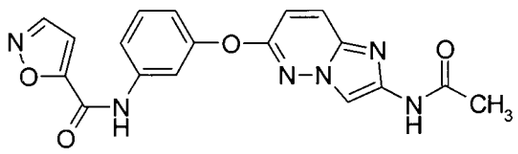
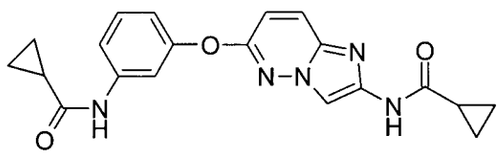
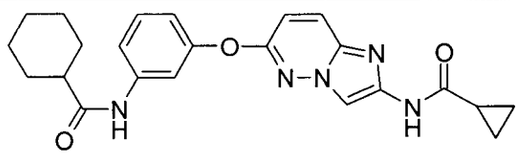
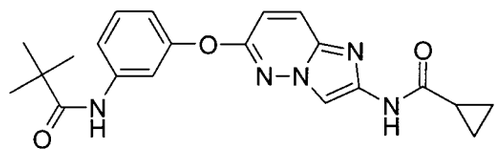
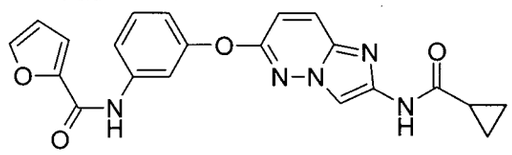
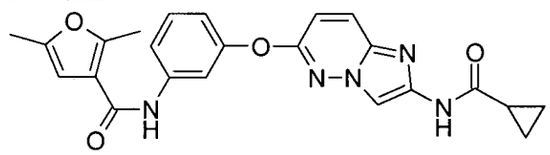
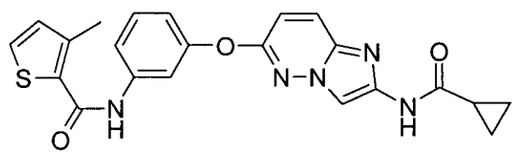
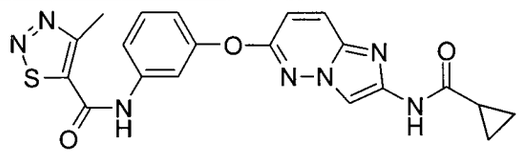
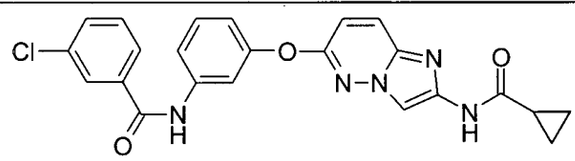
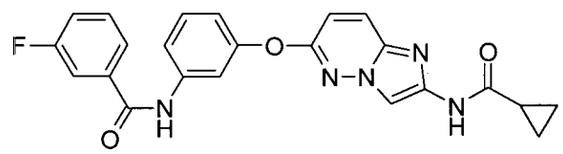
17		408
18		410
19		422
20		406
21		379
22		378

Tabla 4

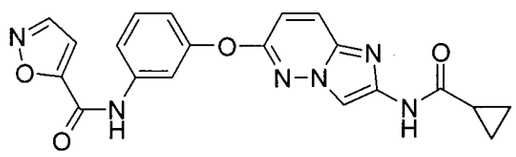
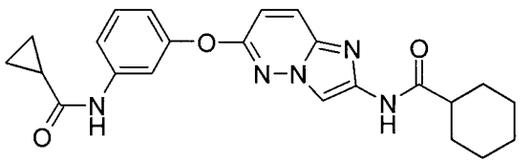
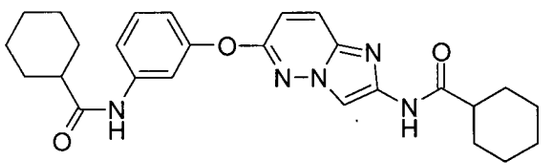
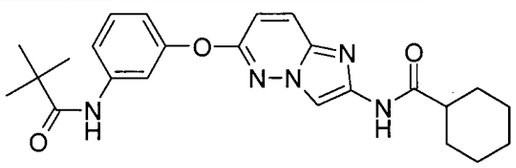
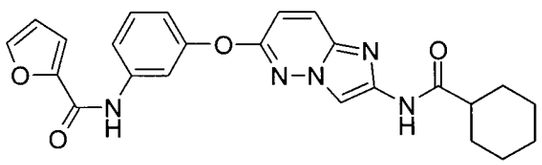
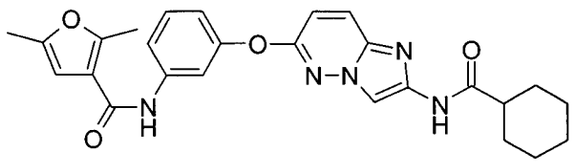
Ejemplo N.º	Fórmula química estructural	MS (m/Z)
23		420

852

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
24		394
25		404
26		432
27		434
28		436
29		448
30		432

853

Tabla 5

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
31		405
32		420
33		462
34		436
35		446
36		474

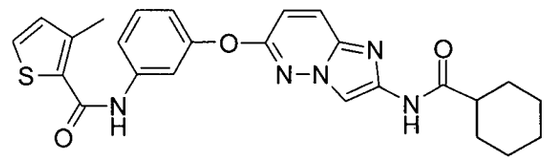
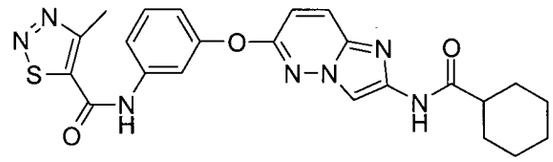
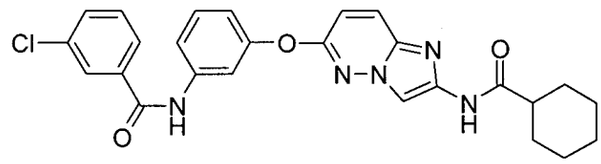
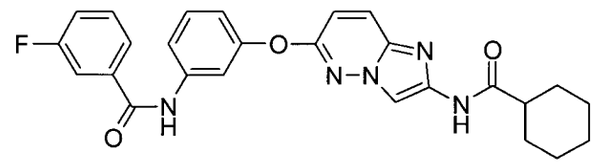
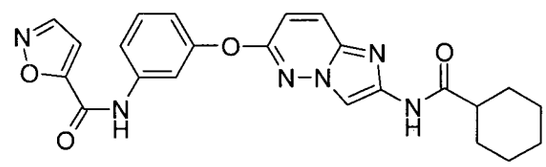
Ejemplo N.º	Fórmula química estructural	MS (m/Z)
37		476
38		478

Tabla 6

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
39		490
40		474
41		447

855

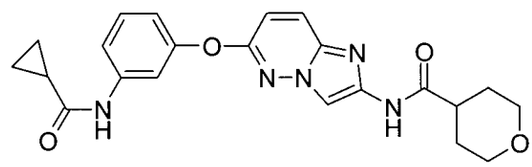
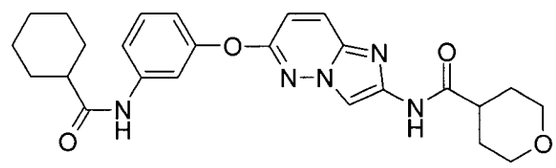
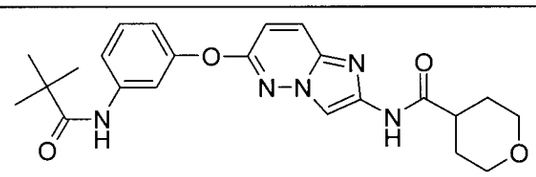
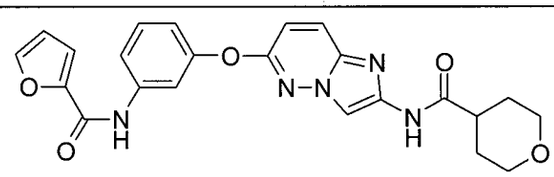
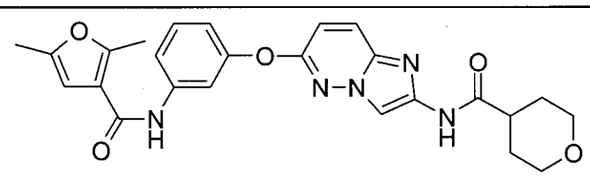
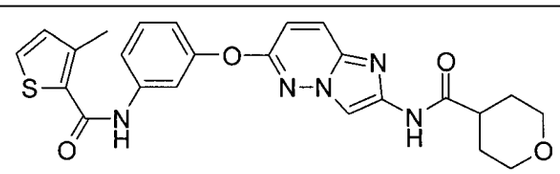
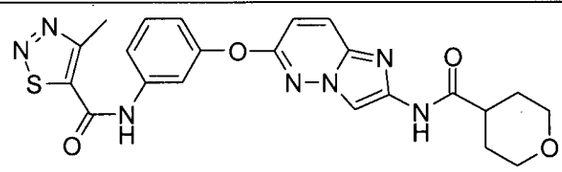
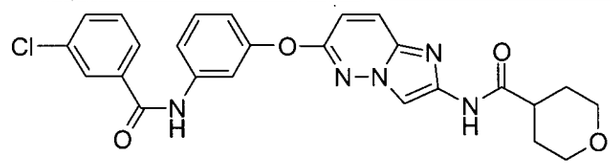
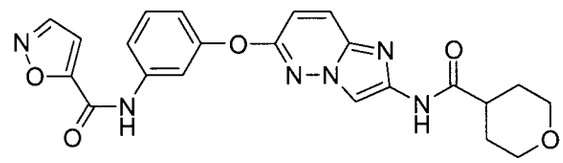
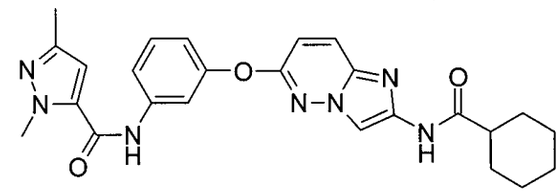
Ejemplo N.º	Fórmula química estructural	MS (m/Z)
42		422
43		464
44		438
45		448
46		476

Tabla 7

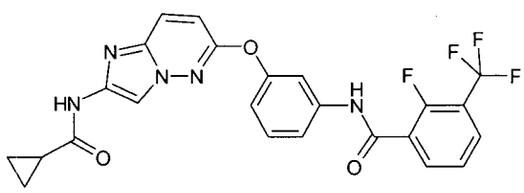
Ejemplo N.º	Fórmula química estructural	MS (m/Z)
47		478

856

Ejemplo N.º	Fórmula química estructural	MS (m/Z)
48		480
49		492
50		449
51		474

Ejemplo 52

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–fluoro–3–(trifluorometil)benzamida

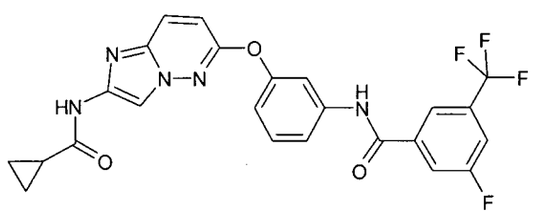


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (309 mg, 1,00 mmol), ácido 2–fluoro–3–(trifluorometil)benzoico (312 mg, 1,50 mmol), 1–hidroxibenzotriazol (203 mg, 1,50 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (288 mg, 1,50 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (380 mg, 76%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,88 – 1,95 (1H, m), 7,03 – 7,09 (2H, m), 7,45 (1H, t, J = 8,1 Hz), 7,52 – 7,57 (2H, m), 7,66 – 7,67 (1H, m), 7,94 – 8,07 (4H, m), 10,79 (1H, s), 11,09 (1H, s).

Ejemplo 53

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–fluoro–5–(trifluorometil)benzamida



Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (309 mg, 1,00 mmol), ácido 3–fluoro–5–(trifluorometil)benzoico (312 mg, 1,50 mmol), 1–hidroxibenzotriazol (203 mg, 1,50 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (288 mg, 1,50 mmol) y N,N–

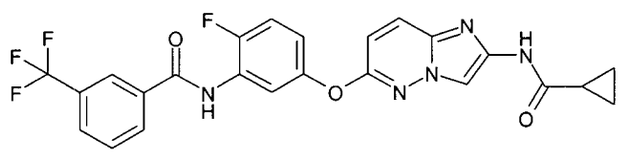
858

dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (437 mg, 88%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,88 – 1,97 (1H, m), 7,04 – 7,10 (2H, m), 7,47 (1H, t, J = 8,4 Hz), 7,64 – 7,72 (2H, m), 7,96 – 8,15 (5H, m), 10,63 (1H, s), 11,10 (1H, s).

Ejemplo 54

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(trifluorometil)benzamida



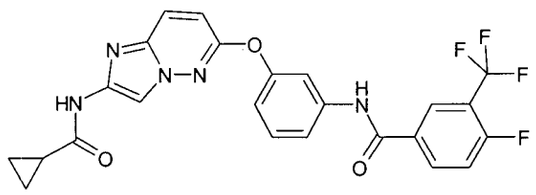
Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (163 mg, 0,50 mmol), ácido 3–(trifluorometil)benzoico (950 mg, 5,00 mmol), 1–hidroxibenzotriazol (676 mg, 5,00 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (959 mg, 5,00 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (160 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,81 (4H, m), 1,88 – 1,95 (1H, m), 7,08 – 7,25 (2H, m), 7,42 (1H, t, J = 9,6 Hz), 7,60 – 7,79 (2H, m), 7,95 – 8,07 (3H, m), 8,25 – 8,30 (2H, m), 10,51 (1H, s), 11,08 (1H, s).

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Ejemplo 55

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–4–fluoro–3–(trifluorometil)benzamida



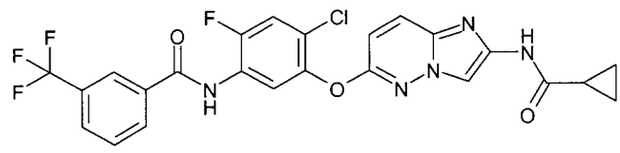
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (309 mg, 1,00 mmol), ácido 4–fluoro–3–(trifluorometil)benzoico (312 mg, 1,50 mmol), 1–hidroxibenzotriazol (203 mg, 1,50 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (288 mg, 1,50 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (380 mg, 76%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,80 – 0,82 (4H, m), 1,88 – 1,96 (1H, m), 7,02 – 7,10 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,63 – 7,74 (3H, m), 7,98 (1H, s), 8,06 – 8,36 (3H, m), 10,59 (1H, s), 11,10 (1H, s).

Ejemplo 56

Producción de N–[4–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(trifluorometil)benzamida

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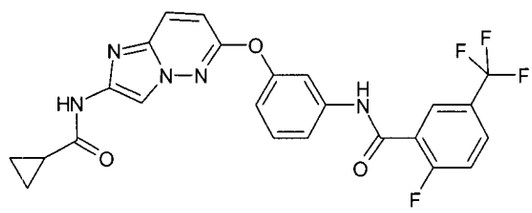


Usando N–[6–(3–amino–6–cloro–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (181 mg, 0,50 mmol), ácido 3–(trifluorometil)benzoico (114 mg, 0,60 mmol), 1–hidroxibenzotriazol (81 mg, 0,60 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (115 mg, 0,60 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (54 mg, 20%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,88 – 1,94 (1H, m), 7,17 (1H, d, J = 9,6 Hz), 7,76 – 7,85 (3H, m), 7,92 (1H, s), 7,98 – 8,08 (2H, m), 8,24 – 8,30 (2H, m), 10,60 (1H, s), 11,08 (1H, s).

Ejemplo 57

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–fluoro–5–(trifluorometil)benzamida



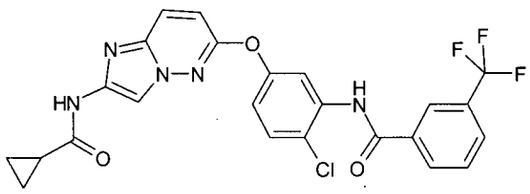
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (309 mg, 1,00 mmol), ácido 2–fluoro–5–

(trifluorometil)benzoico (312 mg, 1,50 mmol), 1–hidroxibenzotriazol (203 mg, 1,50 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (288 mg, 1,50 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (198 mg, 40%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,88 – 1,94 (1H, m), 7,02 – 7,09 (2H, m), 7,43 – 7,68 (4H, m), 7,98 – 8,09 (4H, m), 10,76 (1H, s), 11,09 (1H, s).

Ejemplo 58

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



Una mezcla de N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (103 mg, 0,30 mmol), cloruro de 3–(trifluorometil)benzoílo (75 mg, 0,36 mmol) y N–metilpirrolidona (3,0 mL) se calentó hasta 50 °C, y la mezcla se agitó durante 10 min. La mezcla de reacción se vertió en solución acuosa saturada de hidrógeno–carbonato de sodio, y se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio anhidro. El

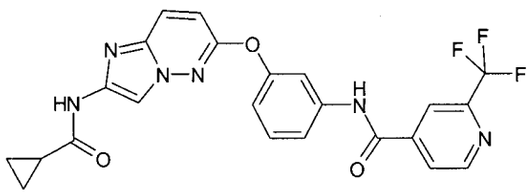
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solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/19→acetato de etilo) para dar el compuesto del título (131 mg, 85%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,90 – 1,94 (1H, m), 7,10 (1H, d, J = 9,9 Hz), 7,27 (1H, dd, J = 2,7 Hz, 8,7 Hz), 7,57 (1H, d, J = 3,0 Hz), 7,65 (1H, d, J = 8,7 Hz), 7,80 (1H, d, J = 7,8 Hz), 7,97 – 8,01 (2H, m), 8,06 (1H, d, J = 9,6 Hz), 8,26 – 8,31 (2H, m), 10,43 (1H, brs), 11,08 (1H, brs).

Ejemplo 59

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–(trifluorometil)isonicotinamida



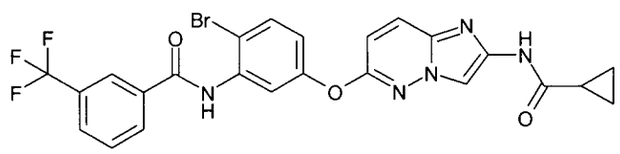
Usando N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (103 mg, 0,30 mmol), ácido 2–(trifluorometil)isonicotínico (86 mg, 0,45 mmol), 1–hidroxibenzotriazol (61 mg, 0,45 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (86 mg, 0,45 mmol) y N,N–dimetilformamida (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (102 mg, 71%) en forma de un polvo de color azul claro.

863

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,81 (4H, m), 1,89 – 1,94 (1H, m), 7,05 – 7,10 (2H, m), 7,48 (1H, t, J = 8,1 Hz), 7,64 – 7,72 (2H, m), 7,98 (1H, s), 8,07 – 8,35 (3H, m), 8,99 (1H, d, J = 5,1 Hz), 10,80 (1H, s), 11,09 (1H, s).

Ejemplo 60

Producción de N–[2–bromo–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

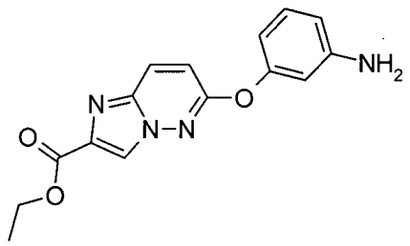


Usando N–[6–(3–amino–4–bromofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (178 mg, 0,46 mmol), cloruro de 3–(trifluorometil)benzoílo (92 mg, 0,44 mmol), trietilamina (0,14 mL, 1,00 mmol) y tetrahidrofurano (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (67 mg, 24%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,90 – 1,95 (1H, m), 7,11 – 7,22 (2H, m), 7,54 (1H, d, J = 2,7 Hz), 7,77 – 7,82 (2H, m), 7,97 – 8,08 (3H, m), 8,26 – 8,31 (2H, m), 10,43 (1H, s), 11,09 (1H, s).

Ejemplo 61

Producción de 6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo

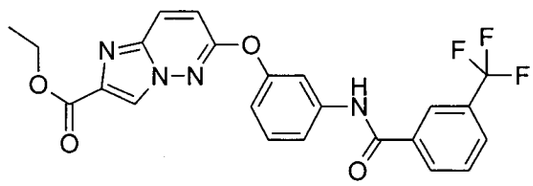


Una mezcla de 6–yodoimidazo[1,2–b]piridazin–2–carboxilato de etilo (951 mg, 3,00 mmol), 3–aminofenol (655 mg, 6,00 mmol), carbonato de potasio (622 mg, 4,50 mmol) y N,N–dimetilformamida (9,0 mL) se agitó a 150 °C durante 6 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadieron acetato de etilo y agua a la mezcla y el material insoluble se filtró a través de celite. La capa orgánica se recogió del filtrado, se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 1/19→acetato de etilo solo) para dar el compuesto del título (350 mg, 39%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,30 (3H, t, J = 7,2 Hz), 4,29 (2H, q, J = 7,2 Hz), 5,34 (2H, brs), 6,35 – 6,48 (3H, m), 7,07 (1H, t, J = 8,1 Hz), 7,17 (1H, d, J = 9,9 Hz), 8,20 (1H, d, J = 9,6 Hz), 8,61 (1H, s).

Ejemplo 62

Producción de 6–(3–{[3–(trifluorometil)benzoil] amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo

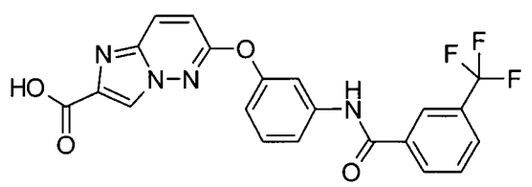


Usando 6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo (350 mg, 1,17 mmol), ácido 3–(trifluorometil)benzoico (342 mg, 1,80 mmol), 1–hidroxibenzotriazol (243 mg, 1,80 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (345 mg, 1,80 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (496 mg, 90%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ1,29 (3H, t, J = 7,1 Hz), 4,29 (2H, q, J = 7,1 Hz), 7,10 (1H, dd, J = 1,5 Hz, 7,5 Hz), 7,29 (1H, d, J = 9,9 Hz), 7,49 (1H, t, J = 8,4 Hz), 7,68 – 7,82 (3H, m), 7,97 – 8,00 (1H, m), 8,25 – 8,28 (3H, m), 8,62 (1H, s), 10,63 (1H, s).

Ejemplo 63

Producción de ácido 6–(3–{[3–(trifluorometil) benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxílico



Una mezcla de 6–(3–{[3–(trifluorometil) benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo

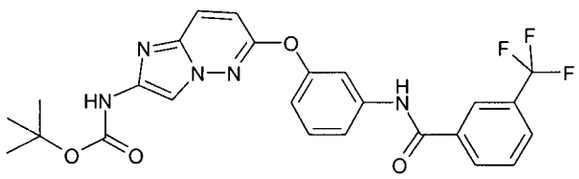
866

(470 mg, 1,00 mmol), solución acuosa 8 N de hidróxido de sodio (2,0 mL) y metanol (6,0 mL) se agitó a temperatura ambiente durante 4 h. Se añadieron ácido clorhídrico 6 N (2,7 mL) y agua (25 mL) a la mezcla, y la mezcla se extrajo con acetato de etilo (50 mL). El extracto se secó sobre sulfato de magnesio anhidro, y el solvente se evaporó a presión reducida para dar el compuesto del título (425 mg, 96%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,10 (1H, dd, J = 2,1 Hz, 7,8 Hz), 7,27 (1H, d, J = 9,9 Hz), 7,48 (1H, t, J = 7,8 Hz), 7,69–7,82 (3H, m), 7,98 (1H, d, J = 7,5 Hz), 8,23 – 8,29 (3H, m), 8,52 (1H, s), 10,62 (1H, s), 12,85 (1H, brs).

Ejemplo 64

Producción de [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de tert–butilo



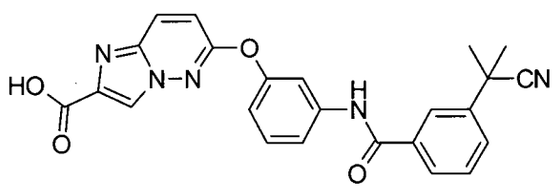
Una suspensión de ácido 6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxílico (111 mg, 0,25 mmol), azida de difenilfosforilo (103 mg, 0,375 mmol), trietilamina (51 mg, 0,5 mmol) y ter–butanol (5,0 mL) se agitó a temperatura ambiente durante 5 min, se calentó hasta 100 °C y se agitó durante la noche. Después de dejar enfriar la mezcla de

reacción hasta temperatura ambiente, se añadió acetato de etilo a la mezcla, y la mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 1/19→acetato de etilo solo) para dar el compuesto del título (79 mg, 39%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,47 (9H, s), 7,00 – 7,05 (2H, m), 7,45 (1H, t, J = 8,1 Hz), 7,65 – 7,81 (4H, m), 7,96 – 8,03 (2H, m), 8,24 – 8,28 (2H, m), 10,04 (1H, brs), 10,58 (1H, brs).

Ejemplo 65

Producción de ácido 6–(3–{[3–(1–ciano–1–metiletil) benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxílico



A una mezcla de ácido 3–(1–ciano–1–metiletil)benzoico (454 mg, 2,40 mmol), tetrahidrofurano (10 mL) y N,N–dimetilformamida (0,01 mL) se añadió cloruro de oxalilo (366 mg, 2,88 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. El solvente se evaporó a presión reducida, se añadió tetrahidrofurano al residuo, y la mezcla se destiló azeotrópicamente dos veces. El residuo se disolvió en N–metilpirrolidona (4 mL), se añadió a una solución de 6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo (350

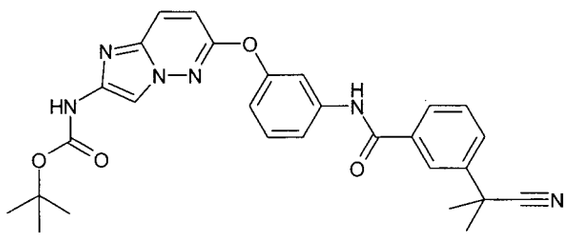
868

mg, 1,17 mmol) en N–metilpirrolidona (6 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió acetato de etilo a la mezcla de reacción, y la mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. Al residuo se añadieron solución acuosa 8 N de hidróxido de sodio (4,0 mL) y metanol (10,0 mL), y la mezcla se agitó a temperatura ambiente durante 10 min. Se añadió ácido clorhídrico 6 N (5,0 mL) y agua (60 mL) a la mezcla, y la mezcla se extrajo con acetato de etilo (150 mL). El extracto se secó sobre sulfato de magnesio anhidro, y el solvente se evaporó a presión reducida. El residuo se lavó con hexano para dar el compuesto del título (828 mg, 94%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ1,75 (6H, s), 7,08 (1H, dd, J = 1,5 Hz, 8,4 Hz), 7,27 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 7,8 Hz), 7,60 – 7,77 (4H, m), 7,92 – 8,03 (2H, m), 8,24 (1H, d, J = 10,2 Hz), 8,52 (1H, s), 10,46 (1H, s), 12,81 (1H, brs).

Ejemplo 66

Producción de [6–(3–{[3–(1–ciano–1–metiletil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de tert–butilo



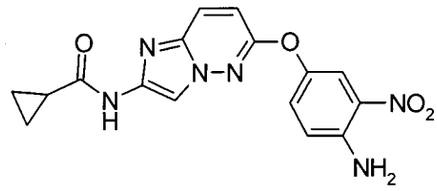
869

Usando ácido 6–(3–{[3–(1–ciano–1–metiletil)benzoil] amino}fenoxi)imidazo[1,2–b]piridazin–2–carboxílico (826 mg, 1,87 mmol), azida de difenilfosforilo (771 mg, 2,81 mmol), trietilamina (381 mg, 3,74 mmol) y ter–butanol (30,0 mL), y de la misma manera que en el Ejemplo 64, se obtuvo el compuesto del título (682 mg, 71%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,47 (9H, s), 1,74 (6H, s), 6,99 – 7,05 (2H, m), 7,44 (1H, t, J = 8,4 Hz), 7,57 – 7,77 (5H, m), 7,91 – 7,94 (1H, m), 8,00 – 8,03 (2H, m), 10,04 (1H, brs), 10,43 (1H, s).

Ejemplo 67

Producción de N–[6–(4–amino–3–nitrofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (656 mg, 2,00 mmol), 4–amino–3–nitrofenol (616 mg, 4,00 mmol), carbonato de potasio (411 mg, 3,00 mmol) y N,N–dimetilformamida (6,0 mL) se agitó a 150 °C durante 3 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadieron acetato de etilo (100 mL), tetrahidrofurano (40 mL) y agua (40 mL) a la mezcla, y el material insoluble se filtró a través de celite. La capa orgánica se recogió del filtrado, se lavó con

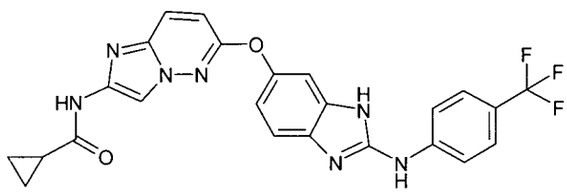
870

solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. Se añadió diclorometano (20 mL) al residuo, y el precipitado se recogió por filtración para dar el compuesto del título (367 mg, 52%). El filtrado se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 1/19→acetato de etilo solo) para dar el compuesto del título (125 mg, 18%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ0,78 – 0,81 (4H, m), 1,84 – 1,91 (1H, m), 7,04 (1H, d, J = 9,3 Hz), 7,11 (1H, d, J = 9,3 Hz), 7,44 (1H, dd, J = 3,0 Hz, 9,3 Hz), 7,51 (2H, m), 7,83 (1H, d, J = 2,4 Hz), 7,91 (1H, s), 8,01 (1H, d, J = 9,3 Hz), 11,04 (1H, s).

Ejemplo 68

Producción de N–{6–[(2–{[4–(trifluorometil)fenil]amino}–1H–bencimidazol–6–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



Una suspensión de N–[6–(4–amino–3–nitrofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (499 mg, 1,38 mmol), paladio sobre carbón al 10% (100 mg) y metanol (20,0 mL) se agitó bajo una atmósfera de hidrógeno (hasta 1 atm) a temperatura

871

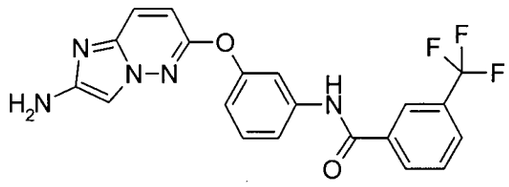
ambiente durante la noche. el material insoluble se filtró a través de celite, y el filtrado se evaporó a presión reducida. El residuo se disolvió en metanol (10 mL), se añadió 4–(trifluorometil)fenilisotiocianato (120 mg, 0,59 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 1 h. Se agregó cloruro de hierro (III) (177 mg, 1,1 mmol) a la mezcla de reacción, y la mezcla luego se agitó a temperatura ambiente durante 1,5 h. Se añadió acetato de etilo a la mezcla de reacción, y la mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. Se añadió diclorometano (20 mL) al residuo, y el precipitado se recogió por filtración para dar el compuesto del título (367 mg, 52%). El filtrado se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo→acetato de etilo/metanol = 9 : 1). Se añadió acetato de etilo a la sustancia oleosa obtenida, y el precipitado se recogió por filtración para dar el compuesto del título (116 mg, 32%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78–0,81 (4H, m), 1,88–1,94 (1H, m), 6,90–7,02 (2H, m), 7,22–7,39 (2H, m), 7,65–8,01 (6H, m), 9,98 (1H, d, J = 8,1 Hz), 11,03 (1H, s), 11,20 (1H, d, J = 16,2 Hz).

Ejemplo 69

Producción de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida

872



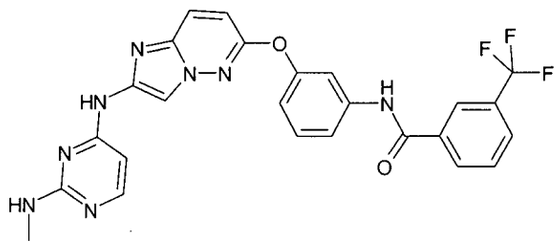
Una mezcla de [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de tert–butilo (2,37 g, 4,62 mmol), solución de ácido clorhídrico 4 N–acetato de etilo (50 mL) y metanol (50 mL) se agitó a temperatura ambiente durante 6 h. El solvente se evaporó a presión reducida, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio al residuo, y la mezcla se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio anhidro y se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo→acetato de etilo/metanol = 4 : 1) para dar el compuesto del título (1,57 g, 82%) en forma de un sólido verde.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ5,33 (2H, brs), 6,80 (1H, d, J = 9,0 Hz), 6,94 (1H, m), 7,15 (1H, s), 7,42 (1H, t, J = 7,8 Hz), 7,63 – 7,80 (4H, m), 7,97 (1H, d, J = 7,5 Hz), 8,23 – 8,27 (2H, m), 10,54 (1H, s).

Ejemplo 70

Producción de N–{3–[(2–{[2–(metilamino)pirimidin–4–il]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida

873



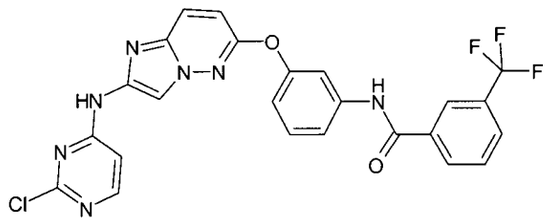
Una mezcla de N–[3–({2–[(2–cloropirimidin–4–il)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (122 mg, 0,23 mmol), solución 2 M de metilamina–tetrahidrofurano (3,0 mL) y etanol (6,0 mL) se calentó hasta 70 °C, y la mezcla se agitó durante la noche. Se añadió acetato de etilo a la mezcla de reacción, y la mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo→acetato de etilo/metanol = 4 : 1). El residuo obtenido se lavó con acetato de etilo–hexano para dar el compuesto del título (60 mg, 50%) en forma de un sólido amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,76 (3H, m), 6,15 (1H, d, J = 5,1 Hz), 6,85 (1H, m), 7,04 – 7,07 (2H, m), 7,47 (1H, t, J = 8,1 Hz), 7,68 – 8,02 (6H, m), 8,24 – 8,28 (2H, m), 8,44 (1H, m), 9,96 (1H, brs), 10,59 (1H, s).

Ejemplo 71

Producción de N–[3–({2–[(2–cloropirimidin–4–il)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

874

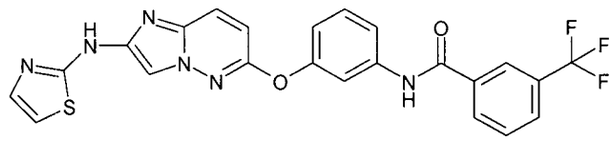


A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (103 mg, 0,25 mmol) en tetrahidrofurano (15 mL) se añadió hidruro de sodio (60% en aceite, 80 mg, 2,0 mmol), y la mezcla se agitó a temperatura ambiente durante 10 min. Se añadió 2,4–dicloropirimidina (149 mg, 1,00 mmol) a la mezcla de reacción, y la mezcla se calentó hasta 60 °C. Al cabo de 1 h, la mezcla de reacción se enfrió hasta temperatura ambiente y se añadió acetato de etilo. La mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 1/19→acetato de etilo solo) y el sólido obtenido se lavó con acetato de etilo/hexano (=1/2) para dar el compuesto del título (27 mg, 21%) en forma de un sólido de color azul claro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,97 – 7,17 (3H, m), 7,48 (1H, t, J = 8,1 Hz), 7,68 – 8,00 (4H, m), 8,08 – 8,29 (5H, m), 10,61 (1H, brs), 10,93 (1H, brs).

Ejemplo 72

Producción de N–(3–{[2–(1,3–tiazol–2–ilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(trifluorometil)benzamida

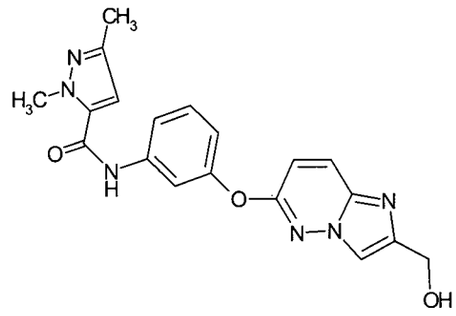


Una mezcla de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (165 mg, 0,4 mmol), tris(dibencilidenacetona)dipaladio (0) (37 mg, 0,04 mmol), (9,9–dimetil–9H–xanten–4,5–diil)bis(difenilfosfina) (46 mg, 0,03 mmol), t–butóxido de sodio (77 mg, 0,8 mmol), 2–bromotiazol (98 mg, 0,6 mmol) y N,N–dimetilacetamida (2 mL) se calentó hasta 70 °C bajo una atmósfera de nitrógeno, y la mezcla se agitó durante 2 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió acetato de etilo a la mezcla, y la mezcla se lavó con solución acuosa saturada de hidrógeno–carbonato de sodio, se secó sobre sulfato de magnesio anhidro, y se filtró. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 1/19→acetato de etilo solo) para dar el compuesto del título (10 mg, 5%) en forma de un sólido de color azul claro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,92 – 7,27 (4H, m), 7,46 (1H, t, J = 7,8 Hz), 7,67 – 8,06 (6H, m), 8,24 – 8,28 (2H, m), 10,58 (1H, brs), 10,90 (1H, brs).

Ejemplo 73

Producción de N–(3–{[2–(hidroximetil)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de (6–yodoimidazo[1,2–b]piridazin–2–il)metanol(400 mg, 1,45 mmol) en N,N–dimetilformamida (4,0 mL) se añadieron N–(3–hidroxifenil)–1,3–dimetil–1H–pirazol–5–carboxamida (504 mg, 2,18 mmol) y carbonato de potasio (402 mg, 2,91 mmol), y la mezcla se agitó a 150 °C durante 16 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/etanol = 100/0→10/1) para dar el compuesto del título (70 mg, 13%) en forma de un polvo blanco.

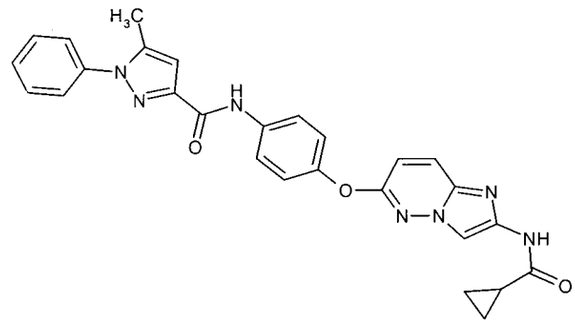
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,98 (3H, s), 4,55 (1H, d, J = 5,4 Hz), 5,19 (1H, d, J = 5,4 Hz), 6,82 (1H, s), 6,98 – 7,03 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,39 – 7,46 (1H, m), 7,59 – 7,63 (1H, m), 7,66 – 7,68 (1H, m), 7,88 (1H, s), 8,10 (1H, d, J = 9,6 Hz), 10,23 (1H, s).

Ejemplo 74

Producción de N–[4–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

877

b]piridazin–6–il}oxi)fenil]–5–metil–1–fenil–1H–pirazol–3–carboxamida



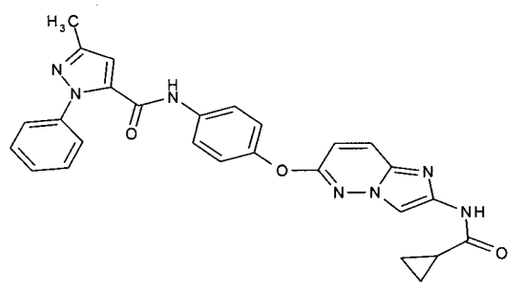
Usando ácido 5–metil–1–fenil–1H–pirazol–3–carboxílico (196 mg, 0,97 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida(30 μL, 0,39 mmol), cloruro de oxalilo (85 μL, 0,97 mmol), N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (223 mg, 70%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 2,31 (3H, s), 6,85 (1H, s), 7,02 (1H, d, J = 9,6 Hz), 7,23 (2H, d, J = 9,3 Hz), 7,36 – 7,46 (5H, m), 7,71 (2H, J = 9,3 Hz), 7,92 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 10,62 (1H, s), 11,05 (1H, s).

Ejemplo 75

Producción de N–[4–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metil–1–fenil–1H–pirazol–5–carboxamida

878

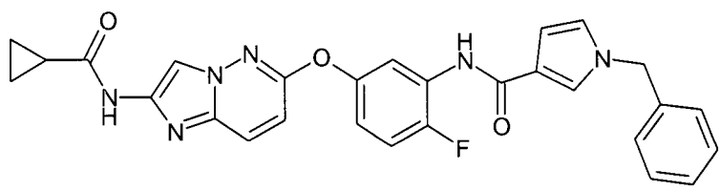


Usando ácido 3–metil–1–fenil–1H–pirazol–5–carboxílico (196 mg, 0,97 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (85 μL, 0,97 mmol), N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (209 mg, 65%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 2,36 (3H, s), 6,80 (1H, s), 7,03 (1H, d, J = 9,5 Hz), 7,21 – 7,25 (2H, m), 7,48 – 7,67 (5H, m), 7,86 – 7,91 (2H, m), 7,92 (1H, s), 8,01 (1H, d, J = 9,5 Hz), 10,18 (1H, s), 11,05 (1H, s).

Ejemplo 76

Producción de 1–bencil–N–[5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1H–pirrol–3–carboxamida



Usando ácido 1–bencil–1H–pirrol–3–carboxílico (276 mg, 1,37

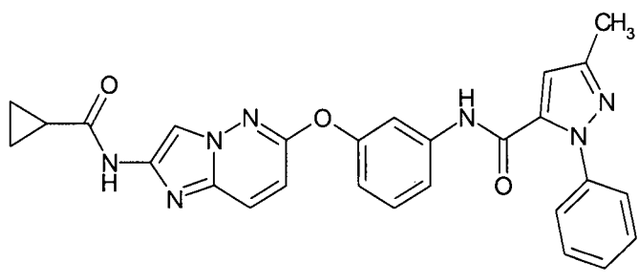
879

mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (120 μL, 1,37 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida (300 mg, 0,92 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (114 mg, 24%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,85 – 1,96 (1H, m), 5,15 (2H, s), 6,62 – 6,64 (1H, m), 6,88 – 6,92 (1H, m), 7,05 (1H, d, J = 9,6 Hz), 7,07 – 7,12 (1H, m), 7,23 – 7,62 (6H, m), 7,56 – 7,62 (2H, m), 7,93 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,43 (1H, s), 11,07 (1H, s).

Ejemplo 77

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metil–1–fenil–1H–pirazol–5–carboxamida



Usando ácido 3–metil–1–fenil–1H–pirazol–5–carboxílico (294 mg, 1,45 mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (127 μL, 1,45 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida

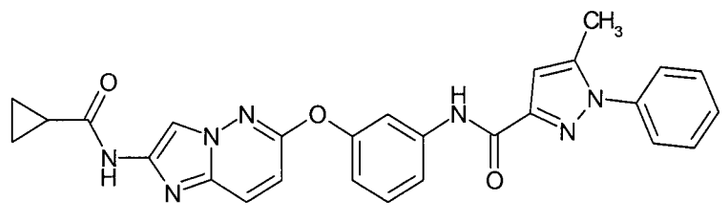
880

(300 mg, 0,97 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (342 mg, 71%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,85 – 1,95 (1H, m), 2,34 (3H, s), 6,78 (1H, s), 6,92 – 6,98 (1H, m), 7,05 (1H, d, J = 9,9 Hz), 7,33 – 7,43 (1H, m), 7,46 – 7,66 (5H, m), 7,69 – 7,78 (2H, m), 7,97 (1H, s), 8,04 (1H, d, J = 9,9 Hz), 10,21 (1H, s), 11,08 (1H, s).

Ejemplo 78

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–metil–1–fenil–1H–pirazol–3–carboxamida



Usando ácido 5–metil–1–fenil–1H–pirazol–3–carboxílico (294 mg, 1,45 mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (127 μL, 1,45 mmol), N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,97 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (317 mg, 66%) en forma de un polvo blanco.

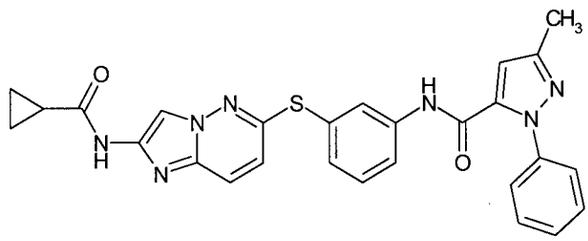
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,84 – 1,96 (1H, m), 2,29 (3H, s), 6,85 (1H, s), 6,96 – 7,01 (1H, m), 7,04

881

(1H, d, J = 9,6 Hz), 7,30 – 7,58 (8H, m), 7,95 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 10,64 (1H, s), 11,08 (1H, s).

Ejemplo 79

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–3–metil–1–fenil–1H–pirazol–5–carboxamida



Usando ácido 3–metil–1–fenil–1H–pirazol–5–carboxílico (186 mg, 0,92 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (80 μL, 0,92 mmol), N–{6–[(3–aminofenil)tio]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (203 mg, 65%) en forma de un polvo blanco.

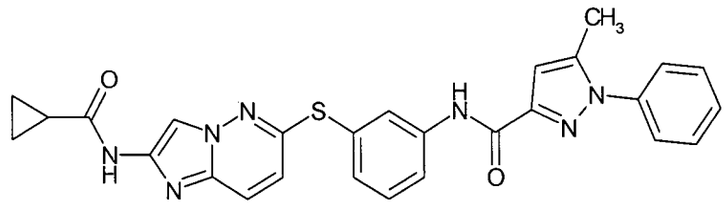
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,84 (4H, m), 1,86 – 1,96 (1H, m), 2,35 (3H, s), 6,78 (1H, s), 6,89 – 6,94 (1H, m), 7,27 – 7,31 (1H, m), 7,40 – 7,65 (7H, m), 7,86 – 7,95 (2H, m), 8,09 – 8,24 (1H, m), 10,25 (1H, s), 11,17 (1H, s).

Ejemplo 80

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–5–metil–1–fenil–1H–pirazol–3–

882

carboxamida

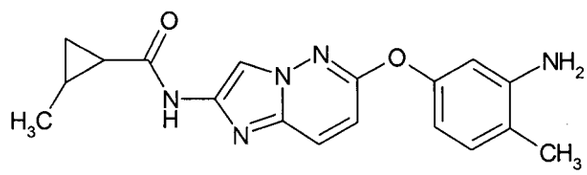


Usando ácido 5–metil–1–fenil–1H–pirazol–3–carboxílico (196 mg, 0,97 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (80 μL, 0,92 mmol), N–{6–[(3–aminofenil)tio]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (155 mg, 49%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,86 (4H, m), 1,85 – 1,96 (1H, m), 2,29 (3H, s), 6,86 (1H, s), 6,94 (1H, d, J = 9,3 Hz), 7,29 – 7,46 (7H, m), 7,71 – 7,76 (1H, m), 7,87 (1H, s), 7,88 (1H, d, J = 9,3 Hz), 8,12 (1H, s), 10,63 (1H, s), 11,16 (1H, s).

Ejemplo 81

Producción de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida



Usando 3–amino–4–metilfenol (1,08 g, 8,77 mmol), N,N–dimetilformamida (30,0 mL), tert-butóxido de potasio (1,02 g, 9,13

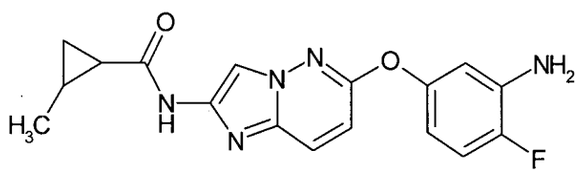
883

mmol), N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilciclopropancarboxamida (2,5 g, 7,31 mmol) y carbonato de potasio (0,51 g, 3,65 mmol), y de la misma manera que en el Ejemplo 216, se obtuvo el compuesto del título (1,38 g, 56%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,69 (1H, m), 0,96 – 1,05 (1H, m), 1,06 – 1,09 (3H, m), 1,19 – 1,27 (1H, m), 1,63 – 1,72 (1H, m), 2,04 (3H, s), 5,05 (2H, s), 6,27 (1H, dd, J = 8,0, 2,4 Hz), 6,41 (1H, d, J = 2,4 Hz), 6,92 (1H, d, J = 9,5 Hz), 6,94 (1H, d, J = 8,0 Hz), 7,94 (1H, s), 7,96 (1H, d, J = 9,5 Hz), 10,96 (1H, s).

Ejemplo 82

Producción de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida



A una solución de 3–amino–4–fluorofenol (0,42 g, 3,29 mmol) en N,N–dimetilformamida (9,0 mL) se añadieron N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilciclopropancarboxamida (0,75 g, 2,19 mmol) y carbonato de potasio (0,61 g, 4,38 mmol), y la mezcla se agitó a 140 °C durante 16 h. Se añadió salmuera saturada a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión

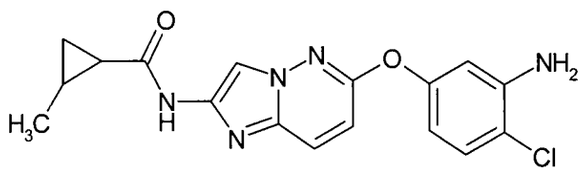
884

reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo), y el residuo obtenido se lavó con hexano/acetato de etilo y se filtró para dar el compuesto del título (0,63 g, 88%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,62 – 0,74 (1H, m), 0,96 – 1,04 (1H, m), 1,07 – 1,09 (3H, m), 1,17 – 1,28 (1H, m), 1,62 – 1,72 (1H, m), 5,36 (2H, s), 6,30 – 6,36 (1H, m), 6,57 (1H, dd, J = 7,8, 2,7 Hz), 6,96 (1H, d, J = 9,6 Hz), 7,02 (1H, dd, J = 11,4, 8,7 Hz), 7,94 (1H, s), 7,96 – 8,00 (1H, m), 10,97 (1H, s).

Ejemplo 83

Producción de N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida



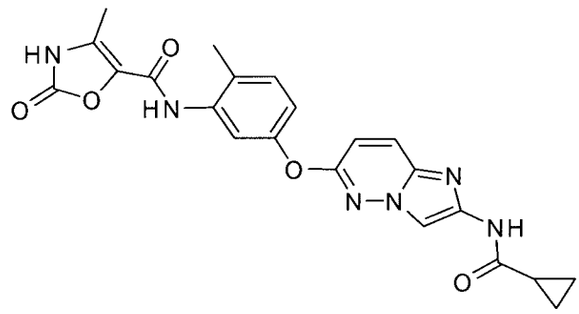
Usando 3–amino–4–clorofenol (1,57 g, 11,0 mmol), N,N–dimetilformamida (25,0 mL), N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilciclopropancarboxamida (2,50 g, 7,31 mmol) y carbonato de potasio (2,02 g, 14,6 mmol), y de la misma manera que en el Ejemplo 82, se obtuvo el compuesto del título (1,92 g, 73%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) d 0,61 – 0,72 (1H, m), 0,97 – 1,04 (1H, m), 1,07 – 1,12 (3H, m), 1,17 – 1,28 (1H, m), 1,63 – 1,73 (1H, m), 5,54 (2H, s), 6,39 (1H, dd, J = 8,6, 2,9 Hz), 6,60 (1H, d, J =

2,9 Hz), 6,99 (1H, d, J = 9,5 Hz), 7,22 (1H, dd, J = 8,6 Hz), 7,96 (1H, s), 8,00 (1H, d, J = 8,6 Hz), 10,98 (1H, s).

Ejemplo 84

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metil–2–oxo–2,3–dihidro–1,3–oxazol–5–carboxamida



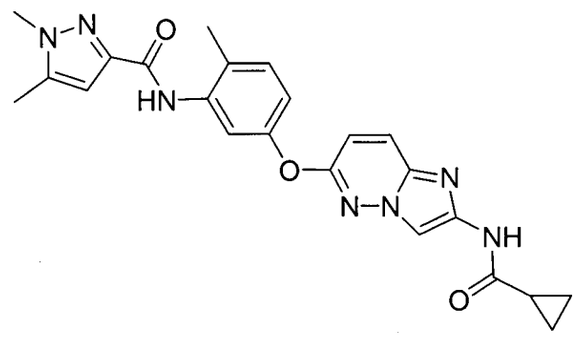
De la misma manera que en el Ejemplo 259 y usando ácido 4–metil–2–oxo–2,3–dihidro–1,3–oxazol–5–carboxílico (159 mg, 1,1 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (382 μL, 4,44 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,93 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (145 mg, 35%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,86 – 1,97 (1H, m), 2,22 (3H, s), 2,27 (3H, s), 6,98 – 7,09 (2H, m), 7,24 – 7,33 (2H, m), 7,94 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,41 (1H, s), 11,07 (1H, s), 11,46 (1H, brs).

Ejemplo 85

886

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,5–dimetil–1H–pirazol–3–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 1,5–dimetil–1H–pirazol–3–carboxílico (145 mg, 1,0 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (320 μL, 4,44 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (250 mg, 0,77 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (57 mg, 17%) en forma de un sólido blanco.

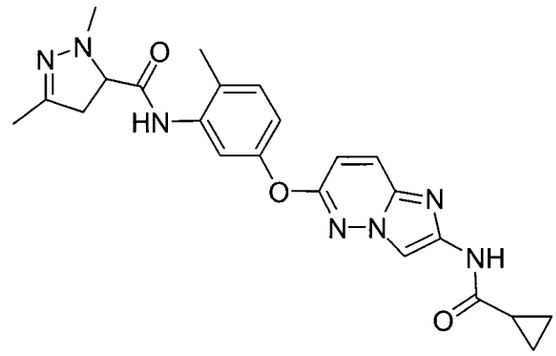
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,87 – 1,97 (1H, m), 2,27 (3H, s), 2,30 (3H, s), 3,83 (3H, s), 6,53 (1H, s), 6,97 – 7,06 (2H, m), 7,25 – 7,34 (1H, m), 7,61 (1H, d, J = 2,3 Hz), 7,92 – 7,97 (1H, m), 8,02 (1H, d, J = 9,5 Hz), 9,35 (1H, s), 11,07 (1H, s).

Ejemplo 86

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–4,5–dihidro–1H–

887

pirazol–5–carboxamida

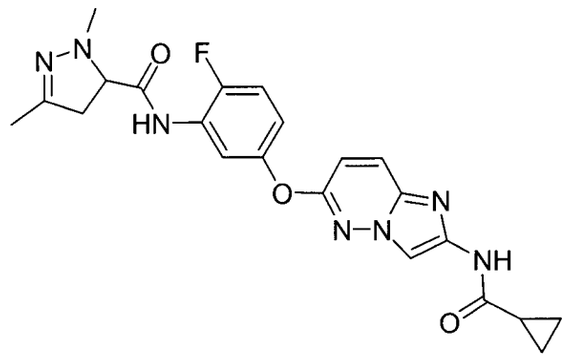


De la misma manera que en el Ejemplo 278 y usando 1,3–dimetil–4,5–dihidro–1H–pirazol–5–carboxílico (120 mg, 0,87 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (330 mg, 0,87 mmol), N,N–diisopropiletilamina (240 mg, 1,8 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (199 mg, 72%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,87 (3H, s), 1,89 – 1,97 (1H, m), 2,23 (3H, s), 2,74 (3H, s), 2,77 – 2,87 (1H, m), 2,98 – 3,13 (1H, m), 3,57 (1H, m), 6,95 – 7,07 (2H, m), 7,30 (1H, d, J = 8,3 Hz), 7,51 (1H, d, J = 2,3 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 9,43 (1H, s), 11,07 (1H, s).

Ejemplo 87

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–4,5–dihidro–1H–pirazol–5–carboxamida

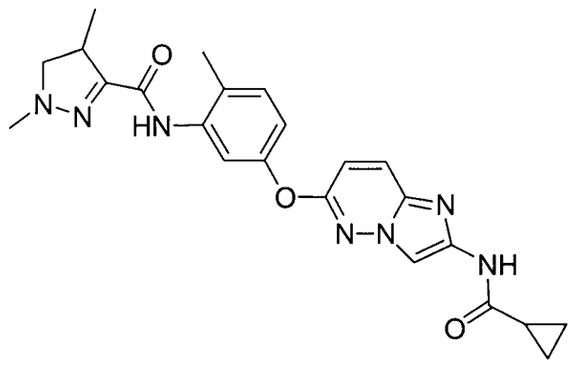


De la misma manera que en el Ejemplo 278 y usando ácido 1,3–dimetil–4,5–dihidro–1H–pirazol–5–carboxílico (170 mg, 1,2 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (280 mg, 0,84 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (450 mg, 1,2 mmol), N,N–diisopropiletilamina (330 mg, 2,5 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (240 mg, 63%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,84 (4H, m), 1,86 (3H, s), 1,89 – 1,96 (1H, m), 2,71 (3H, s), 2,81 (1H, dd, J = 17,4, 12,9 Hz), 2,98 – 3,11 (1H, m), 3,59 – 3,71 (1H, m), 7,06 (1H, d, J = 9,5 Hz), 7,09 – 7,14 (1H, m), 7,38 (1H, dd, J = 10,4, 8,9 Hz), 7,87 (1H, dd, J = 6,4, 3,0 Hz), 7,93 (1H, s), 8,04 (1H, d, J = 9,5 Hz), 9,75 (1H, s), 11,08 (1H, s).

Ejemplo 88

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,4–dimetil–4,5–dihidro–1H–pirazol–3–carboxamida



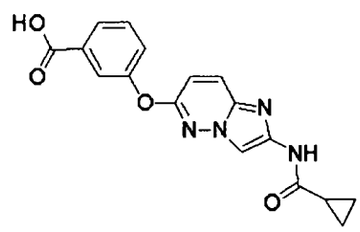
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (300 mg, 0,91 mmol), N–(5–hidroxi–2–metilfenil)–1,4–dimetil–4,5–dihidro–1H–pirazol–3–carboxamida (290 mg, 1,2 mmol), carbonato de cesio (600 mg, 1,8 mmol) y dimetilsulfóxido (2 mL) se agitó a 100 °C durante 6 h. Se añadieron acetato de etilo/tetrahidrofurano y agua a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→100/0) para dar el compuesto del título (300 mg, 73%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,14 (3H, d, J = 6,4 Hz), 1,86 – 1,97 (1H, m), 2,23 (3H, s), 2,92 (3H, s), 3,05 – 3,12 (1H, m), 3,22 – 3,32 (2H, m), 6,98 (1H, dd, J = 8,3, 2,7 Hz), 7,03 (1H, d, J = 9,8 Hz), 7,28 (1H, d, J = 8,3 Hz), 7,53 (1H, d, J = 2,7 Hz), 7,94 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 9,18 (1H, s), 11,08 (1H, s).

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Ejemplo 89

Producción de ácido 3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoico



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (518 mg, 1,58 mmol), 3–hidroxibenzoato de metilo (360 mg, 2,37 mmol), carbonato de potasio (654 mg, 4,73 mmol) y N,N–dimetilformamida (4,0 mL) se agitó a 110 °C durante 2 días. El solvente se evaporó a presión reducida, acetato de etilo, tetrahidrofurano y agua se añadieron al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→85/15) para dar 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoato de metilo (225 mg, 41%) en forma de un polvo blanco.

A una solución de 3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoato de metilo (225 mg, 0,64 mmol) en tetrahidrofurano (5,0 mL) se añadió hidróxido de sodio 1 N (2,5 mL), y la mezcla se agitó a temperatura ambiente durante 24

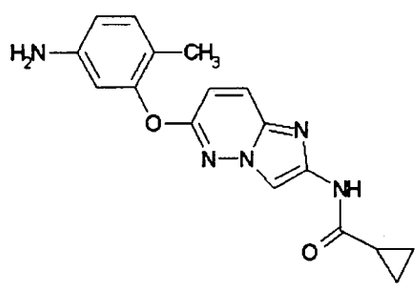
841

h. Se añadieron ácido clorhídrico 1 N se añadió a la mezcla (pH = 3), y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se filtró, y se lavó con acetato de etilo/hexano para dar el compuesto del título (150 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,89 (4H, m), 1,84 – 2,01 (1H, m), 7,09 (1H, d, J = 9,5 Hz), 7,48 – 7,68 (2H, m), 7,73 (1H, s), 7,84 (1H, d, J = 7,2 Hz), 7,94 (1H, s), 8,06 (1H, d, J = 9,5 Hz), 11,08 (1H, s), 13,20 (1H, brs).

Ejemplo 90

Producción de N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



A una suspensión de hidruro de sodio (56 mg, 1,40 mmol) en N,N–dimetilformamida (2,0 mL) se añadió una solución de 5–amino–2–metilfenol (173 mg, 1,40 mmol) en N,N–dimetilformamida (1,0 mL), y la mezcla se agitó a 0 °C durante 30 min. A la mezcla de reacción se añadió una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–

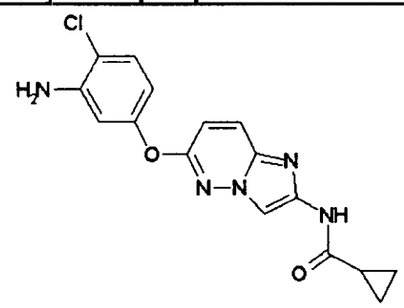
892

il)ciclopropancarboxamida (306 mg, 0,933 mmol) en N,N–dimetilformamida (1,5 mL), y la mezcla se agitó a 110°C durante 24 h. El solvente se evaporó a presión reducida, y se añadieron acetato de etilo y agua al residuo. La capa acuosa se extrajo tres veces con acetato de etilo. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 17/83→90/10) para dar el compuesto del título (94 mg, 31%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,89 (4H, m), 1,84 – 2,01 (1H, m), 1,97 (3H, s), 5,08 (2H, s), 6,30 (1H, d, J = 2,3 Hz), 6,40 (1H, dd, J = 8,0, 2,3 Hz), 6,94 (1H, d, J = 8,0 Hz), 6,95 (1H, d, J = 9,5 Hz), 7,93 (1H, s), 7,99 (1H, d, J = 9,5 Hz), 11,06 (1H, s).

Ejemplo 91

Producción de N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



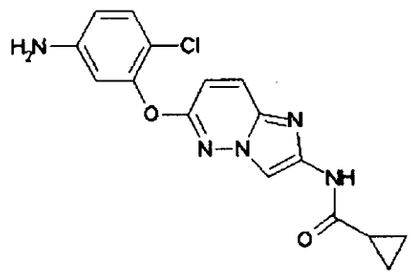
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (800 mg, 2,44 mmol), 3–amino–4–clorofenol (422 mg, 2,93 mmol), carbonato de potasio (843 mg, 6,10

mmol) y N,N–dimetilformamida (6,0 mL) se agitó usando un sintetizador de microondas a 180 °C durante 30 min. El solvente se evaporó a presión reducida, acetato de etilo, tetrahidrofurano y agua se añadieron al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 17/83→75/25) para dar el compuesto del título (610 mg, 73%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,87 (4H, m), 1,84 – 1,98 (1H, m), 5,56 (2H, s), 6,40 (1H, dd, J = 8,5, 2,8 Hz), 6,61 (1H, d, J = 2,8 Hz), 7,00 (1H, d, J = 9,8 Hz), 7,23 (1H, d, J = 8,5 Hz), 7,98 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 11,09(1H, s).

Ejemplo 92

Producción de N–[6–(5–amino–2–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (800 mg, 2,44 mmol), 5–amino–2–clorofenol (422 mg, 2,93 mmol), carbonato de potasio (843 mg, 6,1

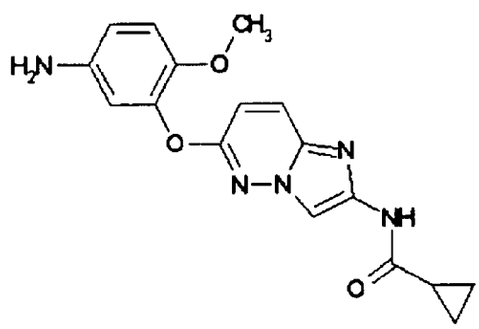
894

mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (226 mg, 27%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,85 – 1,98 (1H, m), 5,47 (2H, s), 6,47 – 6,51 (1H, m), 6,51 (1H, s), 7,04 (1H, d, J = 9,5 Hz), 7,17 (1H, d, J = 9,0 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 11,06 (1H, s).

Ejemplo 93

Producción de N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (800 mg, 2,44 mmol), 5–amino–2–metoxifenol (408 mg, 2,93 mmol), carbonato de potasio (843 mg, 6,10 mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (299 mg, 36%) en forma de un polvo color café.

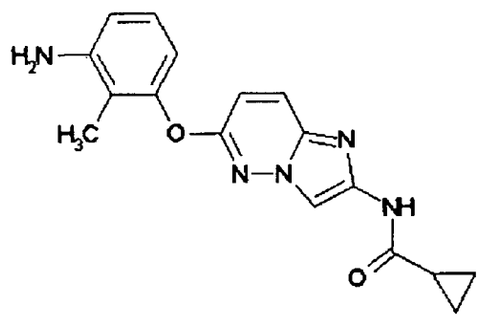
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,85 (4H, m), 1,91 (1H, m), 3,56 (3H, s), 4,87 (2H, s), 6,41 – 6,49 (2H, m), 6,85 – 6,91 (1H, m), 6,95 (1H, d, J = 9,5 Hz), 7,90 (1H, s), 7,96 (1H, d, J = 9,5 Hz),

895.

11,05 (1H, s).

Ejemplo 94

Producción de N–[6–(3–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



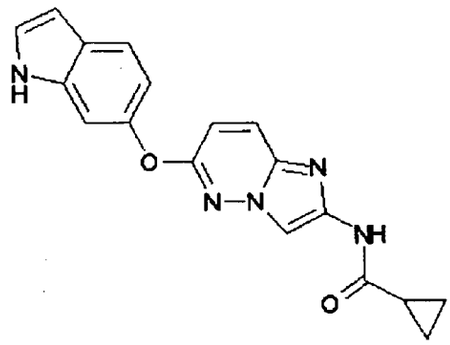
Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (800 mg, 2,44 mmol), 3–amino–2–metilfenol (380 mg, 2,93 mmol), carbonato de potasio (843 mg, 6,10 mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (454 mg, 58%) en forma de un polvo de color café negruzco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,87 (4H, m), 1,83 – 1,98 (1H, m), 1,89 (3H,s), 5,13 (2H, s), 6,32 (1H, d, J = 8,0 Hz), 6,55 (1H, d, J = 6,8 Hz), 6,93 (1H, dd, J = 8,0, 6,8 Hz), 6,94 (1H, d, J = 9,5 Hz), 7,91 (1H, s), 7,98 (1H, d, J = 9,5 Hz), 11,05 (1H, s).

Ejemplo 95

Producción de N–[6–(1H–indol–6–iloxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida

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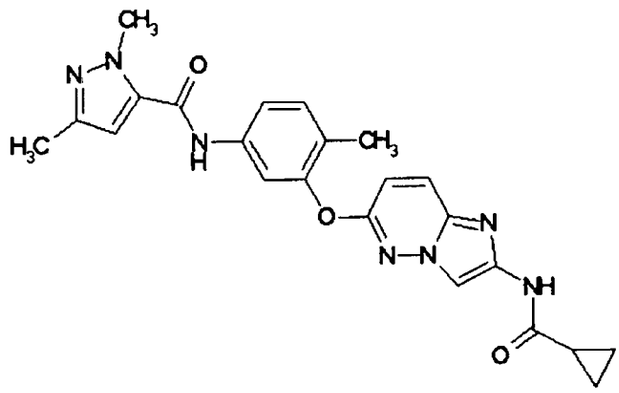
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (473 mg, 1,44 mmol), 1H–indol–6–ol (250 mg, 1,87 mmol), carbonato de potasio (597 mg, 4,32 mmol) y N,N–dimetilformamida (4,0 mL) se agitó a 110 °C durante 2 días. El solvente se evaporó a presión reducida, acetato de etilo, tetrahidrofurano y agua se añadieron al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→85/15), y se precipitó en acetato de etilo/hexano para dar el compuesto del título (48 mg, 10%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,89 (4H, m), 1,83 – 1,97 (1H, m), 6,47 (1H, s), 6,89 (1H, dd, J = 8,3, 2,3 Hz), 7,00 (1H, d, J = 9,5 Hz), 7,26 (1H, d, J = 2,3 Hz), 7,33 – 7,42 (1H, m), 7,58 (1H, d, J = 8,3 Hz), 7,91 (1H, s), 7,99 (1H, d, J = 9,5 Hz), 11,06 (1H, s), 11,17 (1H, s).

Ejemplo 96

894

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (72,6 mg, 0,224 mmol) en tetrahidrofurano (4,0 mL) se añadieron una solución de cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (46,3 mg, 0,29 mmol) en tetrahidrofurano (0,5 mL) y trietilamina (68 mg, 0,672 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con solución acuosa saturada de hidrógeno–carbonato de sodio, y se extrajo tres veces con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se filtró, se lavó con acetato de etilo/hexano para dar el compuesto del título (64 mg, 64%) en forma de un polvo color café.

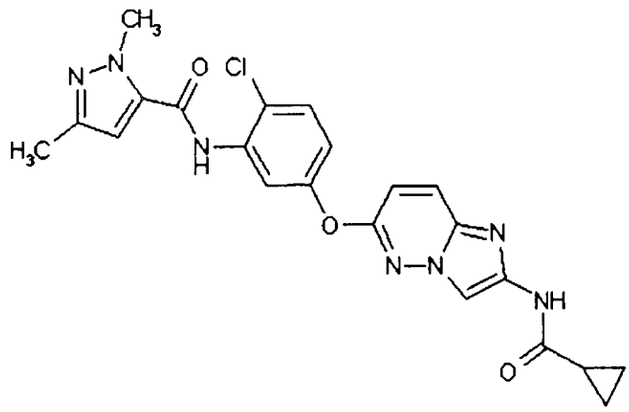
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,88 (4H, m), 1,85 – 1,97 (1H, m), 2,14 (3H, s), 2,18 (3H, s), 3,97 (3H, s), 6,81 (1H, s),

898

7,08 (1H, d, J = 9,5 Hz), 7,32 (1H, d, J = 8,3 Hz), 7,55 (1H, dd, J = 8,3, 1,9 Hz), 7,60 (1H, d, J = 1,9 Hz), 7,92 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 10,18 (1H, s), 11,08 (1H, s).

Ejemplo 97

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (128 mg, 0,373 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (77,2 mg, 0,485 mmol), trietilamina (113 mg, 1,12 mmol) y tetrahidrofurano (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (77 mg, 44%) en forma de un polvo blanco. Punto de fusión 255 °C.

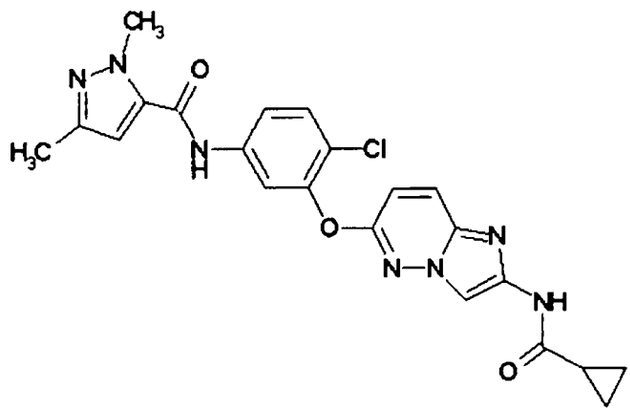
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,85 – 1,98 (1H, m), 2,20 (3H, s), 3,98 (3H, s), 6,84 (1H, s), 7,10 (1H, d, J = 9,6 Hz), 7,26 (1H, dd, J = 8,9, 2,8 Hz), 7,54 (1H, d, J = 2,8 Hz), 7,64 (1H, d, J = 8,9 Hz), 7,96 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 9,99 (1H,

894

s), 11,09 (1H, s).

Ejemplo 98

Producción de N–[4–cloro–3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[6–(5–amino–2–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (131 mg, 0,382 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (91 mg, 0,573 mmol), trietilamina (116 mg, 1,15 mmol) y tetrahidrofurano (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (163 mg, 92%) en forma de un polvo blanco.

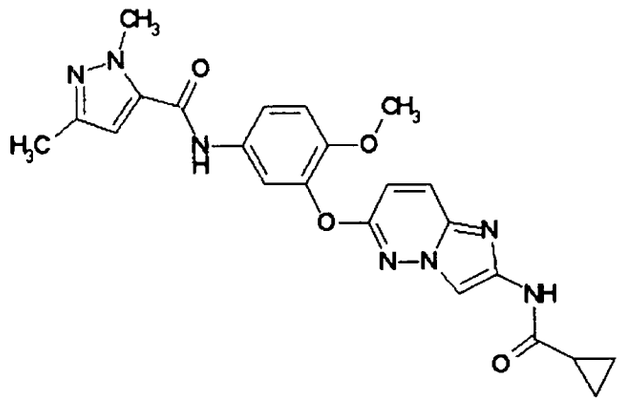
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,67 – 0,82 (4H, m), 1,81 – 1,94 (1H, m), 2,16 (3H, s), 3,96 (3H, s), 6,80 (1H, s), 7,14 (1H, dd, J = 9,6, 1,6 Hz), 7,59 (1H, m), 7,66 (1H, m), 7,83 (1H, d, J = 1,6 Hz), 7,91 (1H, s), 8,07 (1H, d, J = 9,6 Hz), 10,34 (1H, s), 11,08 (1H, s).

Ejemplo 99

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]–1,3–dimetil–1H–pirazol–5–

900

carboxamida

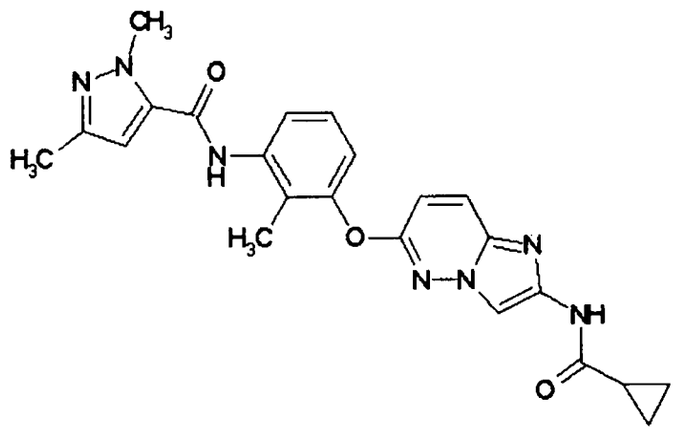


Usando N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (129 mg, 0,379 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (78,3 mg, 0,493 mmol), trietilamina (115 mg, 1,14 mmol) y tetrahidrofurano (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (124 mg, 71%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,85 (4H, m), 1,86 – 1,97 (1H, m), 2,19 (3H, s), 3,71 (3H, s), 3,97 (3H, s), 6,80 (1H, s), 7,06 (1H, d, J = 9,5 Hz), 7,20 (1H, d, J = 8,9 Hz), 7,59 (1H, dd, J = 8,9, 2,5 Hz), 7,68 (1H, d, J = 2,5 Hz), 7,89 (1H, s), 8,01 (1H, d, J = 9,5 Hz), 10,15 (1H, s), 11,07 (1H, s).

Ejemplo 100

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



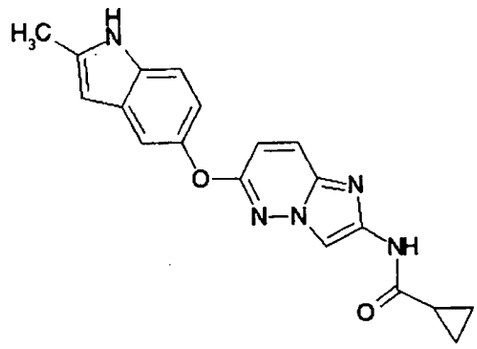
Usando N–[6–(3–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (130 mg, 0,402 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (83 mg, 0,523 mmol), trietilamina (122 mg, 1,21 mmol) y tetrahidrofurano (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (146 mg, 82%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,87 (4H, m), 1,86 – 1,98 (1H, m), 2,06 (3H, s), 2,20 (3H, s), 4,01 (3H, s), 6,84 (1H, s), 7,09 (1H, d, J = 9,5 Hz), 7,15 (1H, dd, J = 6,8, 2,3 Hz), 7,25 – 7,36 (2H, m), 7,88 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 9,95 (1H, s), 11,07 (1H, s).

Ejemplo 101

Producción de N–{6–[(2–metil–1H–indol–5–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida

902

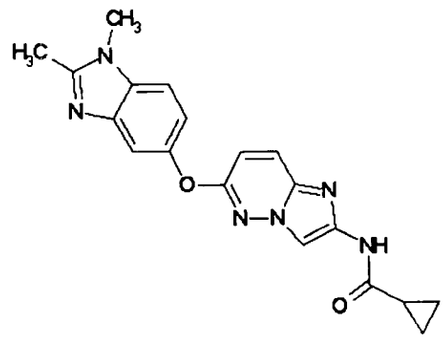


Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il) ciclopropancarboxamida (272 mg, 0,830 mmol), 2–metil–1H–indol–5–ol (244 mg, 1,66 mmol), carbonato de potasio (344 mg, 2,49 mmol) y N,N–dimetilformamida (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 95, se obtuvo el compuesto del título (56 mg, 19%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,82 – 1,97 (1H, m), 2,39 (3H, s), 6,13 (1H, s), 6,86 (1H, dd, J = 8,7, 2,3 Hz), 6,95 (1H, d, J = 9,5 Hz), 7,23 (1H, d, J = 2,3 Hz), 7,30 (1H, d, J = 8,7 Hz), 7,88 (1H, s), 7,96 (1H, d, J = 9,5 Hz), 11,05 (2H, s).

Ejemplo 102

Producción de N–{6–[(1,2–dimetil–1H–bencimidazol–5–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



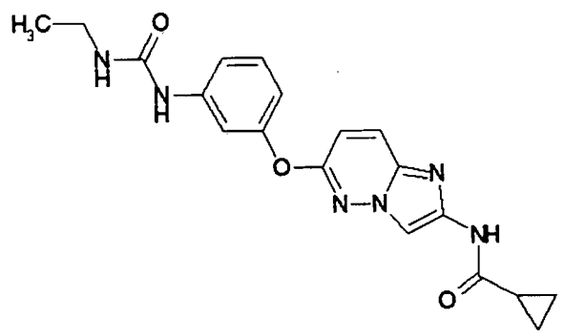
903

Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (254 mg, 0,774 mmol), 1,2–dimetil–1H–bencimidazol–5–ol (163 mg, 1,06 mmol), carbonato de potasio (267 mg, 1,94 mmol) y N,N–dimetilformamida (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 95, se obtuvo el compuesto del título (79 mg, 28%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,84 (4H, m), 1,84 – 1,96 (1H, m), 2,54 (3H, s), 3,77 (3H, s), 7,00 (1H, d, J = 9,8 Hz), 7,09 (1H, dd, J = 8,7, 2,3 Hz), 7,39 (1H, d, J = 2,3 Hz), 7,53 (1H, d, J = 8,7 Hz), 7,86 (1H, s), 7,99 (1H, d, J = 9,8 Hz), 11,05 (1H, s).

Ejemplo 103

Producción de N–[6–(3–{[(etilamino)carbonil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



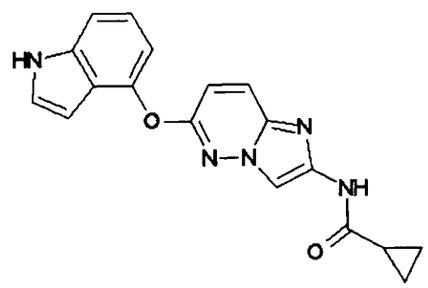
A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (160 mg, 0,517 mmol) en piridina (4,0 mL) se añadió isocianato de etilo (409 µL, 5,17 mmol), y la mezcla se agitó a temperatura ambiente durante 24 h. El solvente se evaporó a presión reducida, acetato de etilo y solución acuosa saturada de hidrógeno–carbonato de sodio se añadieron al residuo, y

la capa acuosa se extrajo tres veces con acetato de etilo. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se filtró, y se lavó con acetato de etilo/hexano para dar el compuesto del título (136 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,00 (3H, t, J = 7,1 Hz), 1,83 – 1,95 (1H, m), 2,97 – 3,12 (2H, m), 6,13 (1H, t, J = 5,5 Hz), 6,72 (1H, dd, J = 8,0, 2,5 Hz), 6,99 (1H, d, J = 9,6 Hz), 7,09 (1H, dd, J = 8,2, 1,1 Hz), 7,25 (1H, t, J = 8,2 Hz), 7,42 (1H, t, J = 1,9 Hz), 7,94 (1H, s), 8,00 (1H, d, J = 9,6 Hz), 8,61 (1H, s), 11,08 (1H, s).

Ejemplo 104

Producción de N–[6–(1H–indol–4–iloxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il) ciclopropancarboxamida (353 mg, 1,08 mmol), 1H–indol–4–ol (241 mg, 1,82 mmol), carbonato de potasio (446 mg, 3,23 mmol) y N,N–dimetilformamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 95, se obtuvo el compuesto del título (66

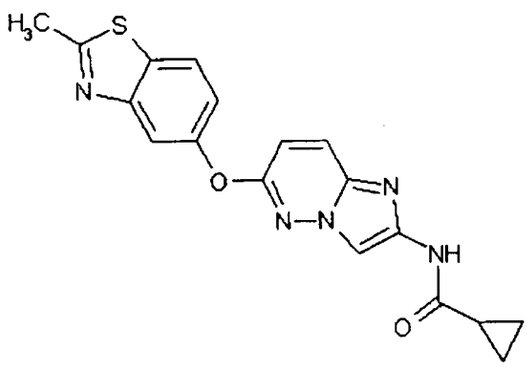
905

mg, 18%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,86 (4H, m), 1,83 – 1,96 (1H, m), 6,16 – 6,23 (1H, m), 6,85 (1H, dd, J = 7,8, 0,8 Hz), 7,01 (1H, d, J = 9,6 Hz), 7,12 (1H, t, J = 7,8 Hz), 7,26 – 7,37 (2H, m), 7,89 (1H, s), 8,00 (1H, d, J = 9,6 Hz), 11,06 (1H, s), 11,37 (1H, s).

Ejemplo 105

Producción de N–{6–[(2–metil–1,3–benzotiazol–5–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



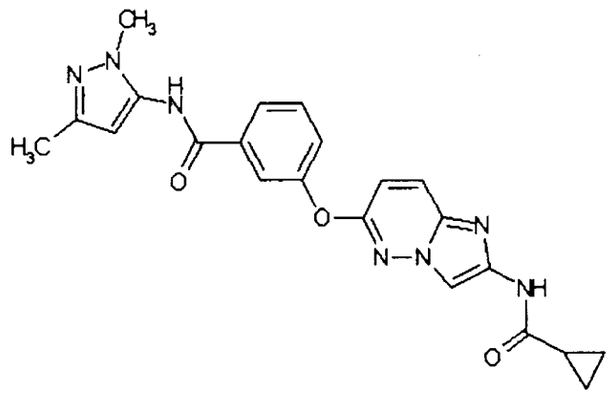
Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il) ciclopropancarboxamida (355 mg, 1,08 mmol), 2–metil–1,3–benzotiazol–5–ol (286 mg, 1,73 mmol), carbonato de potasio (448 mg, 3,24 mmol) y N,N–dimetilformamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 95, se obtuvo el compuesto del título (275 mg, 70%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,83 – 1,97 (1H, m), 2,82 (3H, s), 7,09 (1H, d, J = 9,6 Hz), 7,35 (1H, dd, J = 8,7, 2,3 Hz), 7,82 (1H, d, J = 2,3 Hz), 7,92 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 8,10 (1H, d, J = 8,7 Hz), 11,07 (1H, s).

906

Ejemplo 106

Producción de 3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)-N-(1,3-dimetil-1H-pirazol-5-il)benzamida



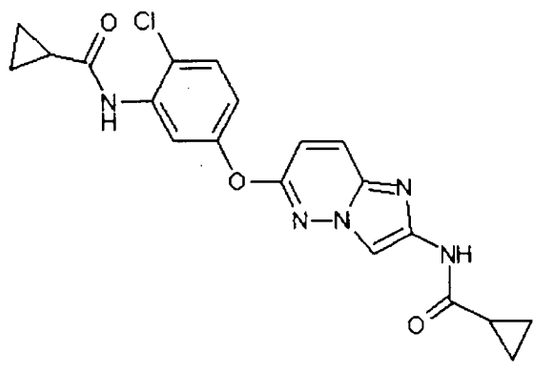
A una solución de ácido 3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)benzoico (121 mg, 0,358 mmol) en N,N-dimetilformamida (5,0 mL) se añadieron 1,3-dimetil-1H-pirazol-5-amina (47,8 mg, 0,43 mmol), 1-hidroxibenzotriazol (58 mg, 0,43 mmol), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (82,4 mg, 0,43 mmol) y trietilamina (45 mg, 0,43 mmol), y la mezcla se agitó a temperatura ambiente durante 24 h. El solvente se evaporó a presión reducida, acetato de etilo, tetrahidrofurano y agua se añadieron al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→90/10, luego metanol/acetato de etilo = 0/100→15/85), y se precipitó en acetato de etilo/hexano para dar el compuesto del título (116 mg,

75%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,86 – 1,96 (1H, m), 2,12 (3H, s), 3,56 (3H, s), 6,02 (1H, s), 7,11 (1H, d, J = 9,6 Hz), 7,50 – 7,57 (1H, m), 7,63 (1H, t, J = 7,9 Hz), 7,79 – 7,92 (2H, m), 7,95 (1H, s), 8,07 (1H, d, J = 9,6 Hz), 10,31 (1H, s), 11,09 (1H, s).

Ejemplo 107

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]ciclopropancarboxamida



Usando N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,435 mmol), cloruro de ciclopropancarbonilo (71,8 mg, 0,652 mmol), trietilamina (132 mg, 1,30 mmol) y tetrahidrofurano (17 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (156 mg, 87%) en forma de un polvo blanco.

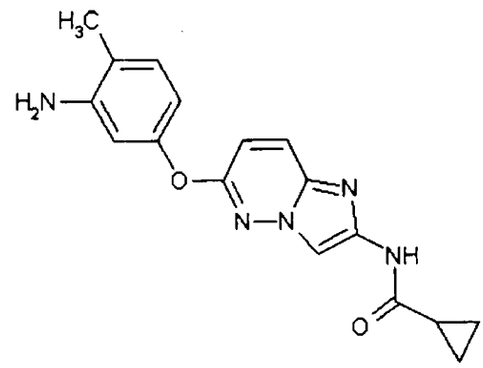
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,89 (8H, m), 1,84 – 1,98 (1H, m), 2,00 – 2,11 (1H, m), 7,06 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,7, 2,8 Hz), 7,56 (1H, d, J = 8,7 Hz), 7,73 (1H, d, J = 2,8

908

Hz), 7,95 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 9,83 (1H, s), 11,09 (1H, s).

Ejemplo 108

Producción de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (743 mg, 2,26 mmol), 3–amino–4–metilfenol (446 mg, 3,62 mmol), carbonato de potasio (782 mg, 5,66 mmol) y N,N–dimetilformamida (5,0 mL) se agitó usando un sintetizador de microondas a 180 °C durante 30 min. El solvente se evaporó a presión reducida, acetato de etilo, tetrahidrofurano y agua se añadieron al residuo, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 17/83→75/25) para dar el compuesto del título (424 mg, 58%) en forma de un polvo color café.

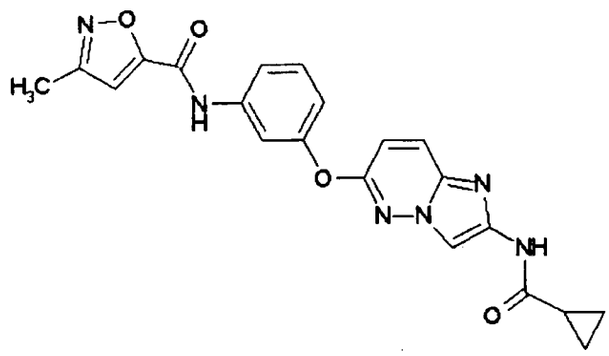
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,84 –

909

1,97 (1H, m), 2,04 (3H, s), 5,06 (2H, s), 6,28 (1H, dd, J = 8,1, 2,4 Hz), 6,42 (1H, d, J = 2,4 Hz), 6,93 (1H, d, J = 9,3 Hz), 6,95 (1H, d, J = 8,1 Hz), 7,96 (1H, s), 7,98 (1H, d, J = 9,3 Hz), 11,07 (1H, s).

Ejemplo 109

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metilisoxazol–5–carboxamida



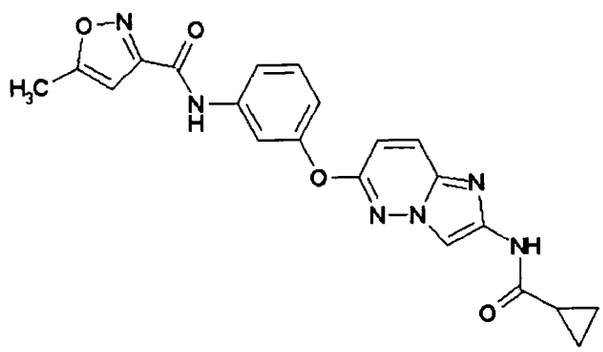
A una solución de ácido 3–metilisoxazol–5–carboxílico (87 mg, 0,679 mmol) en tetrahidrofurano (2,0 mL) se añadieron N,N–dimetilformamida (1 gota) y cloruro de oxalilo (75,8 µL, 0,88 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, y el residuo se disolvió en tetrahidrofurano (1 mL), y se añadió a una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (140 mg, 0,453 mmol) en tetrahidrofurano (12 mL). Luego, se añadió trietilamina (138 mg, 1,36 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se diluyó con solución acuosa saturada de hidrógeno–carbonato de sodio, y se extrajo tres veces con acetato de etilo, y la capa orgánica

se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→80/20) y se precipitó en acetato de etilo/hexano para dar el compuesto del título (42 mg, 22%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,86 – 1,98 (1H, m), 2,32 (3H, s), 7,01 – 7,14 (3H, m), 7,45 (1H, t, J = 8,2 Hz), 7,62 – 7,74 (2H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,8 Hz), 10,82 (1H, s), 11,10 (1H, s).

Ejemplo 110

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–metilisoxazol–3–carboxamida



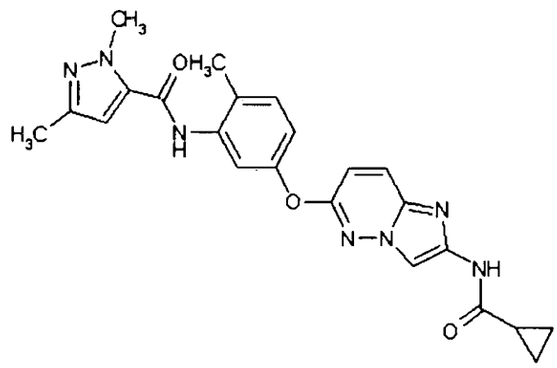
Usando ácido 5–metilisoxazol–3–carboxílico (87 mg, 0,679 mmol), N,N–dimetilformamida (1 gota), cloruro de oxalilo (75,8 μL, 0,88 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (140 mg, 0,453 mmol), trietilamina (138 mg, 1,36 mmol) y tetrahidrofurano (15 mL) como materiales de partida y de la misma manera que en el Ejemplo 109, se obtuvo el

compuesto del título (109 mg, 58%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,85 – 1,96 (1H, m), 2,50 (3H, s), 6,66 (1H, d, J = 0,9 Hz), 6,97 – 7,10 (2H, m), 7,43 (1H, t, J = 8,2 Hz), 7,63 – 7,77 (2H, m), 7,98 (1H, s), 8,05 (1H, d, J = 9,4 Hz), 10,78 (1H, s), 11,09 (1H, s).

Ejemplo 111

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (213 mg, 0,659 mmol) en tetrahidrofurano (10 mL) se añadieron una solución de cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (136 mg, 0,856 mmol) en tetrahidrofurano (0,5 mL) y trietilamina (200 mg, 1,98 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con solución acuosa saturada de hidrógeno–carbonato de sodio, y se extrajo tres veces con acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El

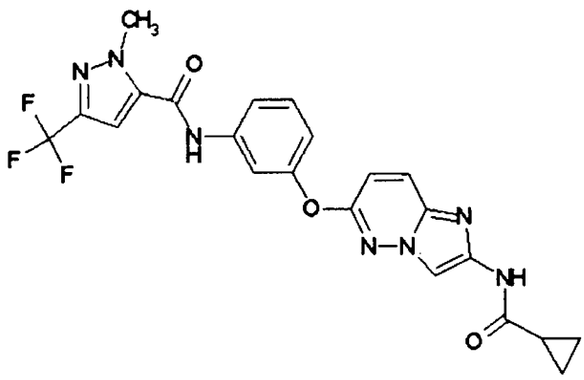
912

solvente se evaporó a presión reducida, y el residuo se filtró y se lavó con acetato de etilo/hexano para dar el compuesto del título (222 mg, 77%) en forma de un polvo blanco. Punto de fusión 223 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,89 (4H, m), 1,86 – 1,97 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,04 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,7, 2,4 Hz), 7,28 (1H, d, J = 2,4 Hz), 7,35 (1H, d, J = 8,7 Hz), 7,93 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,81 (1H, s), 11,08 (1H, s).

Ejemplo 112

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–3–(trifluorometil)–1H–pirazol–5–carboxamida



Usando 1–metil–3–(trifluorometil)–1H–pirazol–5–carboxílico (100 mg, 0,515 mmol), N,N–dimetilformamida (1 gota), cloruro de oxalilo (60 μL, 0,7 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (122,5 mg, 0,396 mmol), trietilamina (120 mg, 1,19 mmol) y tetrahidrofurano (15 mL) como materiales de partida y de la misma manera que en el Ejemplo 109, se obtuvo el compuesto del título (149 mg, 78%) en forma de un

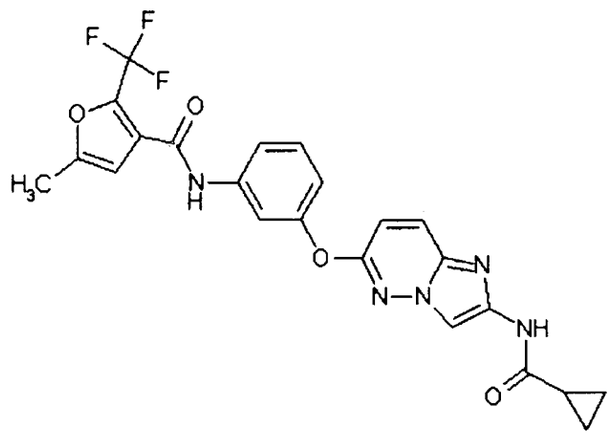
913

polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,84 – 1,97 (1H, m), 4,15 (3H, s), 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,46 (1H, t, J = 8,2 Hz), 7,50 (1H, s), 7,59 – 7,64 (1H, m), 7,66 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,53 (1H, s), 11,10 (1H, s).

Ejemplo 113

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–metil–2–(trifluorometil)–3–furancarboxamida

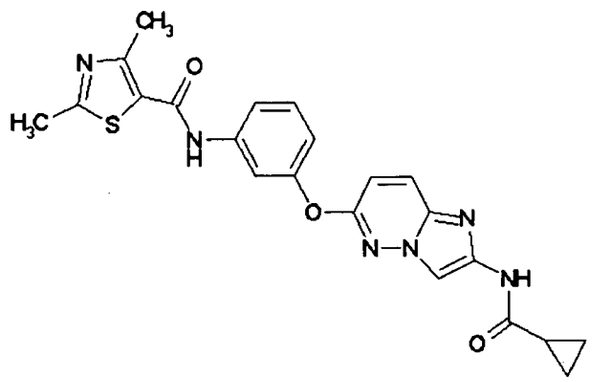


Usando ácido 5–metil–2–(trifluorometil)–3–furancarboxílico (133,6 mg, 0,668 mmol), N,N–dimetilformamida (1 gota), cloruro de oxalilo (75 μL, 0,868 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (159 mg, 0,514 mmol), trietilamina (156 mg, 1,54 mmol) y tetrahidrofurano (15 mL) como materiales de partida y de la misma manera que en el Ejemplo 109, se obtuvo el compuesto del título (145 mg, 58%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,85 – 1,97 (1H, m), 2,40 (3H, s), 6,80 (1H, s), 7,02 (1H, m), 7,06 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,2 Hz), 7,56 (1H, d, J = 8,3 Hz), 7,63 (1H, t, J = 2,0 Hz), 7,97 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,50 (1H, s), 11,09 (1H, s).

Ejemplo 114

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida



Usando ácido 2,4–dimetil–1,3–tiazol–5–carboxílico (78,8 mg, 0,50 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (129 mg, 0,417 mmol), 1–hidroxibenzotriazol (68 mg, 0,50 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (96 mg, 0,50 mmol), trietilamina (50 mg, 0,50 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 106, se obtuvo el compuesto del título (133 mg, 71%) en forma de un polvo blanco. Punto de fusión 249 °C.

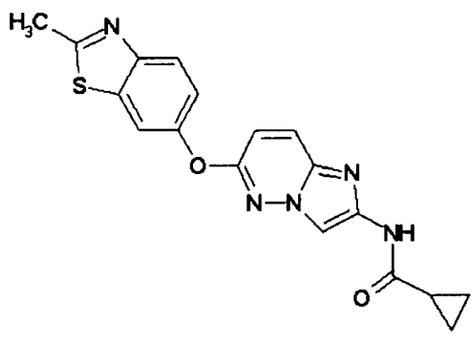
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,88 (4H, m), 1,85 – 1,98 (1H, m), 2,53 (3H, s), 2,65 (3H, s), 7,00 (1H, dd, J = 7,6, 1,9

915

Hz), 7,06 (1H, d, J = 9,5 Hz), 7,41 (1H, t, J = 8,1 Hz), 7,54 (1H, d, J = 8,3 Hz), 7,62 (1H, t, J = 2,1 Hz), 7,97 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 10,22 (1H, s), 11,09 (1H, s).

Ejemplo 115

Producción de N–{6–[(2–metil–1,3–benzotiazol–6–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (309 mg, 0,942 mmol), 2–metil–1,3–benzotiazol–6–ol (250 mg, 1,51 mmol), carbonato de potasio (390 mg, 2,83 mmol) y N,N–dimetilformamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 95, se obtuvo el compuesto del título (151 mg, 44%) en forma de un polvo de color amarillo pálido.

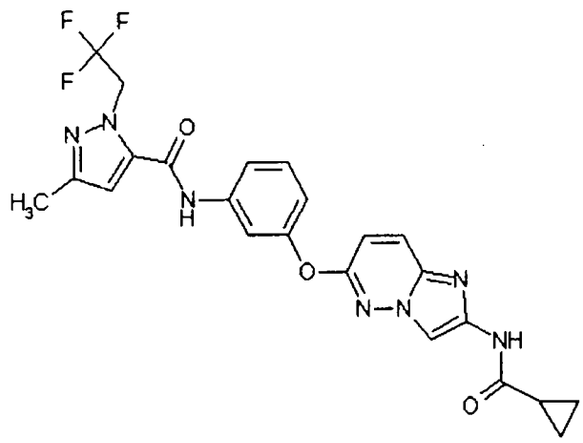
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,83 (4H, m), 1,83 – 1,94 (1H, m), 2,79 (3H, s), 7,07 (1H, d, J = 9,6 Hz), 7,37 (1H, dd, J = 8,8, 2,5 Hz), 7,90 – 7,99 (3H, m), 8,02 (1H, d, J = 9,6 Hz), 11,06 (1H, s).

Ejemplo 116

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

916

b]piridazin–6–il}oxi)fenil]–3–metil–1–(2,2,2–trifluoroetil)–1H–pirazol–5–carboxamida



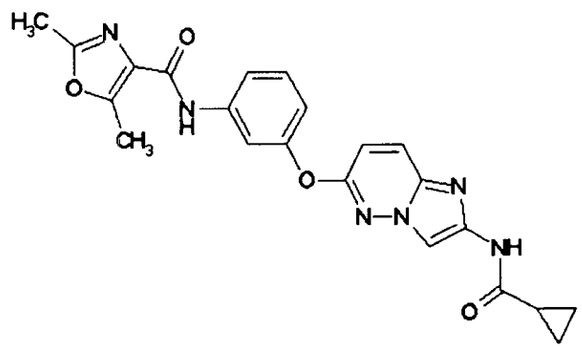
Usando 3–metil–1–(2,2,2–trifluoroetil)–1H–pirazol–5–carboxílico (175 mg, 0,84 mmol), N,N–dimetilformamida (1 gota), cloruro de oxalilo (91 μL, 1,01 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,646 mmol), trietilamina (196 mg, 1,94 mmol) y tetrahidrofurano (15 mL) como materiales de partida y de la misma manera que en el Ejemplo 109, se obtuvo el compuesto del título (281 mg, 87%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,87 – 1,98 (1H, m), 2,25 (3H, s), 5,40 (2H, q, J = 8,9 Hz), 7,00 (1H, s), 7,04 (1H, m), 7,07 (1H, d, J = 9,4 Hz), 7,45 (1H, t, J = 8,2 Hz), 7,58 – 7,69 (2H, m), 7,97 (1H, s), 8,06 (1H, d, J = 9,4 Hz), 10,45 (1H, s), 11,10 (1H, s).

Ejemplo 117

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

b]piridazin-6-il}oxi)fenil]-2,5-dimetil-1,3-oxazol-4-carboxamida



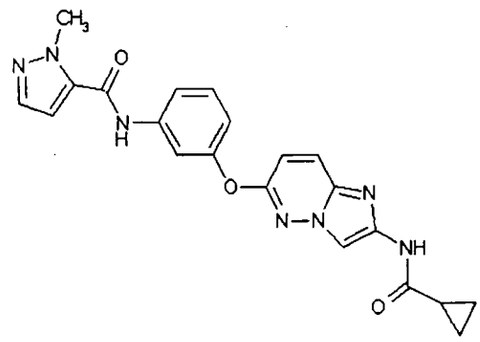
A una solución de N-[6-(3-aminofenoxi)imidazo[1,2-b]piridazin-2-il]ciclopropancarboxamida (202 mg, 0,652 mmol) en N,N-dimetilacetamida (4,0 mL) se añadió una solución de cloruro de 2,5-dimetil-1,3-oxazol-4-carbonilo (135 mg, 0,847 mmol) en N,N-dimetilacetamida (1,0 mL), y la mezcla se agitó a 0 °C durante 1 h. acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno-carbonato de sodio se añadieron a la mezcla, y la capa acuosa se extrajo tres veces con acetato de etilo/tetrahidrofurano. La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→90/10), y se precipitó en acetato de etilo/hexano para dar el compuesto del título (213 mg, 76%) en forma de un polvo blanco. Punto de fusión 224 °C.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,87 – 1,97 (1H, m), 2,44 (3H, s), 2,56 (3H, s), 6,96 (1H, dd, J = 8,3, 2,1

Hz), 7,05 (1H, d, J = 9,5 Hz), 7,38 (1H, t, J = 8,1 Hz), 7,72 (1H, d, J = 8,3 Hz), 7,80 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,04 (1H, d, J = 9,5 Hz), 10,12 (1H, s), 11,09 (1H, s).

Ejemplo 118

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–1H–pirazol–5–carboxamida



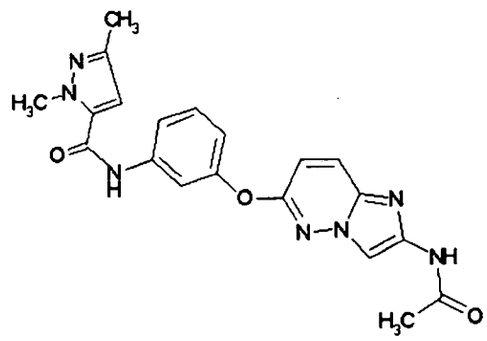
A una solución de ácido 1–metil–1H–pirazol–5–carboxílico (106 mg, 0,840 mmol) en tetrahidrofurano (2,0 mL) se añadieron N,N–dimetilformamida (1 gota) y cloruro de oxalilo (91 μL, 1,01 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, y el residuo se disolvió en N,N–dimetilacetamida (1 mL) y se añadió a una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,646 mmol) en N,N–dimetilacetamida (5,0 mL). La mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se diluyó con solución acuosa saturada de hidrógeno–carbonato de sodio, y se extrajo tres veces con acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato

de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→95/5) y se precipitó en acetato de etilo/hexano para dar el compuesto del título (241 mg, 89%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,87 (4H, m), 1,86 – 1,98 (1H, m), 4,07 (3H, s), 7,00 – 7,05 (1H, m), 7,04 – 7,10 (2H, m), 7,44 (1H, t, J = 8,2 Hz), 7,53 (1H, d, J = 2,1 Hz), 7,59 – 7,69 (2H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,33 (1H, s), 11,10 (1H, s).

Ejemplo 119

Producción de N–(3–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1,3–dimetil–1H–pirazol–5–carboxamida



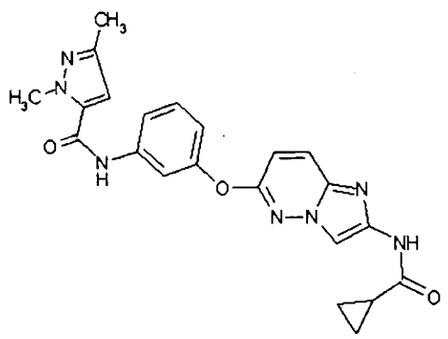
A una solución (4,0 mL) de ácido 1,3–dimetil–1H–pirazol–5–carboxílico (109 mg, 0,85 mmol) en tetrahidrofurano se añadieron N,N–dimetilformamida (30 μL, 0,39 mmol) y cloruro de oxalilo (135 μL, 1,55 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, y una solución de el residuo en N,N–dimetilacetamida (2,0 mL) se añadió gota a gota a una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–

il]acetamida (200 mg, 0,71 mmol) en N,N–dimetilacetamida (2,0 mL). Después de agitar la mezcla de reacción a temperatura ambiente durante 1 h, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo para dar el compuesto del título (182 mg, 67%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,07 (3H, s), 2,19 (3H, s), 3,97 (3H, s), 6,82 (1H, s), 6,98 – 7,03 (1H, m), 7,06 (1H, d, J = 9,6 Hz), 7,42 (1H, t, J = 8,1 Hz), 7,59 – 7,63 (1H, m), 7,66 – 7,68 (1H, m), 7,98 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,24 (1H, s), 10,80 (1H, s).

Ejemplo 120

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,65 mmol) en N,N–dimetilacetamida (2,0 mL) se añadió cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (185 mg, 1,16 mmol). Tras agitar a temperatura

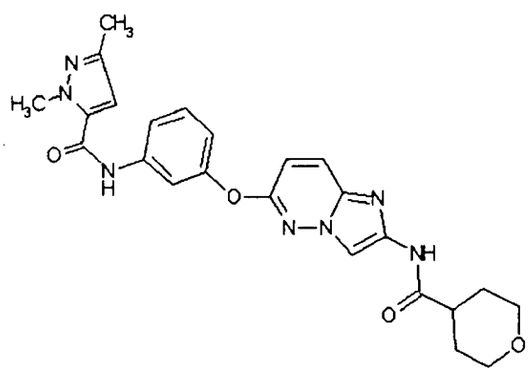
922

ambiente durante 1 h, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/2→acetato de etilo) y se precipitó en hexano/acetato de etilo para dar el compuesto del título (70 mg, 25%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,83 (4H, m), 1,87 – 1,97 (1H, m), 2,19 (3H, s), 3,98 (3H, s), 6,82 (1H, s), 6,99 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,60 – 7,64 (1H, m), 7,65 – 7,68 (1H, m), 7,97 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,24 (1H, s), 11,10 (1H, s).

Ejemplo 121

Producción de 1,3–dimetil–N–[3–({2–[(tetrahidro–2H–piran–4–ilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–pirazol–5–carboxamida



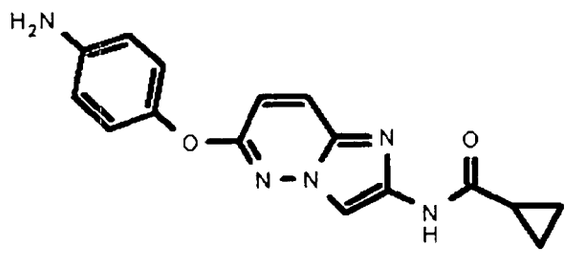
922

Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]tetrahidro–2H–piran–4–carboxamida (200 mg, 0,57 mmol), trietilamina (237 μL, 1,70 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (180 mg, 1,13 mmol) y tetrahidrofurano (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (73 mg, 27%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,72 (4H, m), 2,20 (3H, s), 2,63 – 2,78 (1H, m), 3,27 – 3,37 (2H, m), 3,86 – 3,92 (2H, s), 3,98 (3H, s), 6,83 (1H, s), 6,98 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,59 – 7,63 (1H, m), 7,67 – 7,70 (1H, m), 8,03 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,26 (1H, s), 10,82 (1H, s).

Ejemplo 122

Producción de N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



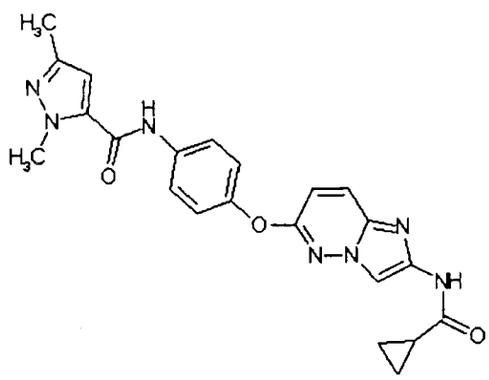
A una solución de 4–aminofenol (0,33 g, 3,05 mmol) en N,N–dimetilformamida (10 mL) se le añadió tert-butóxido de potasio (0,36 g, 3,17 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. Se le agregaron N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (0,80 g, 2,44 mmol) y carbonato de

potasio (0,17 g, 1,22 mmol) a la mezcla de reacción, y la mezcla se agitó usando un sintetizador de microondas con calentamiento a 150 °C durante 30 min. Después de enfriar la mezcla de reacción, se añadió salmuera saturada a la mezcla, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/2→acetato de etilo) para dar el compuesto del título (376 mg, 50%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,81 (4H, m), 1,88 – 1,95 (1H, m), 5,09 (2H, s), 6,57 – 6,61 (2H, s), 6,88 – 6,94 (3H, m), 7,89 – 7,97 (2H, m), 11,05 (1H, s).

Ejemplo 123

Producción de N–[4–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (220 mg, 0,71 mmol), trietilamina (0,30

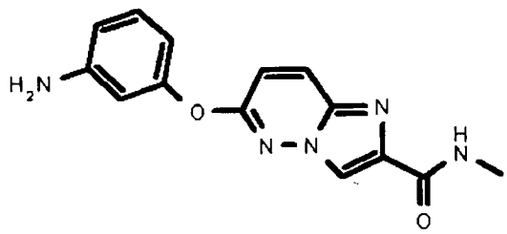
924

mL, 2,13 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (230 mg, 1,42 mmol) y tetrahidrofurano (6,6 mL) como materiales de partida y de la misma manera que en el Ejemplo 96, se obtuvo el compuesto del título (84 mg, 27%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,87 – 1,96 (1H, m), 2,21 (3H, s), 4,00 (3H, s), 6,82 (1H, s), 7,03 (1H, d, J = 9,6 Hz), 7,25 (2H, d, J = 9,0 Hz), 7,78 (2H, d, J = 9,0 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 10,22 (1H, s), 11,07 (1H, s).

Ejemplo 124

Producción de 6–(3–aminofenoxi)–N–metilimidazo[1,2–b]piridazin–2–carboxamida



Usando 6–yodo–N–metilimidazo[1,2–b]piridazin–2–carboxamida (0,30 g, 0,99 mmol), N,N–dimetilformamida (3,0 mL), carbonato de potasio (275 mg, 1,99 mmol) y 3–aminofenol (163 mg, 1,49 mmol) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (0,10 g, 36%) en forma de un polvo color café oscuro.

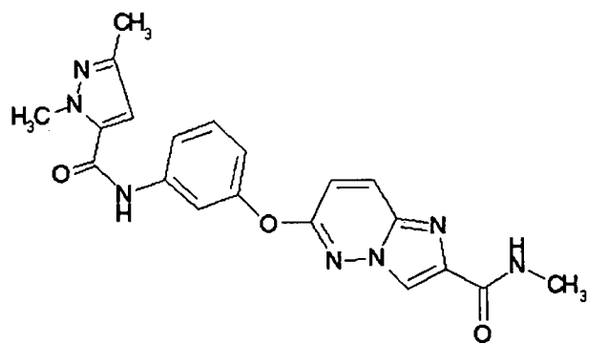
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,77 (3H, d, J = 5,1 Hz), 5,34 (2H, s), 6,32 – 6,40 (2H, m), 6,43 – 6,47 (1H, m), 7,06 (1H, t, J = 8,1 Hz), 7,13 (1H, d, J = 9,6 Hz), 8,15 (1H, d, J = 9,6 Hz), 8,34 (1H, s),

925

8,37 (1H, q, J = 5,1 Hz).

Ejemplo 125

Producción de 6–(3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}fenoxi)–N–metilimidazo[1,2–b]piridazin–2–carboxamida



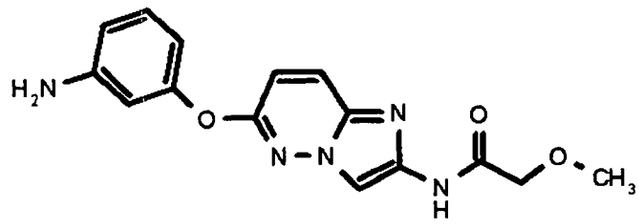
A una solución de 6–(3–aminofenoxi)–N–metilimidazo[1,2–b]piridazin–2–carboxamida (250 mg, 0,88 mmol) en N,N–dimetilacetamida (2,5 mL) se añadió cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (253 mg, 1,59 mmol). Tras agitar a temperatura ambiente durante 1 h, se añadió agua a la mezcla de reacción, y el precipitado se recogió por filtración. El residuo obtenido se lavó con agua, acetonitrilo y éter dietílico para dar el compuesto del título (262 mg, 73%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,20 (3H, s), 2,77 (3H, d, J = 5,1 Hz), 3,99 (3H, s), 6,82 (1H, s), 7,04 – 7,09 (1H, m), 7,24 (1H, d, J = 9,9 Hz), 7,44 (1H, t, J = 8,1 Hz), 7,57 – 7,64 (1H, m), 7,71 – 7,74 (1H, m), 8,20 (1H, d, J = 9,6 Hz), 8,34 (1H, s), 8,35 – 8,41 (1H, m), 10,28 (1H, s).

Ejemplo 126

926

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metoxiacetamida

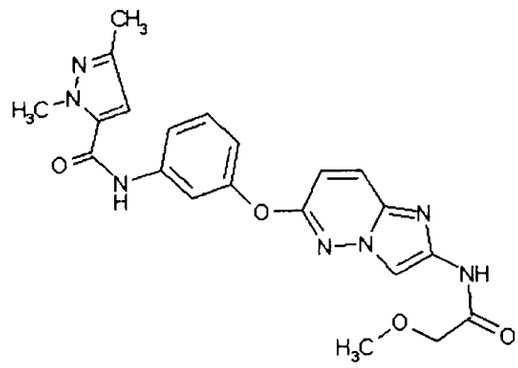


Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metoxiacetamida (0,60 g, 1,81 mmol), N,N–dimetilformamida (6,0 mL), carbonato de potasio (499 mg, 3,61 mmol) y 3–aminofenol (296 mg, 2,71 mmol) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (0,29 g, 51%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,35 (3H, s), 4,06 (2H, s), 5,32 (2H, s), 6,28 – 6,37 (2H, s), 6,41 – 6,45 (1H, m), 6,98 (1H, d, J = 9,6 Hz), 7,05 (1H, t, J = 8,1 Hz), 8,01 (1H, d, J = 9,6 Hz), 8,04 (1H, s), 10,57 (1H, s).

Ejemplo 127

Producción de N–[3–({2–[(metoxiacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



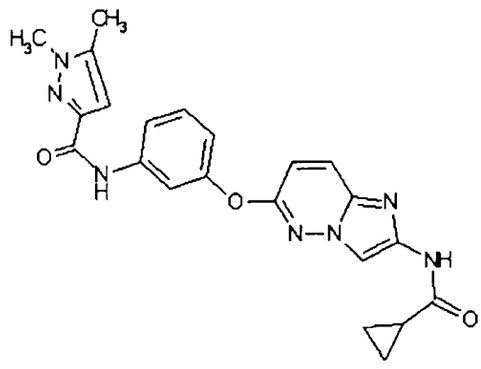
927

Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metoxiacetamida (200 mg, 0,64 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (162 mg, 1,02 mmol) y N,N–dimetilacetamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (176 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,33 (3H, s), 3,98 (3H, s), 4,06 (2H, s), 6,82 (1H, s), 6,97 – 7,04 (1H, m), 7,09 (1H, d, J = 9,3 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,58 – 7,64 (1H, m), 7,66 – 7,69 (1H, m), 8,03 (1H, s), 8,04 (1H, d, J = 9,3 Hz), 10,24 (1H, s), 10,59 (1H, s).

Ejemplo 128

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,5–dimetil–1H–pirazol–3–carboxamida



A una solución de 1,5–dimetil–1H–pirazol–3–carboxílico (109 mg, 0,78 mmol) en tetrahidrofurano (4,0 mL) se añadieron N,N–dimetilformamida (30 μL, 0,39 mmol) y cloruro de oxalilo (135 μL, 1,55 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, y una solución de el

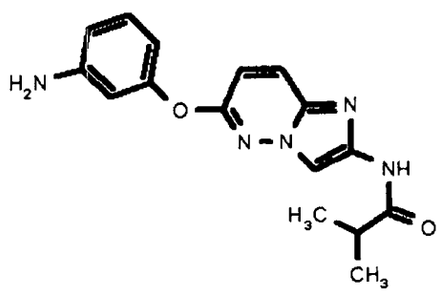
928

residuo en tetrahidrofurano (2,0 mL) se añadió gota a gota a una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (200 mg, 0,65 mmol) y trietilamina (360 μL, 2,59 mmol) en tetrahidrofurano (4,0 mL). Tras agitar a temperatura ambiente durante 2 h, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/4→acetato de etilo) y se precipitó en hexano/acetato de etilo para dar el compuesto del título (118 mg, 42%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,83 (4H, m), 1,88 – 1,96 (1H, m), 2,30 (3H, s), 3,82 (3H, s), 6,54 (1H, s), 6,91 – 6,96 (1H, m), 7,05 (1H, d, J = 9,6 Hz), 7,37 (1H, t, J = 8,1 Hz), 7,69 – 7,73 (1H, m), 7,76 – 7,78 (1H, m), 7,97 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 11,09 (1H, s).

Ejemplo 129

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilpropanamida



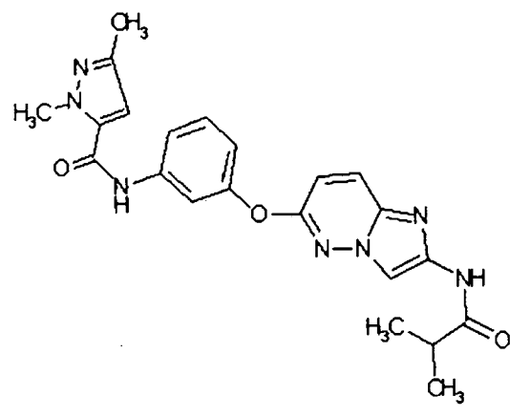
929

Usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilpropanamida (0,60 g, 1,82 mmol), N,N–dimetilformamida (6,0 mL), carbonato de potasio (502 mg, 3,63 mmol) y 3–aminofenol (278 mg, 2,54 mmol) como materiales de partida y de la misma manera que en el Ejemplo 91, se obtuvo el compuesto del título (0,26 g, 47%) en forma de un polvo color café oscuro.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,09 (6H, d, J = 6,9 Hz), 2,66 – 2,74 (1H, m), 5,32 (2H, s), 6,27 – 6,36 (2H, m), 6,40 – 6,44 (1H, m), 6,95 (1H, d, J = 9,6 Hz), 7,05 (1H, t, J = 8,1 Hz), 7,94 – 8,02 (2H, m), 10,74 (1H, s).

Ejemplo 130

Producción de N–(3–{[2–(isobutirilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1,3–dimetil–1H–pirazol–5–carboxamida



Usando ácido 1,3–dimetil–1H–pirazol–5–carboxílico (108 mg, 0,77 mmol), tetrahidrofurano (3,2 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (134 μL, 1,54 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilpropanamida (200 mg, 0,64 mmol) y N,N–dimetilacetamida (4,0 mL) como materiales de

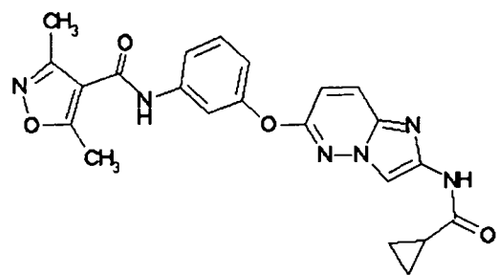
930

partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (201 mg, 72%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,08 (6H, d, J = 6,9 Hz), 2,19 (3H, s), 2,65 – 2,74 (1H, m), 3,98 (3H, s), 6,82 (1H, s), 6,98 – 7,02 (1H, m), 7,06 (1H, d, J = 9,6 Hz), 7,42 (1H, t, J = 8,1 Hz), 7,59 – 7,63 (1H, m), 7,66 – 7,68 (1H, m), 8,01 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,24 (1H, s), 10,75 (1H, s).

Ejemplo 131

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3,5–dimetilisoxazol–4–carboxamida



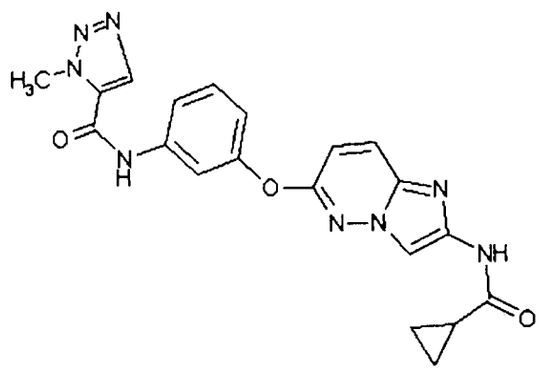
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (160 mg, 0,52 mmol), N,N–dimetilacetamida (3,2 mL) y cloruro de 3,5–dimetilisoxazol–4–carbonilo (99 mg, 0,62 mmol) y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (163 mg, 73%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,88 – 1,95 (1H, m), 2,32 (3H, s), 2,54 (3H, s), 6,98 – 7,02 (1H, m), 7,06 (1H, d, J = 9,6 Hz), 7,42 (1H, t, J = 8,1 Hz), 7,48 – 7,51 (1H, m), 7,61 – 7,64 (1H, m), 7,96 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,19 (1H, s),

11,09 (1H, s).

Ejemplo 132

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–1H–1,2,3–triazol–5–carboxamida



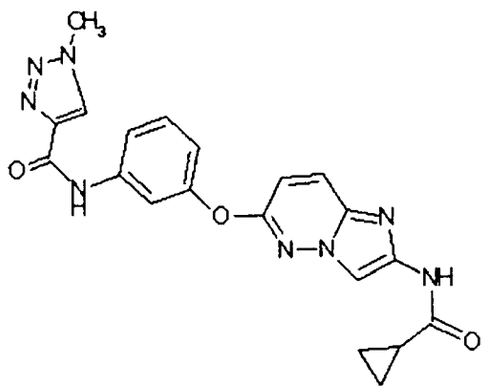
Usando ácido 1–metil–1H–1,2,3–triazol–5–carboxílico (99 mg, 0,78 mmol), tetrahidrofurano (4,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (135 μL, 1,55 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (182 mg, 67%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,87 – 1,96 (1H, m), 4,23 (3H, s), 7,02 – 7,09 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,56 – 7,65 (2H, m), 7,96 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 8,37 (1H, s), 10,61 (1H, s), 11,09 (1H, s).

Ejemplo 133

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

b]piridazin–6–il}oxi)fenil]–1–metil–1H–1,2,3–triazol–4–carboxamida

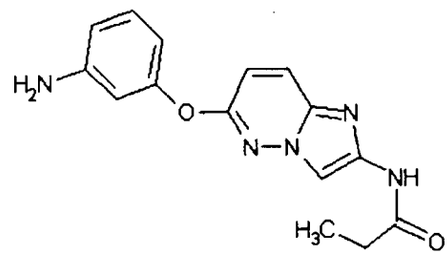


Usando 1–metil–1H–1,2,3–triazol–4–carboxílico (99 mg, 0,78 mmol), tetrahidrofurano (4,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (135 μL, 1,55 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (189 mg, 70%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,82 (4H, m), 1,87 – 1,96 (1H, m), 4,12 (3H, s), 6,98 (1H, dd, J = 11,3, 2,3 Hz), 7,06 (1H, d, J = 9,3 Hz), 7,40 (1H, t, J = 8,1 Hz), 7,72 – 7,76 (1H, m), 7,78 – 7,81 (1H, m), 7,97 (1H, s), 8,04 (1H, d, J = 9,3 Hz), 8,66 (1H, s), 10,60 (1H, s), 11,09 (1H, s).

Ejemplo 134

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]propanamida



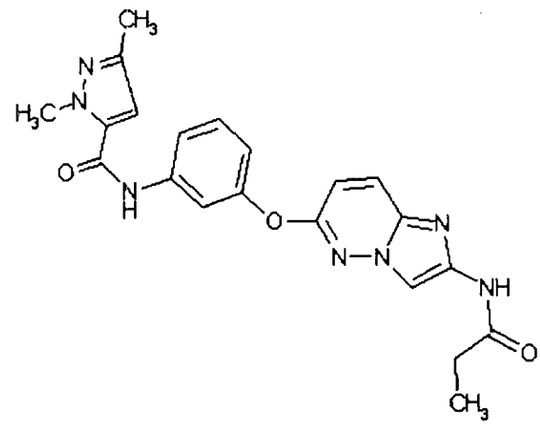
A una solución de 3–aminofenol (331 mg, 3,0 mol) en N,N–dimetilformamida (8,0 mL) se añadió tert-butóxido de potasio (355 mg, 3,16 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se añadieron N–(6–yodoimidazo[1,2–b]piridazin–2–il)propanamida (0,80 g, 2,53 mmol) y carbonato de potasio (175 mg, 1,27 mmol), y la mezcla se agitó a 140 °C durante 16 h. Se añadió salmuera saturada a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/2) y se precipitó en hexano/acetato de etilo para dar el compuesto del título (420 mg, 56%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,07 (3H, t, J = 7,5 Hz), 2,37 (2H, q, J = 7,5 Hz), 5,31 (2H, s), 6,27 – 6,35 (2H, m), 6,40 – 6,44 (1H, m), 6,95 (1H, d, J = 9,3 Hz), 7,04 (1H, d, J = 8,0 Hz), 7,98 (1H, d, J = 9,3 Hz), 8,00 (1H, d, J = 1,5 Hz), 10,73 (1H, s).

934

Ejemplo 135

Producción de 1,3-dimetil-N-(3-{[2-(propionilamino) imidazo[1,2-b]piridazin-6-il]oxi}fenil)-1H-pirazol-5-carboxamida



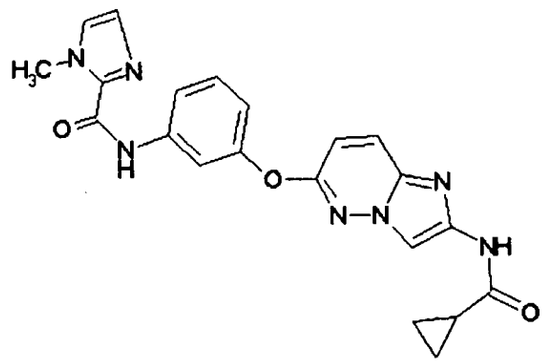
Usando ácido 1,3-dimetil-1H-pirazol-5-carboxílico (113 mg, 0,81 mol), tetrahidrofurano (4,0 mL), N,N-dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (141 μL, 1,61 mmol), N-[6-(3-aminofenoxi)imidazo[1,2-b]piridazin-2-il]propionilcarboxamida (200 mg, 0,67 mmol) y N,N-dimetilacetamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (190 mg, 67%) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 1,07 (3H, t, J = 7,5 Hz), 2,19 (3H, s), 2,37 (2H, q, J = 7,5 Hz), 3,98 (3H, s), 6,83 (1H, s), 6,99 – 7,04 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,60 – 7,64 (1H, m), 7,67 – 7,69 (1H, m), 8,02 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,25 (1H, s), 10,77 (1H, s).

Ejemplo 136

935.

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–1H–imidazol–2–carboxamida



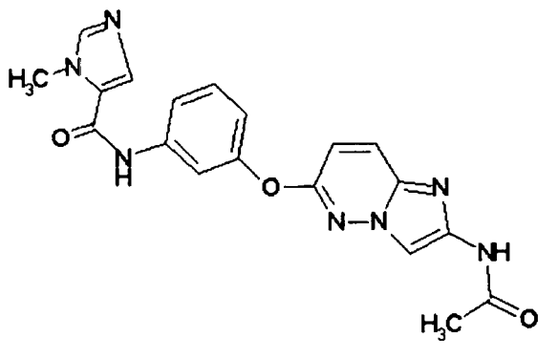
Usando ácido 1–metil–1H–imidazol–2–carboxílico (36,7 mg, 0,29 mol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (51 μL, 0,58 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (75 mg, 0,24 mmol) y N,N–dimetilacetamida (1,5 mL) como materiales de partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (48 mg, 47%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,91 – 1,97 (1H, m), 3,97 (3H,s), 6,97 (1H, dd, J = 8,1, 1,5 Hz), 7,05 (1H, d, J = 9,6 Hz), 7,07 (1H, s), 7,39 (1H, t, J = 8,1 Hz), 7,44 – 7,45 (1H, m), 7,72 (1H, d, J = 8,4 Hz), 7,78 –7,80 (1H, m), 7,97 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,43 (1H, s), 11,08 (1H, s).

Ejemplo 137

Producción de N–(3–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1–metil–1H–imidazol–5–carboxamida

936

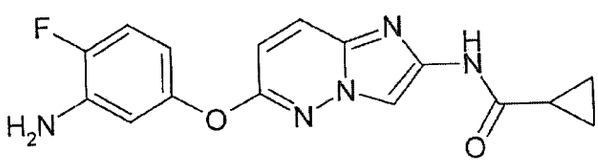


Usando ácido 1–metil–1H–imidazol–5–carboxílico (80 mg, 0,64 mol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (111 μL, 1,27 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (150 mg, 0,53 mmol) y N,N–dimetilacetamida (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (98 mg, 47%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,07 (3H, s), 3,84 (3H, s), 6,96 – 7,00 (1H, m), 7,06 (1H, d, J = 9,3 Hz), 7,42 (1H, t, J = 8,1 Hz), 7,57 – 7,61 (1H, m), 7,64 – 7,67 (1H, m), 7,79 (1H, s), 7,84 (1H, s), 7,99 (1H, s), 8,05 (1H, d, J = 9,3 Hz), 10,16 (1H, s), 10,81 (1H, s).

Ejemplo 138

Producción de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



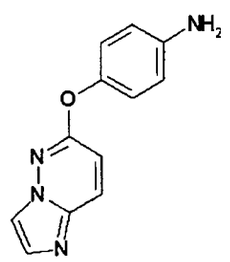
937

Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (2,62 g, 8,0 mmol), 3–amino–4–fluorofenol (2,03 g, 16,0 mmol), carbonato de potasio (1,66 g, 12,0 mmol) y N,N–dimetilformamida (20 mL) se agitó a 150 °C durante 15 h. Se añadieron tetrahidrofurano/acetato de etilo y salmuera saturada a la mezcla de reacción, y el material insoluble se filtró. El filtrado se extrajo con acetato de etilo, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 20/80→0/100) y se recristalizó en acetato de etilo para dar el compuesto del título (1,91 g, 73%) en forma de cristales de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,90 (4H, m), 1,85 – 2,00 (1H, m), 5,36 (2H, s), 6,30–6,40 (1H, m), 6,50–6,60 (1H, m), 6,96 (1H, d, J = 9,8 Hz), 7,00–7,10 (1H, m), 7,95 (1H, s), 7,99 (1H, d, J = 9,8 Hz), 11,06 (1H, s).

Ejemplo 139

Producción de 4–(imidazo[1,2–b]piridazin–6–iloxi)anilina



Una mezcla de 6–cloroimidazo[1,2–b]piridazina (768 mg, 5,0 mmol), 4–aminofenol (818 mg, 7,5 mmol), carbonato de potasio (2073

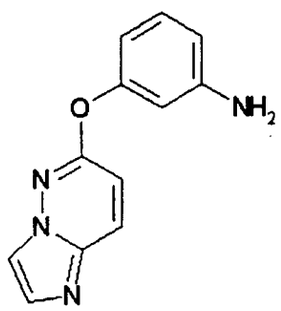
938

mg, 15,0 mmol) y N–metilpirrolidona (5,0 mL) se agitó a 120°C durante 18 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa 1 N de hidróxido de sodio y salmuera saturada, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice NH (hexano/acetato de etilo = 70/30→0/100) y se precipitó en éter diisopropílico para dar el compuesto del título (759 mg, 67%) en forma de un polvo gris.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,07 (2H, s), 6,60 (2H, d, J = 8,9 Hz), 6,92 (2H, d, J = 8,9 Hz), 7,00 (1H, d, J = 9,8 Hz), 7,61 (1H, s), 8,01 (1H, s), 8,09 (1H, d, J = 9,8 Hz).

Ejemplo 140

3–(imidazo[1,2–b]piridazin–6–iloxi)anilina



Una mezcla de 6–cloroimidazo[1,2–b]piridazina (1536 mg, 10,0 mmol), 3–aminofenol (1419 mg, 13,0 mmol), carbonato de potasio (4146 mg, 30,0 mmol) y N–metilpirrolidona (10 mL) se agitó a 120 °C durante 48 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa 1 N de hidróxido de sodio y

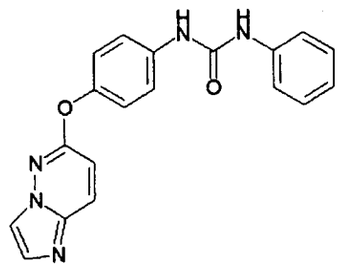
939

salmuera saturada, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice NH (hexano/acetato de etilo = 70/30→0/100), y se precipitó en éter diisopropílico para dar el compuesto del título (932 mg, 41%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,29 (2H, s), 6,31 – 6,35 (1H, m), 6,37 (1H, t, J =2,2 Hz), 6,42 – 6,47 (1H, m), 7,02 (1H, d, J = 9,8 Hz), 7,06 (1H, t, J = 7,9 Hz), 7,65 (1H, d, J = 1,2 Hz), 8,08 (1H, s), 8,13 (1H, d, J = 9,8 Hz).

Ejemplo 141

Producción de N–[4–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–N'–fenilurea



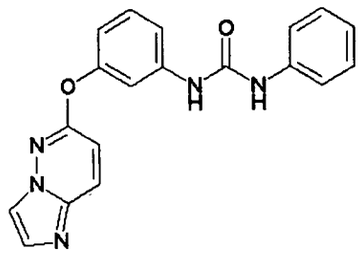
A una solución de 4–(imidazo[1,2–b]piridazin–6–iloxi)anilina (181 mg, 0,80 mmol) y trietilamina (0,011 mL, 0,08 mmol) en tetrahidrofurano (10 mL) se añadió isocianato de fenilo (0,104 mL, 0,96 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/metanol = 100/0→90/10) y se precipitó en acetato de etilo para dar el compuesto del título (223 mg, 81%) en forma de un polvo blanco.

940

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,97 (1H, t, J = 7,6 Hz), 7,09 (1H, d, J = 9,8 Hz), 7,22 (2H, d, J = 8,7 Hz), 7,28 (2H, t, J = 7,6 Hz), 7,46 (2H, d, J = 7,6 Hz), 7,52 (2H, d, J = 8,7 Hz), 7,64 (1H, s), 8,05 (1H, s), 8,15 (1H, d, J = 9,8 Hz), 8,70 (1H, s), 8,76 (1H, s).

Ejemplo 142

Producción de N–[3–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–N'–fenilurea



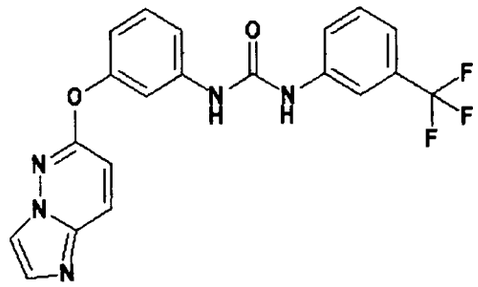
A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)anilina (181 mg, 0,80 mmol) y trietilamina (0,011 mL, 0,08 mmol) en tetrahidrofurano (10 mL) se añadió isocianato de fenilo (0,104 mL, 0,96 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/metanol = 100/0→90/10) y se precipitó en acetato de etilo para dar el compuesto del título (196 mg, 71%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,85 – 6,90 (1H, m), 6,97 (1H, t, J = 7,5 Hz), 7,11 (1H, d, J = 9,6 Hz), 7,22 – 7,31 (3H, m), 7,36 (1H, t, J = 7,9 Hz), 7,43 (2H, d, J = 7,5 Hz), 7,51 (1H, t, J = 2,1 Hz), 7,66 (1H, d, J = 0,9 Hz), 8,08 (1H, s), 8,18 (1H, d, J = 9,6 Hz), 8,72 (1H, s), 8,87 (1H, s).

942

Ejemplo 143

Producción de N–[3–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–N'–[3–(trifluorometil)fenil]urea



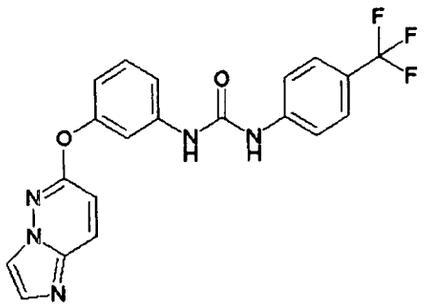
A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)anilina (181 mg, 0,80 mmol) y trietilamina (0,040 mL, 0,29 mmol) en tetrahidrofurano (10 mL) se añadió 3–(trifluorometil)isocianato de fenilo (0,154 mL, 1,12 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→90/10) y se precipitó en metanol para dar el compuesto del título (205 mg, 62%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,89 – 6,94 (1H, m), 7,12 (1H, d, J = 9,8 Hz), 7,26 – 7,34 (2H, m), 7,38 (1H, t, J = 8,1 Hz), 7,47 – 7,60 (3H, m), 7,66 (1H, d, J = 0,9 Hz), 7,99 (1H, s), 8,08 (1H, s), 8,18 (1H, d, J = 9,8 Hz), 9,01 (1H, s), 9,11 (1H, s).

Ejemplo 144

Producción de N–[3–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–N'–[4–(trifluorometil)fenil]urea

942

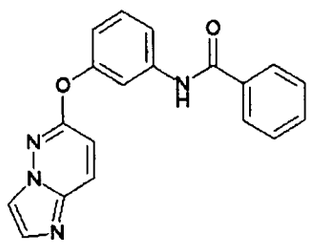


A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)anilina (113 mg, 0,50 mmol) y trietilamina (0,040 mL, 0,29 mmol) en tetrahidrofurano (10 mL) se añadió 4–(trifluorometil)isocianato de fenilo (0,100 mL, 0,70 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, y el residuo se precipitó de metanol para dar el compuesto del título (103 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,86 – 6,94 (1H, m), 7,11 (1H, d, J = 9,8 Hz), 7,24 – 7,31 (1H, m), 7,38 (1H, t, J = 8,2 Hz), 7,51 (1H, t, J = 1,8 Hz), 7,58 – 7,68 (5H, m), 8,08 (1H, s), 8,18 (1H, d, J = 9,8 Hz), 9,00 (1H, s), 9,16 (1H, s).

Ejemplo 145

Producción de N–[3–(imidazo[1,2–b]piridazin–6–iloxi)fenil]benzamida



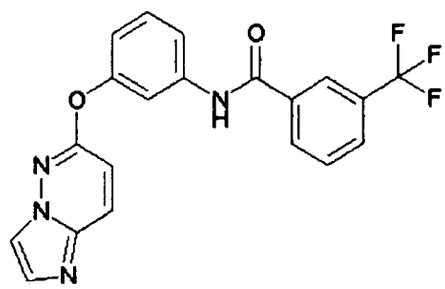
943

A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)anilina (113 mg, 0,50 mmol) en N–metilpirrolidona (1,0 mL) se añadió cloruro de benzoílo (0,116 mL, 1,00 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa 1 N de hidróxido de sodio y salmuera saturada, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→75/25) y se precipitó en acetato de etilo para dar el compuesto del título (122 mg, 74%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,01 – 7,06 (1H, m), 7,14 (1H, d, J = 9,8 Hz), 7,45 (1H, t, J = 8,2 Hz), 7,50 – 7,64 (3H, m), 7,66 – 7,71 (2H, m), 7,77 (1H, t, J = 2,1 Hz), 7,92 – 7,97 (2H, m), 8,09 (1H, s), 8,19 (1H, d, J = 9,8 Hz), 10,39 (1H, s).

Ejemplo 146

Producción de N–[3–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–3–(trifluorometil)benzamida



A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)anilina (113 mg, 0,50 mmol) en N–metilpirrolidona (1,0 mL) se le añadió

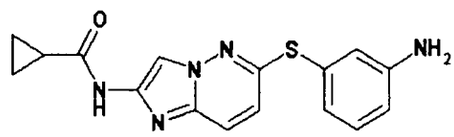
944

cloruro de 3–(trifluorometil)benzoílo (0,151 mL, 1,00 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa 1 N de hidróxido de sodio y salmuera saturada, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→75/25), y se precipitó en éter diisopropílico para dar el compuesto del título (195 mg, 98%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,05 – 7,10 (1H, m), 7,15 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 7,9 Hz), 7,67 – 7,71 (1H, m), 7,67 (1H, d, J = 1,2 Hz), 7,75 (1H, t, J = 2,1 Hz), 7,79 (1H, t, J = 7,8 Hz), 7,98 (1H, d, J = 7,8 Hz), 8,09 (1H, s), 8,20 (1H, d, J = 9,6 Hz), 8,26 (1H, d, J = 8,4 Hz), 8,29 (1H, s), 10,61 (1H, s).

Ejemplo 147

Producción de N–{6–[(3–aminofenil)sulfanil]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



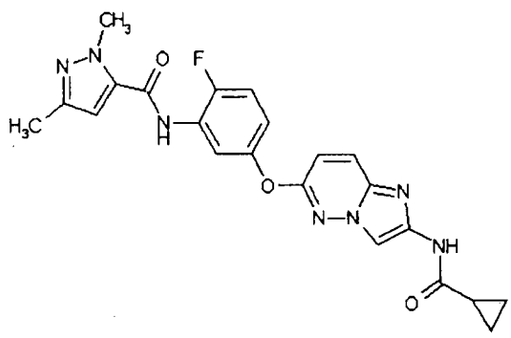
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (500 mg, 1,52 mmol), 3–aminobencenotiol (381 mg, 3,04 mmol), carbonato de potasio (630 mg, 4,56 mmol) y N,N–dimetilformamida (5,0 mL) se agitó a 80°C durante 3 h. La

mezcla de reacción se diluyó con agua, y se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→80/20) y se precipitó en acetato de etilo para dar el compuesto del título (396 mg, 80%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,86 (4H, m), 1,89 – 1,99 (1H, m), 5,38 (2H, s), 6,61 – 6,66 (1H, m), 6,66 – 6,70 (1H, m), 6,74 (1H, t, J = 1,9 Hz), 6,83 (1H, d, J = 9,6 Hz), 7,11 (1H, t, J = 7,8 Hz), 7,86 (1H, d, J = 9,6 Hz), 8,14 (1H, s), 11,16 (1H, s).

Ejemplo 148

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,306 mmol) en N,N–dimetilacetamida (4,0 mL) se le añadió una solución de cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (51 mg, 0,321 mmol) en N,N–dimetilacetamida (1,0 mL) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 30 min. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a

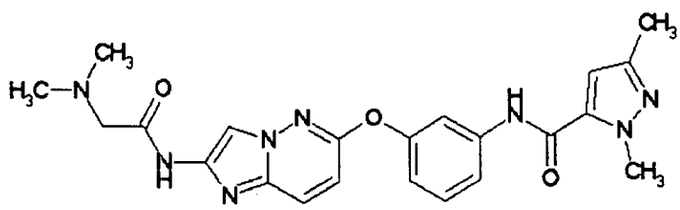
946

la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (metanol/acetato de etilo = 0/100→5/95) y se recristalizó en metanol/acetato de etilo para dar el compuesto del título (88,8 mg, 65%) en forma de cristales de color amarillo pálido. Punto de fusión 237 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,90 (4H, m), 1,85 – 2,00 (1H, m), 2,19 (3H, s), 3,97 (3H, s), 6,84 (1H, s), 7,07 (1H, d, J = 9,3 Hz), 7,15 –7,25 (1H, m), 7,40 (1H, t, J = 9,6 Hz), 7,50–7,60 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 11,07 (1H, s).

Ejemplo 149

Producción de N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–N^2,N^2–dimetilglicinamida (196 mg, 0,6 mmol) en N–metilpirrolidona (5,0 mL) se añadió cloruro de 1,3–dimetilpirazol–5–carbonilo (270 mg, 1,7 mmol), y la mezcla se agitó a temperatura

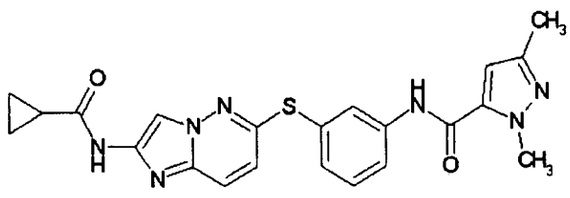
947

ambiente durante 5 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio, y se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→60/40) y se precipitó en acetato de etilo para dar el compuesto del título (131 mg, 49%) en forma de un polvo blanco. Punto de fusión 210 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 2,27 (6H, s), 3,13 (2H, s), 3,98 (3H, s), 6,83 (1H, s), 6,99 – 7,04 (1H, m), 7,09 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,59 – 7,64 (1H, m), 7,68 (1H, t, J = 2,1 Hz), 8,04 (1H, s), 8,07 (1H, d, J = 9,6 Hz), 10,25 (1H, s), 10,37 (1H, s).

Ejemplo 150

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}sulfanil)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–{6–[(3–aminofenil)sulfanil]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (195 mg, 0,6 mmol) en N–metilpirrolidona (3,0 mL) se añadió cloruro de 1,3–dimetilpirazol–5–carbonilo (159 mg, 1,0 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con agua, y

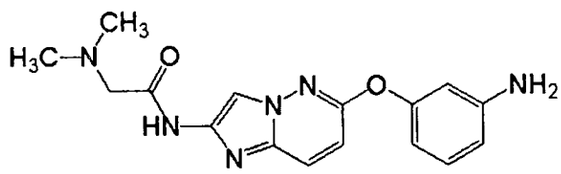
948

se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30) y se precipitó en metanol para dar el compuesto del título (245 mg, 91%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,87 (4H, m), 1,89 – 1,99 (1H, m), 2,19 (3H, s), 3,98 (3H, s), 6,82 (1H, s), 6,94 (1H, d, J = 9,4 Hz), 7,31 – 7,36 (1H, m), 7,47 (1H, t, J = 7,8 Hz), 7,81 – 7,86 (1H, m), 7,90 (1H, dd, J = 9,4, 0,5 Hz), 7,99 (1H, t, J = 1,9 Hz), 8,15 (1H, s), 10,25 (1H, s), 11,16 (1H, s).Punto de fusión 251°C.

Ejemplo 151

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–N^2,N^2–dimetilglicinamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)–N^2,N^2–dimetilglicinamida (517 mg, 1,5 mmol), 3–aminofenol (491 mg, 4,5 mmol), carbonato de potasio (415 mg, 3,0 mmol) y N,N–dimetilformamida (3,0 mL) se agitó usando un sintetizador de microondas a 180 °C durante 40 min. La mezcla de reacción se diluyó con agua, y el precipitado se recogió por filtración, se lavó con agua, y se secó a presión reducida. El sólido obtenido se lavó con acetato de etilo para dar el compuesto del título (410 mg, 84%)

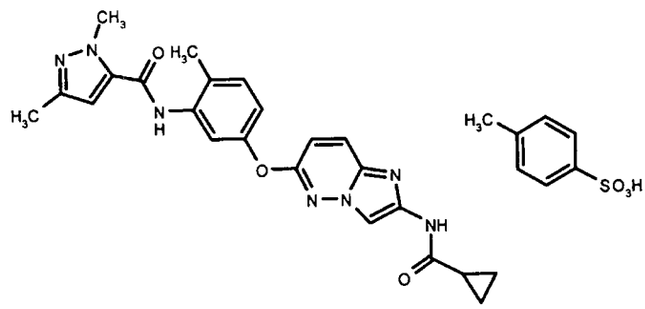
949

en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,27 (6H, s), 3,13 (2H, s), 5,31 (2H, s), 6,28 – 6,33 (1H, m), 6,36 (1H, t, J = 2,1 Hz), 6,41 – 6,46 (1H, m), 6,98 (1H, d, J = 9,6 Hz), 7,05 (1H, t, J = 8,1 Hz), 8,01 (1H, d, J = 9,6 Hz), 8,04 (1H, s), 10,35 (1H, s).

Ejemplo 152

Producción de p–toluensulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



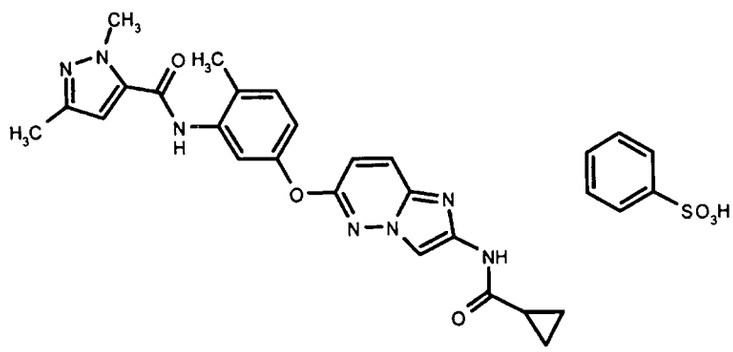
A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,49 mmol) se añadió etanol (80 mL), y la mezcla se calentó hasta 70 °C para dar una solución uniforme. Se añadió ácido p–toluensulfónico monohidratado (0,90 g, 4,71 mmol) a la mezcla, y la mezcla se enfrió naturalmente hasta temperatura ambiente. El solvente se evaporó a presión reducida. Al residuo obtenido se añadió hexano/etanol (3/1, 40 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Los cristales precipitados se recogieron por filtración y se lavaron con hexano/etanol (3:1). Los

cristales obtenidos se disolvieron en etanol (40 mL) por calentamiento y la mezcla se enfrió naturalmente hasta temperatura ambiente. Los cristales precipitados se recogieron por filtración y se lavaron con etanol. Los cristales se secaron a 70 °C durante 3 h a presión reducida para dar el compuesto del título (2,34 g, 84%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,87 – 1,97 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 2,29 (3H, s), 3,98 (3H, s), 6,82 (1H, s), 7,09 – 7,15 (4H, m), 7,29 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,4 Hz), 7,47 – 7,51 (2H, m), 7,96 (1H, s), 8,08 (1H, d, J = 9,6 Hz), 9,81 (1H, s), 11,17 (1H, s).

Ejemplo 153

Producción de bencensulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,49 mmol), etanol (100 mL) y ácido bencensulfónico monohidratado (0,83 g, 4,71 mmol), y de la misma

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manera que en el Ejemplo 152, se obtuvo el compuesto del título (2,02 g, 75%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,84 (4H, m), 1,87 – 1,97 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 3,97 (3H, s), 6,80 (1H, s), 7,06 – 7,12 (2H, m), 7,26 – 7,36 (5H, m), 7,57 – 7,61 (2H, m), 7,94 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 9,79 (1H, s), 11,13 (1H, s).

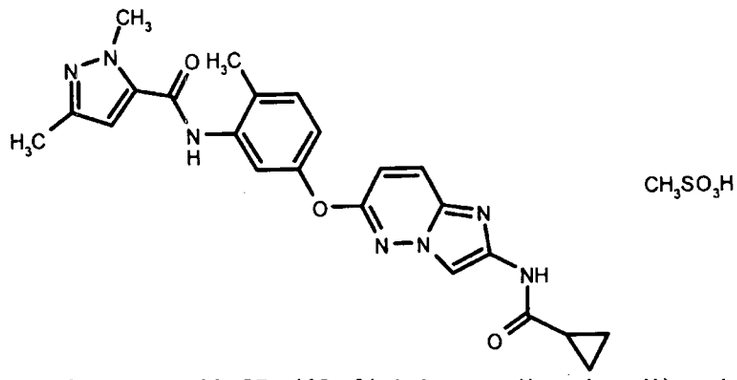
Análisis elemental ($C_{23}H_{23}N_7O_3 \cdot C_6H_6O_3S$)

Calculado: C, 57,70; H, 4,84 ; N, 16,24.

Encontrado: C, 57,73 ; H, 4,80 ; N, 16,30.

Ejemplo 154

Producción de metansulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,49 mmol), etanol (80 mL) y ácido metansulfónico (0,34 mL, 4,71 mmol), y de la misma manera que en el Ejemplo 152, se obtuvo el compuesto del título (1,63 g, 67%) en forma de cristales blancos.

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^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,84 (4H, m), 1,87 – 1,97 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 2,40 (3H, s), 3,97 (3H, s), 6,81 (1H, s), 7,07 – 7,12 (2H, m), 7,28 (1H, d, J = 2,4 Hz), 7,34 (1H, d, J = 8,7 Hz), 7,94 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 9,80 (1H, s), 11,13 (1H, s).

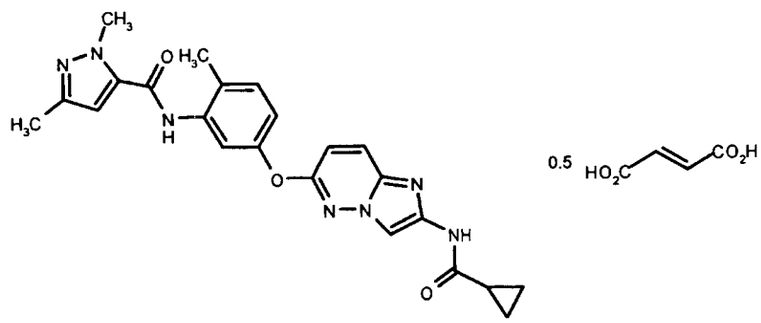
Análisis elemental ($C_{23}H_{23}N_7O_3 \cdot CH_4O_3S$)

Calculado: C, 53,23 ; H, 5,03 ; N, 18,10.

Encontrado: C, 53,14 ; H, 5,05 ; N, 18,15.

Ejemplo 155

Producción de 0.5 fumarato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,49 mmol) se le añadió etanol (100 mL) y la mezcla se calentó hasta 75 °C para dar una solución uniforme. Se añadió ácido fumárico (0,55 g, 4,71 mmol) a la mezcla, y la mezcla se enfrió naturalmente hasta temperatura ambiente y se agitó durante 3 h. Los cristales precipitados se recogieron por filtración y se lavaron con

etanol. El agua madre obtenida se concentró a presión reducida, y se agregó etanol (30 mL) al residuo obtenido. La mezcla se agitó a 60 °C durante 30 min. La mezcla se enfrió hasta temperatura ambiente y se dejó reposar durante 2 h, y los cristales precipitados se recogieron por filtración y se lavaron con etanol. Los cristales se secaron a presión reducida a 70 °C durante 3 h para dar el compuesto del título (1,73 g, 77%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,83 (4H, m), 1,87 – 1,97 (1H, m), 2,20 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,63 (1H, s), 6,81 (1H, s), 7,05 (1H, d, J = 9,5 Hz), 7,10 (1H, dd, J = 8,6, 2,6 Hz), 7,28 (1H, d, J = 2,6 Hz), 7,35 (1H, d, J = 8,6 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,80 (1H, s), 11,08 (1H, s).

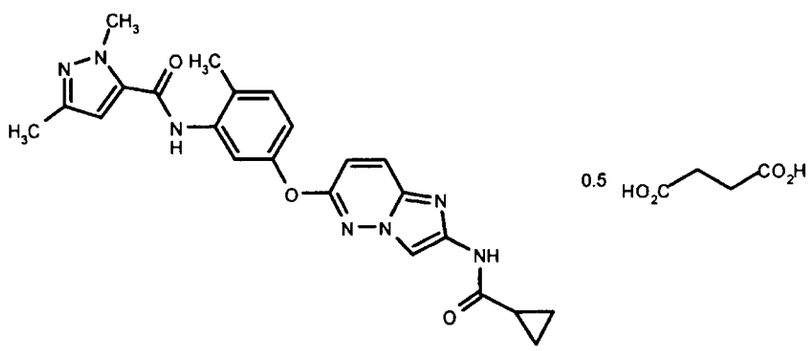
Análisis elemental ($C_{23}H_{23}N_7O_3 \cdot 0{,}5C_4H_4O_4$)

Calculado: C, 59,63 ; H, 5,00 ; N, 19,47.

Encontrado: C, 59,58 ; H, 4,98 ; N, 19,47.

Ejemplo 156

Producción de 0.5 succinato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,49 mmol), etanol (100 mL) y ácido succínico (0,56 g, 4,71 mmol), y de la misma manera que en el Ejemplo 155, se obtuvo el compuesto del título (1,04 g, 46%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,83 (4H, m), 1,87 – 1,96 (1H, m), 2,19 (3H, s), 2,24 (3H, s), 2,49 (2H, s), 3,97 (3H, s), 6,80 (1H, s), 7,04 (1H, d, J = 9,6 Hz), 7,09 (1H, dd, J = 8,3, 2,6 Hz), 7,27 (1H, d, J = 2,6 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,79 (1H, s), 11,06 (1H, s).

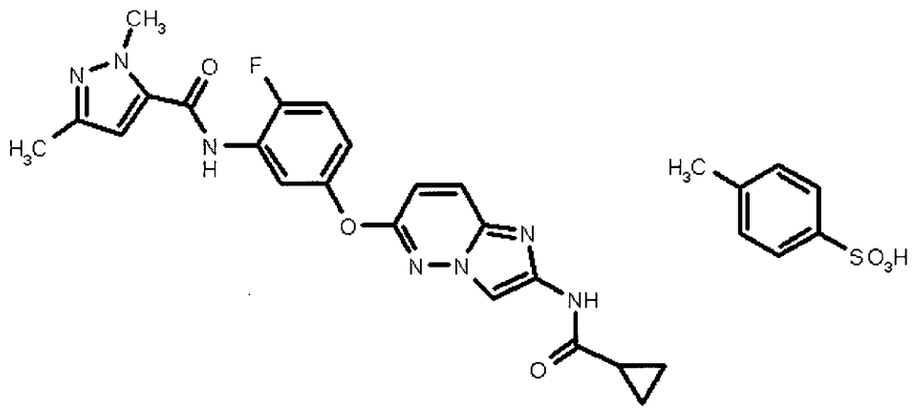
Análisis elemental ($C_{23}H_{23}N_7O_3 \cdot 0{,}5C_4H_6O_4$)

Calculado: C, 59,52 ; H, 5,19 ; N, 19,43.

Encontrado: C, 59,36 ; H, 5,19 ; N, 19,37.

Ejemplo 157

Producción de p–toluensulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida



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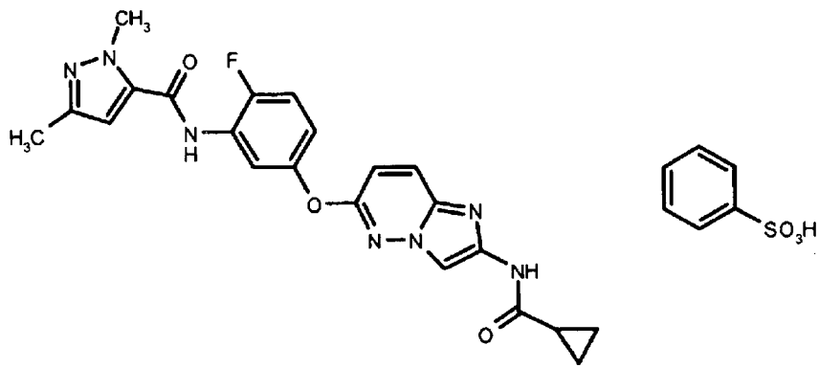
A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (225 mg, 0,5 mmol) se le añadieron tetrahidrofurano (5,0 mL) y etanol (5,0 mL), se disolvió a 70 °C, y se agregó ácido p–toluensulfónico monohidratado (95 mg, 0,5 mmol). También se agregó etanol (15,0 mL) a la mezcla y el material insoluble se filtró. El filtrado se concentró, se añadieron acetato de etilo (10 mL) y etanol (10 mL) y la mezcla se volvió a concentrar. Se agregaron acetato de etilo (10 mL) y etanol (1,0 mL), y la mezcla se dejó reposar a temperatura ambiente durante 6 h. Los cristales precipitados se recogieron por filtración, se lavaron sucesivamente con una pequeña cantidad de etanol y éter dietílico, y se secó a presión reducida a 80 °C durante 6 h para dar el compuesto del título (285 mg, 92%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,85 – 1,95 (1H, m), 2,19 (3H, s), 2,29 (3H, s), 3,98 (3H, s), 6,85 (1H, s), 7,08 (1H, d, J = 9,6 Hz), 7,11 (2H, d, J = 7,7 Hz), 7,15 – 7,25 (1H, m), 7,40 (1H, t, J = 9,6 Hz), 7,47 (2H, d, J = 7,7 Hz), 7,50–7,55 (1H, m), 7,94 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 11,09 (1H, s).

Ejemplo 158

Producción de bencensulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida

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A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (1,00 g, 2,23 mmol) se añadió etanol (50 mL), y la mezcla se agitó a 80 °C durante 20 min. Se agregó ácido bencensulfónico monohidratado (0,41 g, 2,33 mmol) a la mezcla, y la mezcla se agitó luego durante 10 min. El material insoluble se eliminó por filtración, y la mezcla se enfrió naturalmente hasta temperatura ambiente. La mezcla se dejó reposar a temperatura ambiente durante 16 h, y los cristales precipitados se recogieron por filtración y se lavaron con etanol. Los cristales precipitados se secaron a presión reducida a 80°C durante 6 h para dar el compuesto del título (1,17 g, 86%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,84 (4H, m), 1,88 – 1,97 (1H, m), 2,19 (3H, s), 3,98 (3H, s), 6,85 (1H, s), 7,10 (1H, d, J = 9,6 Hz), 7,18 – 7,24 (1H, m), 7,30 – 7,34 (3H, m), 7,41 (1H, t, J = 9,5 Hz), 7,52 – 7,56 (1H, m), 7,58 – 7,62 (2H, m), 7,95 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 11,11 (1H, s).

Análisis elemental ($C_{22}H_{20}FN_7O_3 \cdot C_6H_6O_3S$)

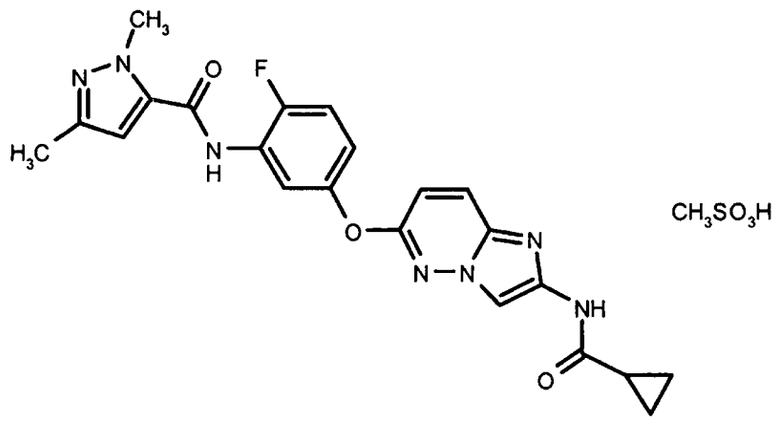
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Calculado: C, 55,35 ; H, 4,31 ; N, 16,14.

Encontrado: C, 55,25 ; H, 4,33 ; N, 16,14.

Ejemplo 159

Producción de metansulfonato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Una solución de N–[5–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (1,00 g, 2,23 mmol) en etanol (50 mL) se agitó a 70 °C durante 20 min. Se agregó ácido metansulfónico (0,17 mL, 2,33 mmol) a la mezcla, y la mezcla se agitó luego durante 10 min. La mezcla se enfrió naturalmente hasta temperatura ambiente, y el solvente se evaporó a presión reducida. Al residuo obtenido se añadió hexano/etanol (3:1, 40 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. El precipitado se recogió por filtración, y se lavó con hexano/etanol (3:1). El precipitado obtenido se disolvió en etanol (40 mL) por calentamiento, y la mezcla se enfrió naturalmente hasta temperatura ambiente. Los cristales precipitados

se recogieron por filtración, se añadió acetato de etilo (20 mL) a la mezcla, y la mezcla se agitó a 80 °C por calentamiento. Tras enfriar la mezcla hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con acetato de etilo y se secó a presión reducida a 100 °C durante 3 h para dar el compuesto del título (0,32 g, 26%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 2,19 (3H, s), 2,33 (3H, s), 3,97 (3H, s), 6,84 (1H, s), 7,08 (1H, d, J = 9,6 Hz), 7,18 – 7,23 (1H, m), 7,39 (1H, t, J = 9,6 Hz), 7,51 – 7,55 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,09 (1H, s), 11,08 (1H, s).

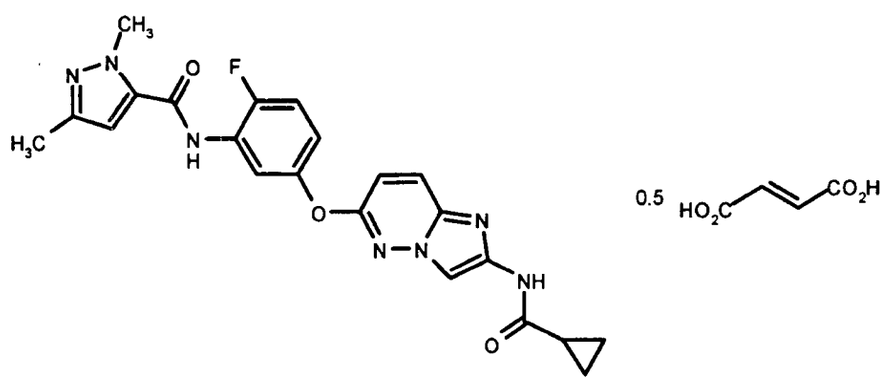
Análisis elemental ($C_{22}H_{20}FN_7O_3 \cdot CH_4O_3S$)

Calculado: C, 50,64 ; H, 4,43 ; N, 17,97.

Encontrado: C, 50,63 ; H, 4,38 ; N, 18,11.

Ejemplo 160

Producción de 0,5 fumarato de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida



959

A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,00 g, 4,45 mmol) se añadió tetrahidrofurano (100 mL), y la mezcla se calentó hasta 60°C para dar una solución uniforme. Se añadió ácido fumárico (0,54 g, 4,67 mmol) a la mezcla y la mezcla se dejó enfriar hasta temperatura ambiente. Se filtró el material insoluble, se añadió acetato de etilo (50 mL) al filtrado, y el solvente se evaporó hasta 1/4 a presión reducida. Los cristales precipitados se recogieron por filtración, se lavaron con acetato de etilo y se secó a presión reducida a 80 °C durante 3 h para dar el compuesto del título (1,88 g, 83%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,82 (4H, m), 1,87 – 1,96 (1H, m), 2,19 (3H, s), 3,97 (3H, s), 6,61 (1H, s), 6,84 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,18 – 7,23 (1H, m), 7,39 (1H, t, J = 9,6 Hz), 7,51 – 7,54 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,09 (1H, s), 11,06 (1H, s).

Análisis elemental ($C_{22}H_{20}FN_7O_3 \cdot 0,5C_4H_4O_4$)

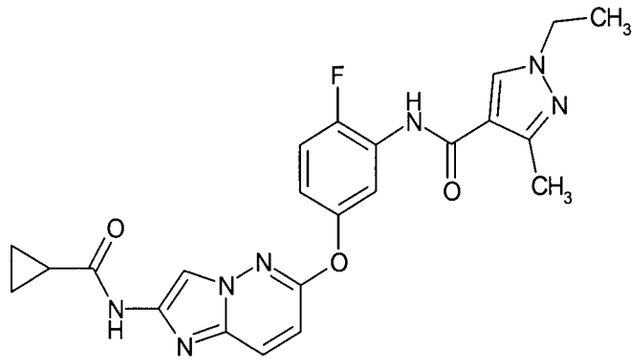
Calculado: C, 56,80 ; H, 4,37 ; N, 19,32.

Encontrado: C, 56,73 ; H, 4,33 ; N, 19,24.

Ejemplo 161

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–4–carboxamida

960



A una solución de ácido 1–etil–3–metil–1H–pirazol–4–carboxílico (2,00 g, 13,0 mmol) y N,N–dimetilformamida (3 gotas) en tetrahidrofurano (30 mL) se añadió cloruro de oxalilo (2,23 mL, 26,0 mmol) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida. El residuo se disolvió en N,N–dimetilacetamida (20 mL) con agitación bajo enfriamiento con hielo, se añadió N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (3,27 g, 10,0 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio (50 mL) y se extrajo con un solvente mixto de acetato de etilo/tetrahidrofurano (1:1, 80 mL, 40 mL×2). La capa orgánica se lavó con agua (10 mL×3), y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30) y se cristalizó en acetato de etilo para dar el compuesto del título (2,39 g, rendimiento 52%) en forma de un sólido blanco. Punto de fusión 199 °C.

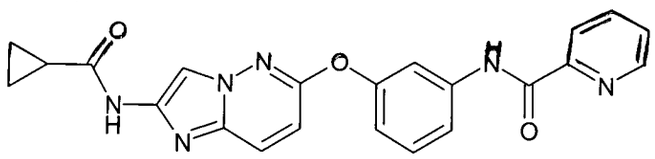
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,38 (3H,

961

t, J = 7,3Hz), 1,86 – 1,98 (1H, m), 2,33 (3H, s), 4,09 (2H, q, J = 7,3Hz), 7,06 (1H, d, J = 9,6Hz), 7,07 – 7,15 (1H, m), 7,36 (1H, dd, J = 10,2, 9,0Hz), 7,66 (1H, dd, J = 6,3, 3,0Hz), 7,94 (1H, s), 8,04 (1H, dd, J = 9,6, 0,6Hz), 8,39 (1H, s), 9,54 (1H, s), 11,07 (1H, s).

Ejemplo 162

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]piridin–2–carboxamida



A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol) en N–metilpirrolidona (3 mL) se añadió clorhidrato de cloruro de piridin–2–carbonilo (107 mg, 0,60 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa al 5% de hidrógeno–carbonato de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→80/20) y se cristalizó en acetato de etilo para dar el compuesto del título (131 mg, rendimiento 63%) en forma de un sólido blanco.

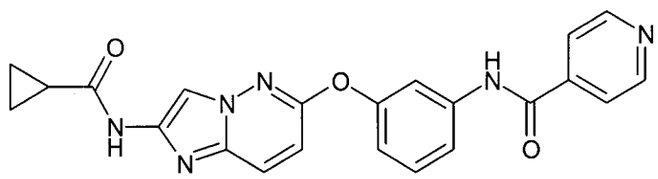
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,86 – 1,99 (1H, m), 7,02 (1H, ddd, J = 8,1, 2,5, 0,7Hz), 7,07 (1H, d, J = 9,3Hz), 7,44 (1H, t, J = 8,2Hz), 7,68 (1H, ddd, J = 7,3, 4,7, 1,3Hz),

962

7,80 – 7,85 (1H, m), 7,90 (1H, t, J = 2,3Hz), 7,99 (1H, s), 8,03 – 8,10 (2H, m), 8,12 – 8,18 (1H, m), 8,72 – 8,76 (1H, m), 10,81 (1H, s), 11,09 (1H, s).

Ejemplo 163

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]isonicotinamida



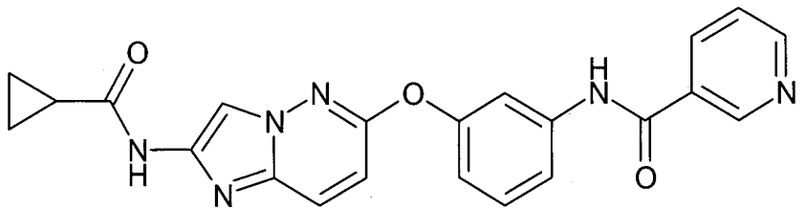
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), N–metilpirrolidona (3 mL) y clorhidrato de cloruro de piridin–4–carbonilo (107 mg, 0,60 mmol), y de la misma manera que en el Ejemplo 162, se obtuvo el compuesto del título (163 mg, rendimiento 78%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,84 – 2,00 (1H, m), 7,01 – 7,07 (1H, m), 7,08 (1H, d, J = 9,6Hz), 7,46 (1H, t, J = 8,1Hz), 7,63 – 7,69 (1H, m), 7,73 (1H, t, J = 2,1Hz), 7,82 – 7,87 (2H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6Hz), 8,76 – 8,81 (2H, m), 10,62 (1H, s), 11,09 (1H, s).

Ejemplo 164

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]nicotinamida

963

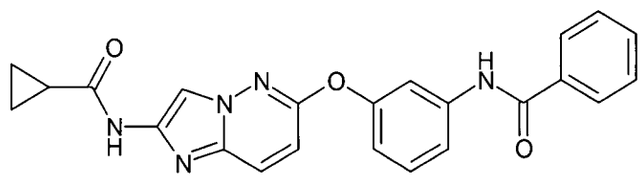


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), N–metilpirrolidona (3 mL) y clorhidrato de cloruro de piridin–3–carbonilo (107 mg, 0,60 mmol), y de la misma manera que en el Ejemplo 162, se obtuvo el compuesto del título (89 mg, rendimiento 43%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,87 (4H, m), 1,86 – 1,99 (1H, m), 7,03 (1H, dd, J = 7,8, 1,8Hz), 7,08 (1H, d, J = 9,6Hz), 7,45 (1H, t, J = 8,4Hz), 7,57 (1H, dd, J = 7,8, 4,8Hz), 7,66 (1H, d, J = 8,1Hz), 7,73 (1H, t, J = 1,9Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6Hz), 8,28 (1H, dt, J = 7,9, 1,9Hz), 8,76 (1H, d, J = 3,9Hz), 9,09 (1H, s), 10,57 (1H, s), 11,09 (1H, s).

Ejemplo 165

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida



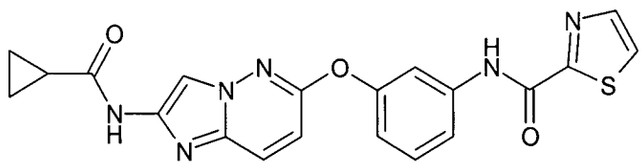
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), N–metilpirrolidona (3 mL) y cloruro de benzoílo (0,070 mL, 0,60 mmol), y de la misma

manera que en el Ejemplo 162, se obtuvo el compuesto del título (176 mg, rendimiento 85%). Punto de fusión 265 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,86 (4H, m), 1,87 – 1,99 (1H, m), 7,00 (1H, ddd, J = 8,1, 2,4, 0,8Hz), 7,07 (1H, d, J = 9,5Hz), 7,43 (1H, t, J = 8,1Hz), 7,49 – 7,64 (3H, m), 7,68 (1H, d, J = 8,4Hz), 7,74 (1H, t, J = 2,1Hz), 7,90 – 7,97 (2H, m), 7,98 (1H, s), 8,05 (1H, d, J = 9,5Hz), 10,38 (1H, s), 11,09 (1H, s).

Ejemplo 166

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–tiazol–2–carboxamida



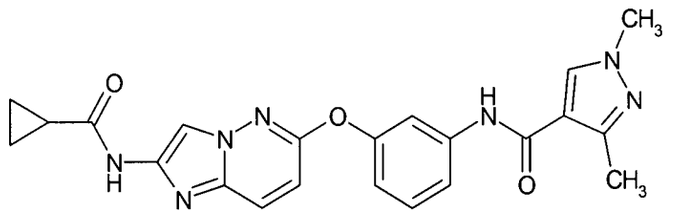
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), N–metilpirrolidona (3 mL) y cloruro de 1,3–tiazol–2–carbonilo (89 mg, 0,60 mmol), y de la misma manera que en el Ejemplo 162, se obtuvo el compuesto del título (136 mg, rendimiento 65%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,86 – 1,99 (1H, m), 7,03 (1H, ddd, J = 8,2, 2,4, 1,0Hz), 7,07 (1H, d, J = 9,6Hz), 7,44 (1H, t, J = 8,1Hz), 7,75 – 7,83 (2H, m), 7,98 (1H, s), 8,06 (1H, dd, J = 9,6, 0,6Hz), 8,11 (1H, d, J = 3,0Hz), 8,15 (1H, d, J = 3,0Hz), 10,94 (1H, s), 11,09 (1H, s).

Ejemplo 167

965

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–4–carboxamida



A una suspensión de ácido 1,3–dimetil–1H–pirazol–4–carboxílico (140 mg, 1,0 mmol) en diclorometano (10 mL) se añadieron N,N–dimetilformamida (2 gotas), luego cloruro de oxalilo (0,171 mL, 2,0 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida. El residuo se diluyó con N–metilpirrolidona (5 mL), se añadió N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), y la mezcla se agitó a temperatura ambiente durante 6 h. A la mezcla de reacción se añadió solución acuosa 0,5 N de hidróxido de sodio, y la mezcla se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30). La fracción objeto se concentró a presión reducida, y el residuo se lavó con éter diisopropílico para dar el compuesto del título (126 mg, rendimiento 58%) en forma de un sólido blanco.

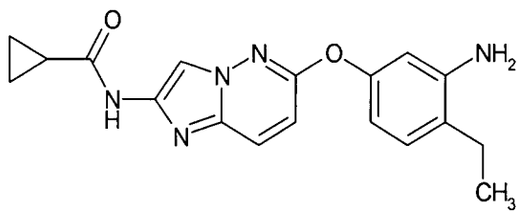
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,87 (4H, m), 1,86 – 1,99 (1H, m), 2,33 (3H, s), 3,81 (3H, s), 6,93 (1H, dd, J = 8,1,

966

1,8Hz), 7,05 (1H, d, J = 9,6Hz), 7,38 (1H, t, J = 8,1Hz), 7,55 (1H, d, J = 8,1Hz), 7,64 (1H, t, J = 2,1Hz), 7,97 (1H, s), 8,05 (1H, d, J = 9,6Hz), 8,27 (1H, s), 9,78 (1H, s), 11,09 (1H, s).

Ejemplo 168

Producción de N–[6–(3–amino–4–etilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (984 mg, 3,0 mmol), 3–amino–4–etilfenol (617 mg, 4,5 mmol), carbonato de potasio (829 mg, 6,0 mmol) y N,N–dimetilformamida (9 mL) se agitó a 150 °C durante 24 h. La mezcla de reacción se diluyó con agua y se extrajo con un solvente mixto de acetato de etilo/tetrahidrofurano (3:1). La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 50/50→0/100) y se recristalizó en un solvente mixto de acetato de etilo/éter diisopropílico para dar el compuesto del título (706 mg, rendimiento 70%) en forma de un sólico de color caqui.

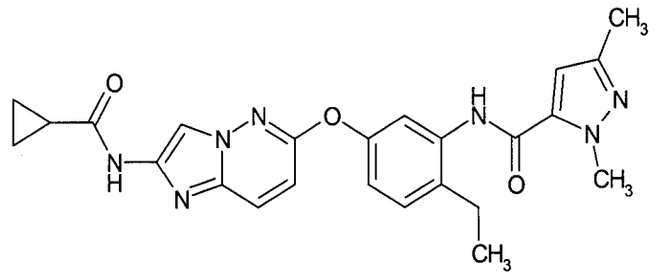
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,14 (3H, t, J = 7,4Hz), 1,85 – 2,00 (1H, m), 2,43 (2H, q, J = 7,4Hz), 5,07 (2H, s), 6,31 (1H, dd, J = 8,1, 2,7Hz), 6,42 (1H, d, J = 2,7Hz), 6,93 (1H, d, J = 9,6Hz), 6,95 (1H, d, J = 7,8Hz), 7,97 (1H, s), 7,98 (1H, d, J =

964

9,0Hz), 11,05 (1H, s).

Ejemplo 169

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–etilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–amino–4–etilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (202 mg, 0,60 mmol) en N–metilpirrolidona (3 mL) se le añadió cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (143 mg, 0,90 mmol), y la mezcla se agitó a temperatura ambiente durante 8 h. Una solución acuosa 1 N de hidróxido de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→80/20) y se recristalizó en un solvente mixto de acetato de etilo/éter diisopropílico para dar el compuesto del título (167 mg, rendimiento 61%) en forma de un sólido blanco.

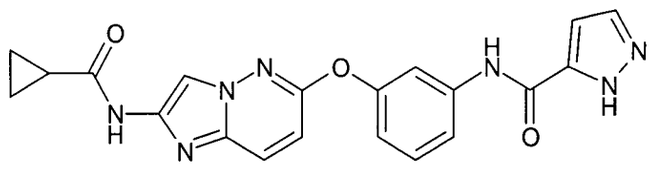
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,15 (3H, t, J = 7,6Hz), 1,84 – 2,00 (1H, m), 2,19 (3H, s), 2,63 (2H, q, J = 7,6Hz), 3,97 (3H, s), 6,80 (1H, s), 7,04 (1H, d, J = 9,6Hz), 7,15 (1H, dd, J = 8,6, 2,6Hz), 7,23 (1H, d, J = 2,6Hz), 7,37 (1H, d, J = 8,6Hz),

962

7,94 (1H, s), 8,03 (1H, dd, J = 9,6, 0,6Hz), 9,82 (1H, s), 11,07 (1H, s).

Ejemplo 170

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–pirazol–5–carboxamida



A una mezcla de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol), ácido 1H–pirazol–5–carboxílico (84 mg, 0,75 mmol), 1–hidroxibenzotriazol (101 mg, 0,75 mmol) y N,N–dimetilformamida (5 mL) se añadieron clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (192 mg, 1,0 mmol), trietilamina (0,279 mL, 2,0 mmol), 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 un solvente mixto de acetato de etilo/tetrahidrofurano. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30) y se cristalizó en acetato de etilo para dar el compuesto del título (43 mg, rendimiento 21%) en forma de un sólido blanco.

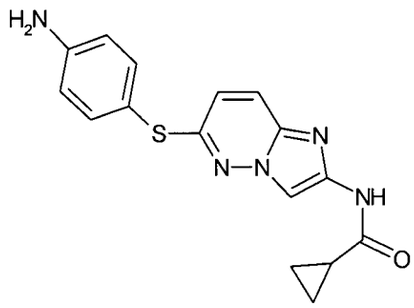
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,87 – 1,99 (1H, m), 6,76 (1H, s), 6,95 (1H, dd, J = 8,1, 1,8Hz), 7,05 (1H, d, J = 9,6Hz), 7,39 (1H, t, J = 8,4Hz), 7,73 (1H, d, J = 8,4Hz), 7,79 (1H,

969

s), 7,89 (1H, s), 7,98 (1H, s), 8,04 (1H, d, J = 9,6Hz), 10,20 (1H, s), 11,07 (1H, s), 13,42 (1H, s).

Ejemplo 171

Producción de N–{6–[(4–aminofenil)tio]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida

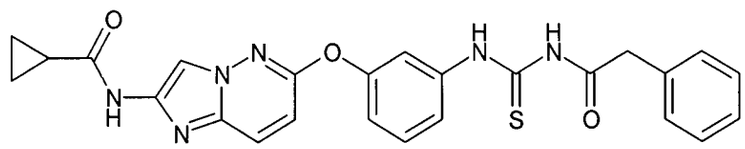


A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)–2–metilciclopropancarboxamida (2,0 g, 6,10 mmol) en N,N–dimetilformamida (20,0 mL) se le añadieron carbonato de potasio (1,27 g, 9,14 mmol) y 4–aminotiofenol (0,92 g, 7,31 mmol), y la mezcla se agitó a 80 °C durante 4 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, y el residuo se recogió por filtración y se lavó con acetato de etilo para dar el compuesto del título (1,53 g, 77%) en forma de cristales marrones.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,85 (4H, m), 1,87 – 1,97 (1H, m), 5,68 (2H, s), 6,60 – 6,67 (3H, m), 7,24 – 7,29 (2H, m), 7,78 (1H, d, J = 9,5 Hz), 8,06 (1H, s), 11,09 (1H, s).

Ejemplo 172

Producción de N–{6–[3–({[(fenilacetil)amino]tiocarbonil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



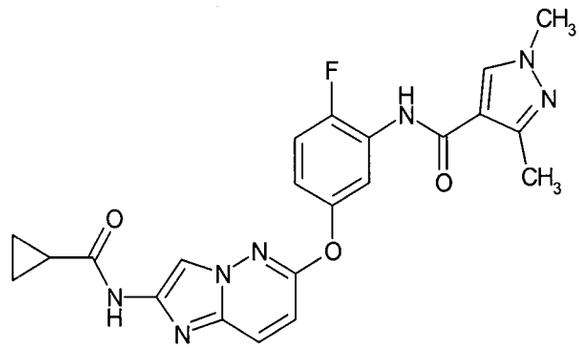
A una solución de cloruro de fenilacetilo (155 mg, 1,0 mmol) en acetonitrilo (20 mL) se le añadió tiocianato de potasio (292 mg, 3,0 mmol), y la mezcla se agitó a 60°C durante 3 h y se concentró a presión reducida. El residuo se diluyó con tetrahidrofurano (20 mL). Se le añadió N–[6–(3–Aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (155 mg, 0,50 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 18 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 concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30) y se precipitó en éter diisopropílico para dar el compuesto del título (142 mg, rendimiento 58%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,86 – 1,98 (1H, m), 3,81 (2H, s), 7,04 (1H, d, J = 9,6Hz), 7,10 – 7,19 (1H, m), 7,23 – 7,38 (5H, m), 7,45 (2H, d, J = 5,1Hz), 7,74 (1H, s), 7,96 (1H, s), 8,03 (1H, d, J = 9,6Hz), 11,07 (1H, s), 11,72 (1H, s), 12,46 (1H, s).

971

Ejemplo 173

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–4–carboxamida



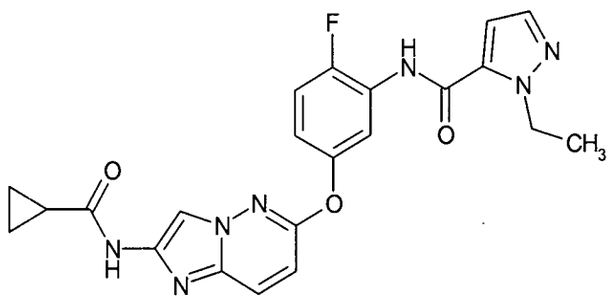
A una solución de ácido 1,3–dimetil–1H–pirazol–4–carboxílico (140 mg, 1,0 mmol) y N,N–dimetilformamida (2 gotas) en tetrahidrofurano (10 mL) se le añadió cloruro de oxalilo (0,171 mL, 2,0 mmol) con agitación bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró a presión reducida. El residuo se disolvió en N–metilpirrolidona (5 mL) con agitación bajo enfriamiento con hielo, se agregó N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con acetato de etilo (80 mL), y se lavó con solución acuosa 1 N de hidróxido de sodio (10 mL) y agua (10 mL×3). La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→70/30) y se recristalizó en acetato de etilo para dar el

compuesto del título (88 mg, rendimiento 39%) en forma de un sólido blanco. Punto de fusión 205 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,86 – 1,99 (1H, m), 2,32 (3H, s), 3,81 (3H, s), 7,06 (1H, d, J = 9,5Hz), 7,06 – 7,14 (1H, m), 7,36 (1H, dd, J = 10,2, 9,0Hz), 7,66 (1H, dd, J = 6,4, 3,2Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,5Hz), 8,32 (1H, s), 9,53 (1H, s), 11,06 (1H, s).

Ejemplo 174

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–5–carboxamida



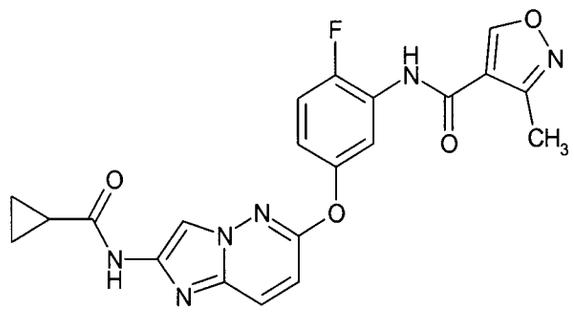
Usando ácido 1–etil–1H–pirazol–5–carboxílico (140 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (10 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (119 mg, rendimiento 53%). Punto de fusión 209 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,31 (3H, t, J = 7,2Hz), 1,86 – 1,98 (1H, m), 4,50 (2H, q, J = 7,2Hz), 7,07 (1H,

d, J = 2,0Hz), 7,08 (1H, d, J = 9,5Hz), 7,22 (1H, ddd, J = 9,0, 3,9, 3,0Hz), 7,41 (1H, dd, J = 10,2, 9,0Hz), 7,52 – 7,57 (1H, m), 7,55 (1H, d, J = 2,0Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,5Hz), 10,19 (1H, s), 11,06 (1H, s).

Ejemplo 175

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metilisoxazol–4–carboxamida



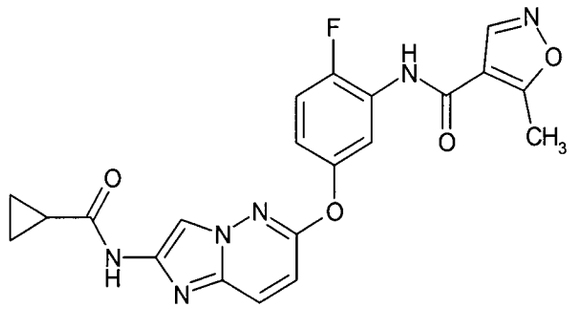
Usando ácido 3–metilisoxazol–4–carboxílico (127 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (10 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (143 mg, rendimiento 65%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,86 – 1,99 (1H, m), 2,40 (3H, s), 7,07 (1H, d, J = 9,3Hz), 7,14 – 7,21 (1H, m), 7,40 (1H, dd, J = 10,2, 9,0Hz), 7,66 (1H, dd, J = 6,3, 2,7Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,3Hz), 9,48 (1H, s), 10,19 (1H, s), 11,06 (1H, s).

974

Ejemplo 176

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–5–metilisoxazol–4–carboxamida

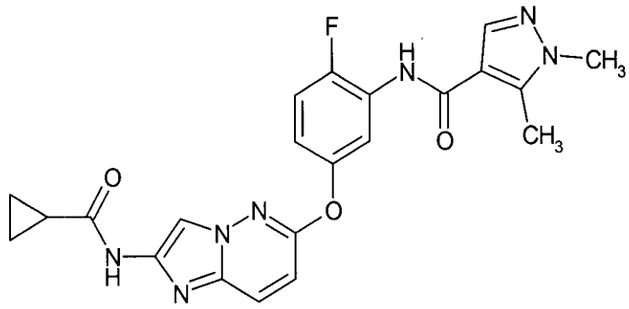


Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), N–metilpirrolidona (5 mL) y cloruro de 5–metilisoxazol–4–carbonilo (146 mg, 1,00 mmol), y de la misma manera que en el Ejemplo 162, se obtuvo el compuesto del título (112 mg, rendimiento 51%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,86 – 1,98 (1H, m), 2,66 (3H, s), 7,08 (1H, d, J = 9,6Hz), 7,19 (1H, ddd, J = 9,0, 3,9, 3,0Hz), 7,41 (1H, dd, J = 9,9, 9,0Hz), 7,62 (1H, dd, J = 6,3, 3,0Hz), 7,94 (1H, s), 8,05 (1H, dd, J = 9,6, 0,6Hz), 9,06 (1H, s), 10,09 (1H, s), 11,08 (1H, s).

Ejemplo 177

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,5–dimetil–1H–pirazol–4–carboxamida

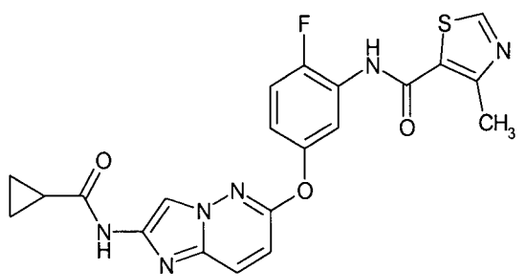


Usando ácido 1,5–dimetil–1H–pirazol–4–carboxílico (140 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (10 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (106 mg, rendimiento 47%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,85 – 1,98 (1H, m), 2,48 (3H, s), 3,75 (3H, s), 7,06 (1H, d, J = 9,6Hz), 7,13 (1H, ddd, J = 8,9, 3,8, 3,1Hz), 7,36 (1H, dd, J = 10,2, 9,0Hz), 7,58 (1H, dd, J = 6,3, 3,0Hz), 7,94 (1H, s), 8,04 (1H, s), 8,04 (1H, dd, J = 9,6, 0,6Hz), 9,63 (1H, s), 11,07 (1H, s).

Ejemplo 178

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–4–metil–1,3–tiazol–5–carboxamida



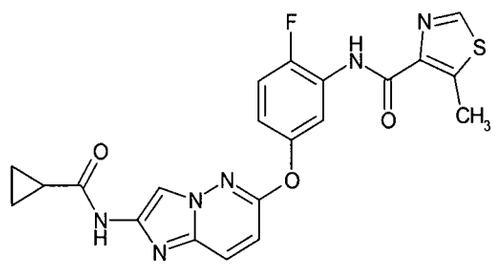
976

Usando ácido 4–metil–1,3–tiazol–5–carboxílico (143 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (10 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (179 mg, rendimiento 79%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73–0,86 (4H, m), 1,85 – 1,98 (1H, m), 2,63 (3H, s), 7,08 (1H, d, J = 9,5Hz), 7,20 (1H, ddd, J = 8,8, 3,7, 3,2Hz), 7,40 (1H, dd, J = 9,9, 9,3Hz), 7,59 (1H, dd, J = 6,6, 3,0Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,5Hz), 9,14 (1H, s), 10,13 (1H, s), 11,07 (1H, s).

Ejemplo 179

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–5–metil–1,3–tiazol–4–carboxamida



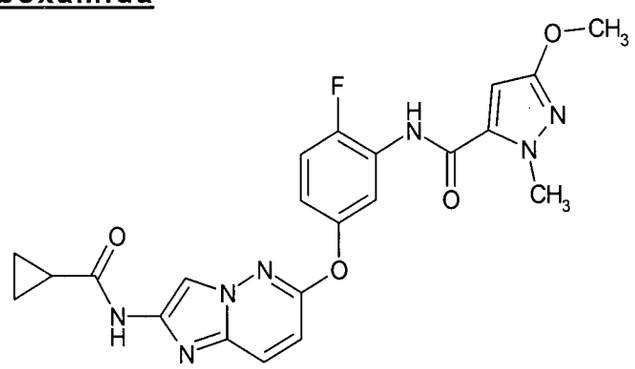
Usando ácido 5–metil–1,3–tiazol–4–carboxílico (143 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (10 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma

manera que en el Ejemplo 173, se obtuvo el compuesto del título (107 mg, rendimiento 47%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,86 – 1,98 (1H, m), 2,78 (3H, s), 7,08 (1H, d, J = 9,6Hz), 7,08 – 7,16 (1H, m), 7,42 (1H, dd, J = 10,5, 9,0Hz), 7,95 (1H, s), 8,00 (1H, dd, J = 6,6, 3,0Hz), 8,05 (1H, d, J = 9,6Hz), 9,02 (1H, s), 9,94 (1H, s), 11,08 (1H, s).

Ejemplo 180

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida



Usando ácido 3–metoxi–1–metil–1H–pirazol–5–carboxílico (156 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (15 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (85 mg, rendimiento 36%).

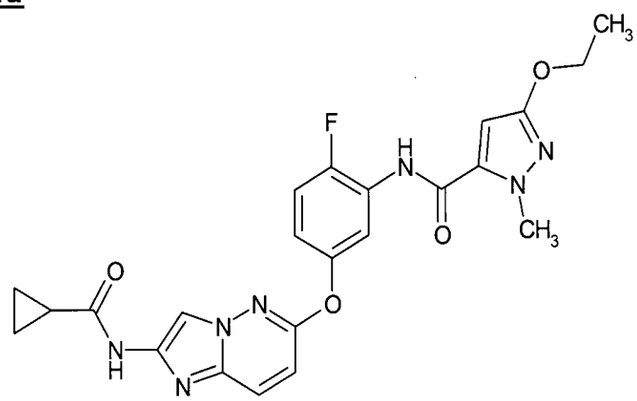
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,86 –

978

1,98 (1H, m), 3,80 (3H, s), 3,92 (3H, s), 6,50 (1H, s), 7,08 (1H, d, J = 9,6Hz), 7,21 (1H, ddd, J = 9,1, 4,0, 3,1Hz), 7,40 (1H, dd, J = 10,0, 9,1Hz), 7,53 (1H, dd, J = 6,3, 3,0Hz), 7,94 (1H, s), 8,05 (1H, dd, J = 9,6, 0,6Hz), 10,14 (1H, s), 11,07 (1H, s).

Ejemplo 181

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etoxi–1–metil–1H–pirazol–5–carboxamida



Usando ácido 3–etoxi–1–metil–1H–pirazol–5–carboxílico (170 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (15 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (92 mg, rendimiento 38%).

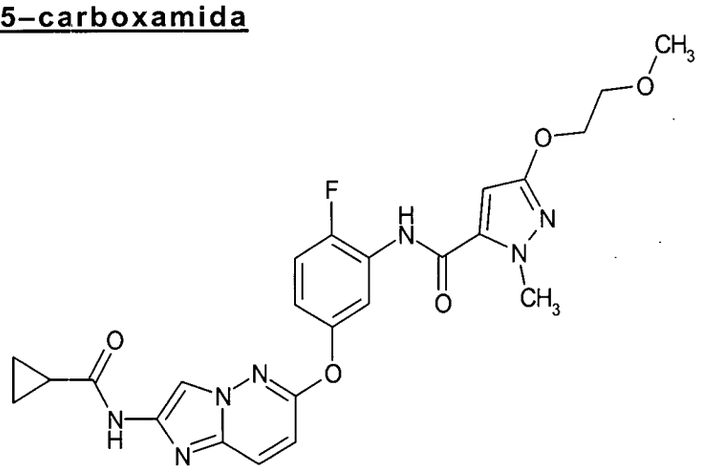
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,30 (3H, t, J = 7,0Hz), 1,85 – 1,99 (1H, m), 3,91 (3H, s), 4,12 (2H, q, J = 7,0Hz), 6,48 (1H, s), 7,08 (1H, d, J = 9,6Hz), 7,18 – 7,25 (1H, m), 7,36 – 7,45 (1H, m), 7,53 (1H, dd, J = 6,5, 3,1Hz), 7,94 (1H, s), 8,05

979

(1H, dd, J = 9,6, 0,4Hz), 10,12 (1H, s), 11,07 (1H, s).

Ejemplo 182

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carboxamida



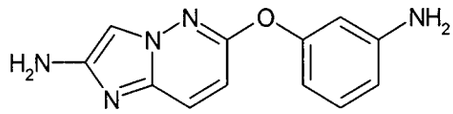
Usando ácido 3–(2–metoxietoxi)–1–metil–1H–pirazol–5–carboxílico (200 mg, 1,0 mmol), N,N–dimetilformamida (2 gotas), tetrahidrofurano (15 mL), cloruro de oxalilo (0,172 mL, 2,0 mmol), N–metilpirrolidona (5 mL) y N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (164 mg, 0,50 mmol), y de la misma manera que en el Ejemplo 173, se obtuvo el compuesto del título (128 mg, rendimiento 50%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,85 – 1,99 (1H, m), 3,29 (3H, s), 3,59 – 3,67 (2H, m), 3,91 (3H, s), 4,15 – 4,23 (2H, m), 6,49 (1H, s), 7,08 (1H, d, J = 9,5Hz), 7,18 – 7,25 (1H, m), 7,41 (1H, dd, J = 10,1, 9,1Hz), 7,53 (1H, dd, J = 6,4, 2,9Hz), 7,94 (1H, s), 8,05 (1H, dd, J = 9,5, 0,7Hz), 10,14 (1H, s), 11,07 (1H, s).

Ejemplo 183

980

Producción de 6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–amina



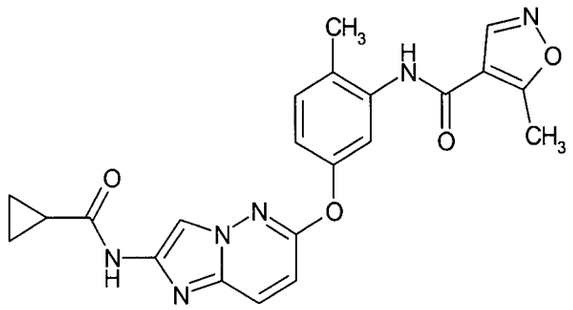
Una mezcla de 6–yodoimidazo[1,2–b]piridazin–2–amina (390 mg, 1,5 mmol), 3–aminofenol (491 mg, 4,5 mmol), carbonato de potasio (415 mg, 3,0 mmol) y N,N–dimetilformamida (3 mL) se agitó usando un sintetizador de microondas a 180 °C durante 40 min. La mezcla de reacción se diluyó con agua y se extrajo con un solvente mixto de acetato de etilo/tetrahidrofurano (1:1). La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→60/40). La fracción objeto se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/metanol = 100/0→80/20) y se precipitó en acetato de etilo para dar el compuesto del título (133 mg, rendimiento 37%) en forma de un sólido púrpura.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,27 (2H, s), 5,31 (2H, s), 6,23 (1H, ddd, J = 7,8, 2,4, 0,9Hz), 6,27 (1H, t, J = 2,1Hz), 6,38 (1H, ddd, J = 8,1, 2,1, 0,9Hz), 6,69 (1H, d, J = 9,3Hz), 7,02 (1H, t, J = 7,9Hz), 7,14 (1H, s), 7,68 (1H, dd, J = 9,3, 0,6Hz).

Ejemplo 184

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–5–metilisoxazol–4–carboxamida

981

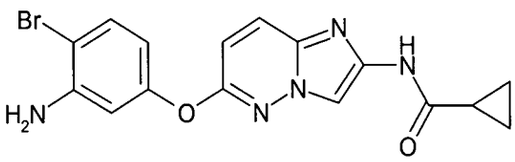


Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (162 mg, 0,50 mmol), N–metilpirrolidona (5 mL) y cloruro de 5–metilisoxazol–4–carbonilo (146 mg, 1,0 mmol), y de la misma manera que en el Ejemplo 162, se obtuvo el compuesto del título (174 mg, rendimiento 80%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,86 – 1,99 (1H, m), 2,26 (3H, s), 2,66 (3H, s), 7,04 (1H, d, J = 9,6Hz), 7,09 (1H, dd, J = 8,6, 2,6Hz), 7,29 (1H, d, J = 2,6Hz), 7,35 (1H, d, J = 8,6Hz), 7,93 (1H, s), 8,03 (1H, dd, J = 9,6, 0,4Hz), 9,02 (1H, s), 9,75 (1H, s), 11,07 (1H, s).

Ejemplo 185

Producción de N–[6–(3–amino–4–bromofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (3,28 g, 10 mmol), 3–amino–4–bromofenol (2,82 g, 15 mmol), carbonato de potasio (2,76 g, 20 mmol) y N,N–dimetilformamida (20 mL) se agitó a 110 °C durante 24 h, luego a

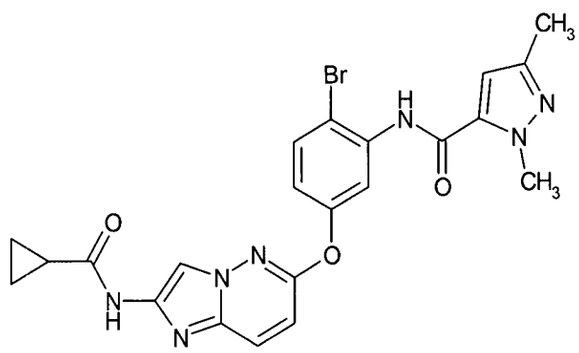
982

150°C durante 24 h. La mezcla de reacción se diluyó con agua y se extrajo con un solvente mixto de acetato de etilo/tetrahidrofurano (1:1). La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 50/50→0/100) y se recristalizó en acetato de etilo para dar el compuesto del título (1,85 g, rendimiento 48%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,88 (4H, m), 1,86 – 1,98 (1H, m), 5,51 (2H, s), 6,35 (1H, dd, J = 8,6, 2,8Hz), 6,62 (1H, d, J = 2,8Hz), 7,01 (1H, d, J = 9,6Hz), 7,37 (1H, d, J = 8,6Hz), 7,99 (1H, s), 8,02 (1H, d, J = 9,6Hz), 11,08 (1H, s).

Ejemplo 186

Producción de N–[2–bromo–5–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de N–[6–(3–amino–4–bromofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (582 mg, 1,50 mmol) en N–metilpirrolidona (5 mL) se añadió cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (310 mg, 1,95 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa al 5% de hidrógeno–

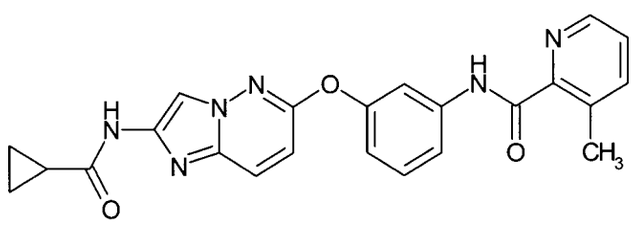
983

carbonato de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con un solvente mixto de acetato de etilo/tetrahidrofurano (1:1). La capa orgánica se lavó con agua, se secó sobre sulfato de sodio anhidro, se filtró, y se concentró a presión reducida. El residuo se suspendió en acetato de etilo, y la mezcla se agitó con calentamiento a reflujo durante 15 min. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con acetato de etilo, y se secó a presión reducida para dar el compuesto del título (658 mg, rendimiento 86%) en forma de un sólido de color crema.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,86 – 1,98 (1H, m), 2,20 (3H, s), 3,98 (3H, s), 6,83 (1H, s), 7,10 (1H, d, J = 9,6Hz), 7,20 (1H, dd, J = 8,9, 2,9Hz), 7,51 (1H, dd, J = 2,9Hz), 7,79 (1H, d, J = 8,9Hz), 7,95 (1H, s), 8,06 (1H, dd, J = 9,6, 0,6Hz), 9,97 (1H, s), 11,09 (1H, s).

Ejemplo 187

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metilpiridin–2–carboxamida



A una solución de ácido N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,323 mmol), 3–metilpiridin–2–carboxílico (66 mg, 0,485 mmol) y 1–

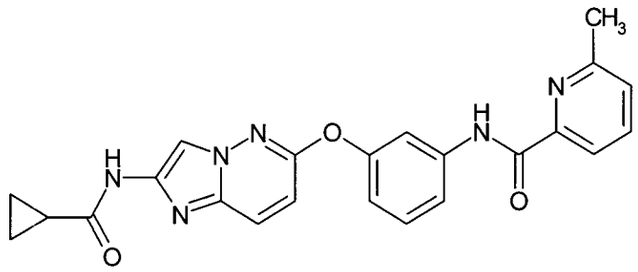
984

hidroxibenzotriazol (71 mg, 0,522 mmol) en N,N–dimetilformamida (4,0 mL) se añadieron trietilamina (0,08 mL, 0,549 mmol) y clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (99 mg, 0,517 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 20 h. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 80/20→100/0) y se recristalizó en acetato de etilo/metanol para dar el compuesto del título (98 mg, 71%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70–0,90 (4H, m), 1,85 – 2,00 (1H, m), 2,55 (3H, s), 6,95 – 7,05 (1H, m), 7,05 (1H, d, J = 9,6 Hz), 7,41 (1H, t, J = 7,8 Hz), 7,45 – 7,55 (1H, m), 7,71 (1H, d, J = 8,4 Hz), 7,75 – 7,85 (2H, m), 8,04 (1H, d, J = 8,7 Hz), 8,50 – 8,55 (1H, m), 10,68 (1H, s), 11,07 (1H, s).

Ejemplo 188

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–6–metilpiridin–2–carboxamida



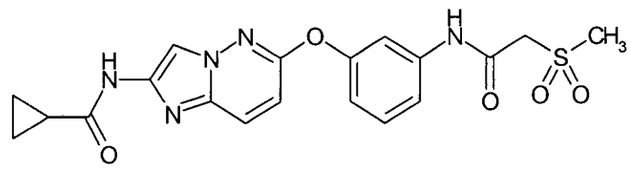
985.

Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,323 mmol), ácido 6–metilpiridin–2–carboxílico (66 mg, 0,485 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (99 mg, 0,517 mmol), 1–hidroxibenzotriazol (71 mg, 0,522 mmol), trietilamina (0,08 mL, 0,549 mmol) y N,N–dimetilformamida (4,0 mL), y por reacción de la misma manera que en el Ejemplo 187, se obtuvo el compuesto del título (100 mg, 72%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,85 – 1,95 (1H, m), 2,62 (3H, s), 7,00 – 7,05 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,44 (1H, t, J = 7,8 Hz), 7,50 – 7,55 (1H, m), 7,79 (1H, d, J = 7,8 Hz), 7,85 – 7,95 (3H, m), 8,05 (1H, d, J = 9,6 Hz), 7,97 (1H, s), 10,56 (1H, s), 11,08 (1H, s).

Ejemplo 189

Producción de N–[6–(3–{[(metilsulfonil)acetil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



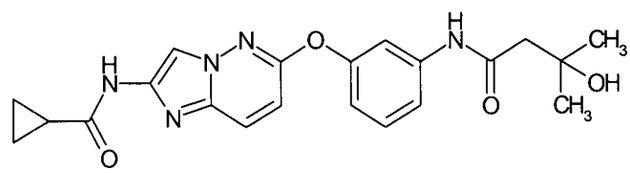
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,323 mmol), ácido (metilsulfonil)acético (67 mg, 0,485 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (99 mg, 0,517 mmol), 1–hidroxibenzotriazol (71 mg, 0,522 mmol), trietilamina (0,08 mL, 0,549 mmol) y N,N–dimetilformamida (4,0 mL), y por reacción de la misma

manera que en el Ejemplo 187, se obtuvo el compuesto del título (87 mg, 63%) en forma de cristales de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,90 – 2,00 (1H, m), 3,15 (3H, s), 4,27 (2H, s), 6,95 – 7,05 (1H, m), 7,05 (1H, d, J = 9,3 Hz), 7,35 – 7,45 (2H, m), 7,57 (1H, s), 7,95 (1H, s), 8,04 (1H, d, J = 9,3 Hz), 10,58 (1H, s), 11,08 (1H, s).

Ejemplo 190

Producción de N–(6–{3–[(3–hidroxi–3–metilbutanoil)amino] fenoxi}imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



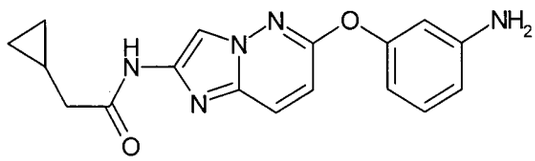
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,323 mmol), ácido 3–hidroxi–3–metilbutanoico (57 mg, 0,485 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (99 mg, 0,517 mmol), 1–hidroxibenzotriazol (71 mg, 0,522 mmol), trietilamina (0,08 mL, 0,549 mmol) y N,N–dimetilformamida (4,0 mL), y por reacción de la misma manera que en el Ejemplo 187, se obtuvo el compuesto del título (22 mg, 16%) en forma de cristales de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,21 (6H, s), 1,90 – 2,00 (1H, m), 2,41 (2H, s), 4,69 (1H, s), 6,90 – 6,95 (1H, m), 7,03 (1H, d, J = 9,4 Hz), 7,30 – 7,45 (2H, m), 7,55 – 7,60 (1H, m), 7,96 (1H, s), 8,04 (1H, d, J = 9,4 Hz), 9,97 (1H, s), 11,09 (1H, s).

987

Ejemplo 191

Producción de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–ciclopropilacetamida



Una mezcla de 2–ciclopropil–N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (501 mg, 1,46 mmol), 3–aminofenol (479 mg, 4,39 mmol), carbonato de potasio (807 mg, 5,84 mmol) y N,N–dimetilformamida (5 mL) se agitó a 120 °C durante 12 h. Se añadieron tetrahidrofurano/acetato de etilo y salmuera saturada a la mezcla de reacción, y el material insoluble se filtró. El filtrado se extrajo con acetato de etilo, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 20/80→0/100) para dar el compuesto del título (156 mg, 33%) en forma de un polvo de color amarillo pálido.

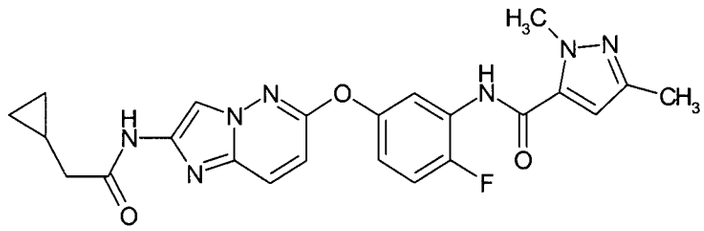
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,10 – 0,25 (2H, m), 0,45 – 0,55 (2H, m), 1,00 – 1,10 (1H, m), 2,25 (2H, d, J = 7,2 Hz), 5,31 (2H, s), 6,30 (1H, d, J = 8,1 Hz), 6,35 (1H, s), 6,43 (1H, d, J = 8,1 Hz), 6,95 (1H, d, J = 9,6 Hz), 7,05 (1H, t, J = 8,1 Hz), 7,99 (1H, d, J = 9,6 Hz), 8,03 (1H, s), 10,70 (1H, s).

Ejemplo 192

Producción de N–[5–({2–[(ciclopropilacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–

988

carboxamida

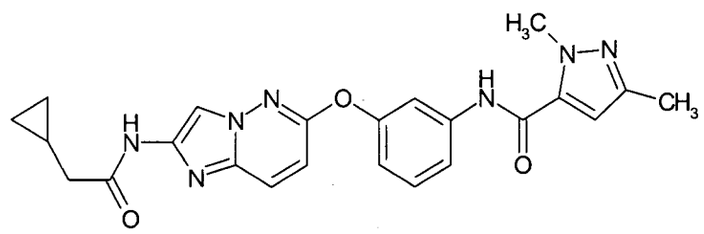


Usando 2–ciclopropil–N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (171 mg, 0,5 mmol), N–(2–fluoro–5–hidroxifenil)–1,3–dimetil–1H–pirazol–5–carboxamida (150 mg, 0,6 mmol), carbonato de potasio (104 mg, 0,75 mmol) y N,N–dimetilformamida (4 mL), y por reacción de la misma manera que en el Ejemplo 191, se obtuvo el compuesto del título (53 mg, 23%) en forma de cristales de color rosado pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,10 – 0,20 (2H, m), 0,40 – 0,50 (2H, m), 1,00 – 1,15 (1H, m), 2,19 (3H, s), 2,24 (2H, d, J = 7,2 Hz), 3,97 (3H, s), 6,84 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,40 (1H, t, J = 9,6 Hz), 7,50 – 7,60 (1H, m), 7,98 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 10,09 (1H, s), 10,68 (1H, s).

Ejemplo 193

Producción de N–[3–({2–[(ciclopropilacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



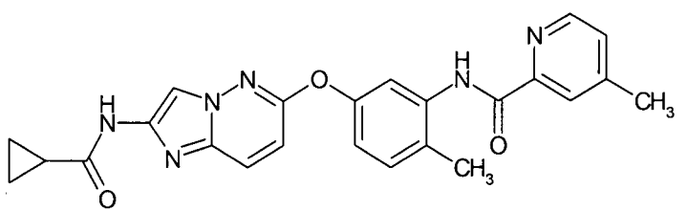
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–

ciclopropilacetamida (100 mg, 0,309 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (64 mg, 0,404 mmol) y N,N–dimetilacetamida (5,0 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (85 mg, 62%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,15 – 0,25 (2H, m), 0,40 – 0,50 (2H, m), 1,00 – 1,15 (1H, m), 2,19 (3H, s), 2,25 (2H, d, J = 6,9 Hz), 3,97 (3H, s), 6,82 (1H, s), 7,00 (1H, d, J = 8,1 Hz), 7,05 (1H, d, J = 9,6 Hz), 7,42 (1H, t, J = 8,1 Hz), 7,60 (1H, d, J = 8,1 Hz), 7,67 (1H, s), 8,02 (1H, s), 8,05 – 8,10 (1H, m), 10,23 (1H, s), 10,70 (1H, s).

Ejemplo 194

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metilpiridin–2–carboxamida



Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (120 mg, 0,371 mmol), ácido 4–metilpiridin–2–carboxílico (76 mg, 0,557 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (114 mg, 0,594 mmol), 1–hidroxibenzotriazol (81 mg, 0,600 mmol), trietilamina (0,09 mL, 0,631 mmol) y N,N–dimetilformamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 187, se obtuvo el compuesto del título (40

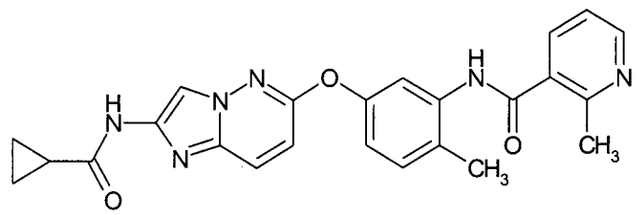
990

mg, 24%) en forma de cristales de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75–0,85 (4H, m), 1,85–2,00 (1H, m), 2,35 (3H, s), 2,44 (3H, s), 7,00 – 7,10 (2H, m), 7,34 (1H, d, J = 8,7 Hz), 7,50 – 7,55 (1H, m), 7,85 – 8,00 (3H, m), 8,02 (1H, d, J = 9,3 Hz), 8,58 (1H, d, J = 4,8 Hz), 10,31 (1H, s), 11,07 (1H, s).

Ejemplo 195

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2–metilnicotinamida



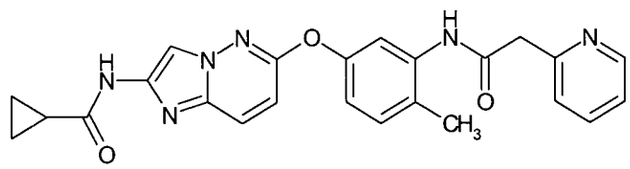
Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (120 mg, 0,371 mmol), ácido 2–metilpiridin–3–carboxílico (76 mg, 0,557 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (114 mg, 0,594 mmol), 1–hidroxibenzotriazol (81 mg, 0,600 mmol), trietilamina (0,09 mL, 0,631 mmol) y N,N–dimetilformamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 187, se obtuvo el compuesto del título (52 mg, 31%) en forma de cristales de color rosado pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75–0,85 (4H, m), 1,85 – 1,95 (1H, m), 2,30 (3H, s), 2,59 (3H, s), 7,00 – 7,10 (2H, m), 7,30 – 7,35 (2H, m), 7,40 – 7,45 (1H, m), 7,85 – 7,90 (1H, m), 7,93 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 8,54 (1H, d, J = 3,0 Hz), 9,98 (1H, s), 11,06 (1H, s).

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Ejemplo 196

Producción de N–(6–{4–metil–3–[(piridin–2–ilacetil)amino]fenoxi}imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (120 mg, 0,371 mmol) y clorhidrato de ácido piridin–2–ilacético (129 mg, 0,742 mmol) en N,N–dimetilformamida (4,0 mL) se añadieron gota a gota trietilamina (0,21 mL, 1,484 mmol) y cianofosfato de dietilo (0,12 mL, 0,816 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. Bajo enfriamiento con hielo, se le añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→95/5) y se recristalizó en acetato de etilo para dar el compuesto del título (67 mg, 41%) en forma de cristales de color amarillo pálido.

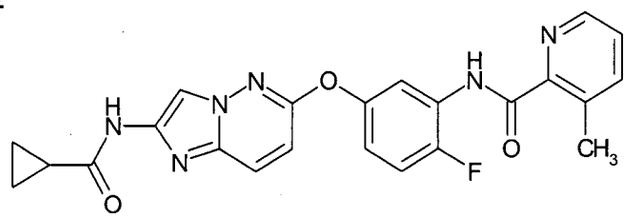
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,90–2,00 (1H, m), 2,25 (3H, s), 3,90 (2H, s), 6,90 – 7,00 (1H, m), 7,00 (1H, d, J = 9,6 Hz), 7,20 – 7,30 (2H, m), 7,40 (1H, t, J = 7,8 Hz), 7,50 – 7,55 (1H, m), 7,70 – 7,80 (1H, m), 7,91 (1H, s), 7,99 (1H, d, J = 9,6 Hz),

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8,50 – 8,55 (1H, m), 9,79 (1H, s), 11,05 (1H, s).

Ejemplo 197

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metilpiridin–2–carboxamida



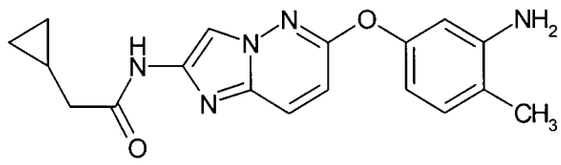
Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,611 mmol), ácido 3–metilpiridin–2–carboxílico (126 mg, 0,917 mmol), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (187 mg, 0,978 mmol), 1–hidroxibenzotriazol (133 mg, 0,988 mmol), trietilamina (0,14 mL, 1,039 mmol) y N,N–dimetilformamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 187, se obtuvo el compuesto del título (128 mg, 47%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,90 (4H, m), 1,85 – 2,00 (1H, m), 2,63 (3H, s), 7,05 – 7,20 (2H, m), 7,35 – 7,50 (1H, m), 7,50 – 7,60 (1H, m), 7,84 (1H, d, J = 7,5 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,9 Hz), 8,10 – 8,15 (1H, m), 8,55 – 8,60 (1H, m), 10,57 (1H, s), 11,07 (1H, s).

Ejemplo 198

Producción de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]–2–ciclopropilacetamida

993

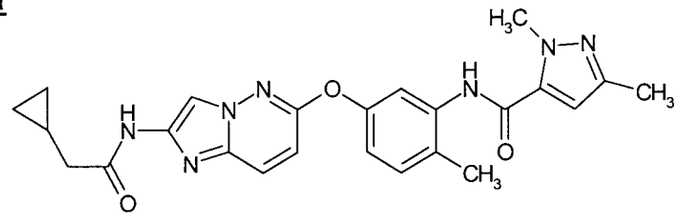


Usando 2–ciclopropil–N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (300 mg, 0,877 mmol), 3–amino–4–metilfenol (216 mg, 1,754 mmol), carbonato de potasio (182 mg, 1,316 mmol) y N,N–dimetilformamida (3 mL), y por reacción de la misma manera que en el Ejemplo 191, se obtuvo el compuesto del título (138 mg, 47%) en forma de un polvo anaranjado.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,15 – 0,25 (2H, m), 0,40 – 0,50 (2H, m), 1,00 – 1,10 (1H, m), 2,05 (3H, s), 2,25 (2H, d, J = 6,9 Hz), 5,07 (2H, s), 6,28 (1H, d, J = 7,5 Hz), 6,42 (1H, s), 6,90 – 7,00 (2H, m), 7,97 (1H, d, J = 9,6 Hz), 8,01 (1H, s), 10,68 (1H, s).

Ejemplo 199

Producción de N–[5–({2–[(ciclopropilacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]–2–ciclopropilacetamida (120 mg, 0,356 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (59 mg, 0,374 mmol) y N,N–dimetilacetamida (4,0 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (99 mg, 61%) en forma de un polvo

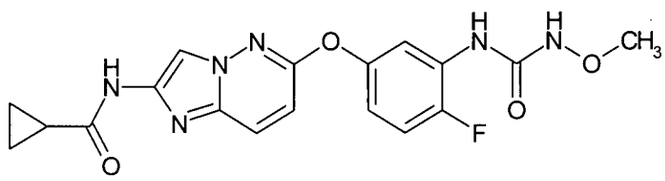
994

de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,15 – 0,25 (2H, m), 0,40 – 0,50 (2H, m), 1,00 – 1,15 (1H, m), 2,19 (3H, s), 2,25 – 2,30 (5H, m), 3,97 (3H, s), 6,80 (1H, s), 7,04 (1H, d, J = 9,8 Hz), 7,05 – 7,15 (1H, m), 7,25 – 7,30 (1H, m), 7,34 (1H, d, J = 8,1 Hz), 7,98 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 9,80 (1H, s), 10,68 (1H, s).

Ejemplo 200

Producción de N–[6–(4–fluoro–3–{[(metoxiamino)carbonil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



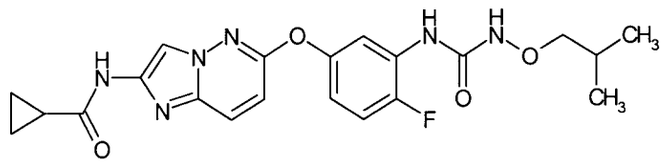
Una solución de 1,1'–carbonildiimidazol (297 mg, 1,833 mmol), cloruro de O–metilhidroxiamonio (153 mg, 1,833 mmol) y trietilamina (0,25 mL, 1,833 mmol) en N,N–dimetilformamida (4,0 mL) se agitó a temperatura ambiente durante 30 min. Una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,611 mmol) en N,N–dimetilformamida (2,0 mL) también se agregó a la mezcla, y la mezcla se agitó a temperatura ambiente durante 2 días. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se recristalizó en

tetrahidrofurano/etanol para dar el compuesto del título (67 mg, 27%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,85 – 2,00 (1H, m), 3,63 (3H, s), 6,95 – 7,05 (1H, m), 7,05 (1H, d, J = 9,3 Hz), 7,25 – 7,40 (1H, m), 7,70 – 7,75 (1H, m), 7,93 (1H, s), 8,03 (1H, d, J = 9,3 Hz), 8,55 (1H, s), 9,76 (1H, s), 11,07 (1H, s).

Ejemplo 201

Producción de N–[6–(4–fluoro–3–{[(isobutoxiamino)carbonil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida

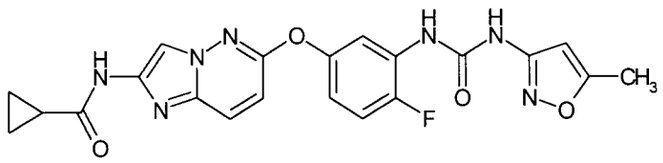


Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,611 mmol), 1,1'–carbonildiimidazol (297 mg, 1,833 mmol), clorhidrato de 1–(aminooxi)–2–metilpropano (230 mg, 1,833 mmol), trietilamina (0,25 mL, 1,833 mmol) y N,N–dimetilformamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 200, se obtuvo el compuesto del título (170 mg, 63%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 0,92 (6H, d, J = 6,9 Hz), 1,85–2,00 (1H, m), 3,58 (2H, d, J = 6,9 Hz), 6,95 – 7,05 (1H, m), 7,04 (1H, d, J = 9,9 Hz), 7,33 (1H, t, J = 9,9 Hz), 7,80 – 7,90 (1H, m), 7,92 (1H, s), 8,02 (1H, d, J = 9,9 Hz), 8,31 (1H, s), 9,80 (1H, s), 11,06 (1H, s).

Ejemplo 202

Producción de N–{6–[4–fluoro–3–({[(5–metilisoxazol–3–il)amino]carbonil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



A una solución de piridina (475 mg, 6 mmol) y 3–amino–5–metilisoxazol (147 mg, 1,5 mmol) en N,N–dimetilformamida (2,0 mL) se añadió gota a gota una solución de clorocarbonato de fenilo (235 mg, 1,5 mmol) en N,N–dimetilformamida (2,0 mL) bajo enfriamiento con hielo. Después de agitar la mezcla a temperatura ambiente durante 2 h, se añadió N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol) a la mezcla, y la mezcla se agitó a 80 °C durante 15 h y a 100 °C durante 2 h. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice básica (acetato de etilo/hexano = 80/20→100/0) y se recristalizó en tetrahidrofurano/etanol para dar el compuesto del título (101 mg, 22%) en forma de cristales incoloros.

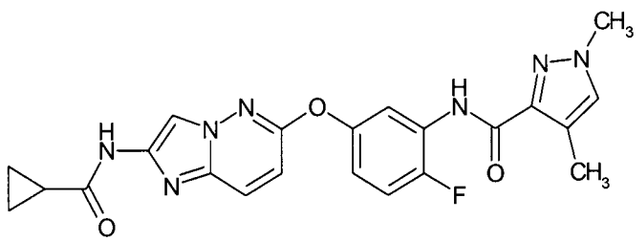
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,90 (4H, m), 1,85 –

994

2,00 (1H, m), 2,34 (3H, s), 6,48 (1H, s), 6,90 – 7,00 (1H, m), 7,04 (1H, d, J = 9,3 Hz), 7,35 (1H, t, J = 9,9 Hz), 7,90 (1H, s), 8,03 (1H, d, J = 9,3 Hz), 9,00 (1H, br s), 9,85 (1H, br s), 11,06 (1H, s).

Ejemplo 203

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,4–dimetil–1H–pirazol–3–carboxamida



A una suspensión de 1,4–dimetil–1H–pirazol–3–carboxílico (151 mg, 1,08 mmol) en tetrahidrofurano (2,0 mL) se añadieron N,N–dimetilformamida (1 gota) y cloruro de tionilo (0,08 mL, 1,1 mmol), y la mezcla se agitó a temperatura ambiente durante 50 min. La mezcla de reacción se concentró a presión reducida y se disolvió en N,N–dimetilacetamida (2,0 mL). Por otro lado, a una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol) en N,N–dimetilacetamida (6,0 mL) se añadió gota a gota la solución antes mencionada bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 2 h. Bajo enfriamiento con hielo, se añadió solución acuosa de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio

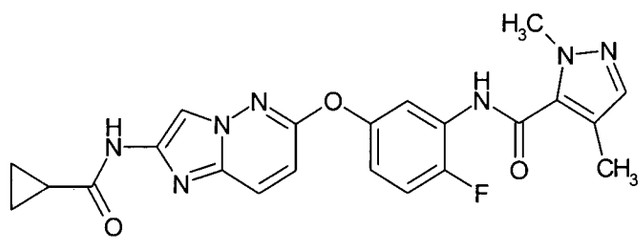
998

anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice básica (acetato de etilo/hexano = 80/20→100/0) y se recristalizó en tetrahidrofurano/etanol para dar el compuesto del título (283 mg, 63%) en forma de cristales de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75–0,85 (4H, m), 1,85–2,00 (1H, m), 2,21 (3H, s), 3,89 (3H, s), 7,05–7,15 (2H, m), 7,38 (1H, t, J = 9,6 Hz), 7,65 (1H, s), 7,90–8,00 (2H, m), 8,03 (1H, d, J = 9,6 Hz), 9,40 (1H, s), 11,06 (1H, s).

Ejemplo 204

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,4–dimetil–1H–pirazol–5–carboxamida



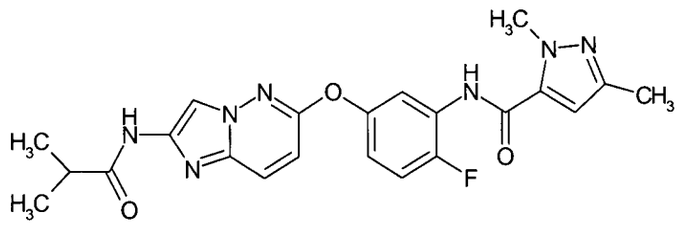
Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol), ácido 1,4–dimetil–1H–pirazol–5–carboxílico (154 mg, 1,1 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (1 gota), cloruro de tionilo (0,08 mL, 1,1 mmol) y N,N–dimetilacetamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 203, se obtuvo el compuesto del título (300 mg, 67%) en forma de cristales de color amarillo pálido.

999

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,85 – 2,00 (1H, m), 2,19 (3H, s), 3,90 (3H, s), 7,07 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,33 (1H, s), 7,40 (1H, t, J = 9,6 Hz), 7,75 – 7,80 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,06 (1H, s), 11,06 (1H, s).

Ejemplo 205

Producción de N–(2–fluoro–5–{[2–(isobutirilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1,3–dimetil–1H–pirazol–5–carboxamida



Usando clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol), cloruro de 2–metilpropanoílo (53 mg, 0,50 mmol) y N,N–dimetilacetamida (5,0 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (98 mg, 45%) en forma de cristales de color azul pálido.

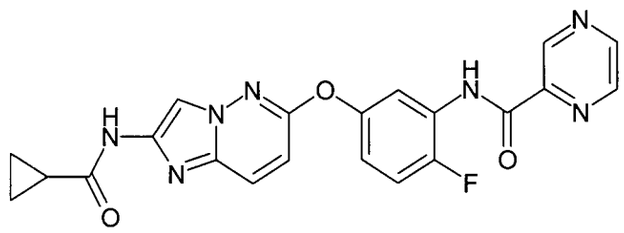
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,08 (6H, d, J = 6,9 Hz), 2,19 (3H, s), 2,65 – 2,75 (1H, m), 3,97 (3H, s), 6,84 (1H, s), 7,06 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,40 (1H, t, J = 9,6 Hz), 7,50 – 7,60 (1H, m), 7,98 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 10,09 (1H, s), 10,72 (1H, s).

Ejemplo 206

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

1000

b]piridazin–6–il}oxi)–2–fluorofenil]pirazin–2–carboxamida

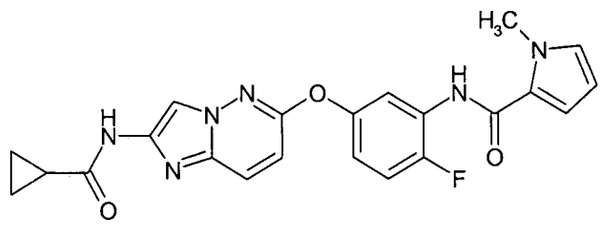


Usando una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol) y cloruro de 2–pirazincarbonilo (171 mg, 1,2 mmol) en N,N–dimetilacetamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (113 mg, 26%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,85 (4H, m), 1,85 – 2,00 (1H, m), 7,09 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,44 (1H, t, J = 9,6 Hz), 7,90 – 8,00 (2H, m), 8,05 (1H, d, J = 9,6 Hz), 8,83 (1H, s), 8,96 (1H, s), 9,28 (1H, s), 10,44 (1H, s), 11,07 (1H, s).

Ejemplo 207

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirrol–2–carboxamida



Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol), cloruro

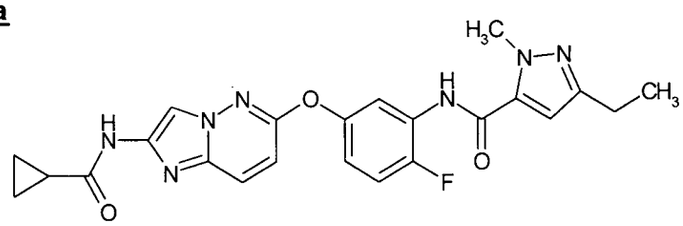
1002

de 1–metil–1H–pirrol–2–carbonilo (151 mg, 1,05 mmol) y N,N–dimetilacetamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 148, se obtuvo el compuesto del título (268 mg, 62%) en forma de cristales incoloros.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,90 – 2,00 (1H, m), 3,84 (3H, s), 6,05 – 6,10 (1H, m), 7,00 – 7,20 (4H, m), 7,35 (1H, t, J = 9,6 Hz), 7,50 – 7,60 (1H, m), 7,93 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,63 (1H, s), 11,06 (1H, s).

Ejemplo 208

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etil–1–metil–1H–pirazol–5–carboxamida



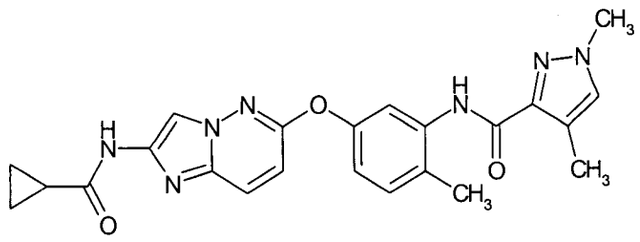
Usando N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (327 mg, 1,0 mmol), ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (170 mg, 1,1 mmol) tetrahidrofurano (2,0 mL), N,N–dimetilformamida (1 gota), cloruro de tionilo (0,08 mL, 1,1 mmol) y N,N–dimetilacetamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 203, se obtuvo el compuesto del título (256 mg, 55%) en forma de cristales incoloros. Punto de fusión 236 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,19 (3H, t, J = 7,5 Hz), 1,90 – 2,00 (1H, m), 2,56 (2H, q, J = 7,5 Hz), 3,98 (3H,

s), 6,89 (1H, s), 7,06 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,39 (1H, t, J = 9,6 Hz), 7,50 – 7,55 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 11,07 (1H, s).

Ejemplo 209

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,4–dimetil–1H–pirazol–3–carboxamida



Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (323 mg, 1,0 mmol), ácido 1,4–dimetil–1H–pirazol–3–carboxílico (154 mg, 1,1 mmol) tetrahidrofurano (2,0 mL), N,N–dimetilformamida (1 gota), cloruro de tionilo (0,08 mL, 1,1 mmol) y N,N–dimetilacetamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 203, se obtuvo el compuesto del título (208 mg, 47%) en forma de cristales de color amarillo pálido.

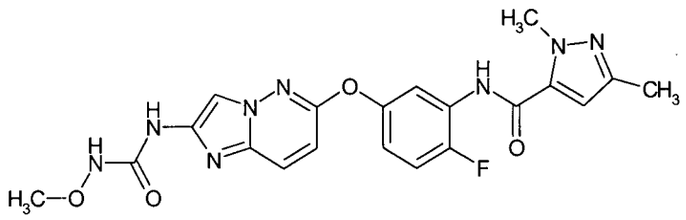
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,85 – 2,00 (1H, m), 2,20 (3H, s), 2,28 (3H, s), 3,88 (3H, s), 6,95 – 7,05 (1H, m), 7,02 (1H, d, J = 9,6 Hz), 7,30 (1H, d, J = 8,7 Hz), 7,63 (1H, s), 7,65 – 7,70 (1H, m), 7,93 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,28 (1H, s), 11,06 (1H, s).

Ejemplo 210

Producción de N–{2–fluoro–5–[(2–{[(metoxiamino)carbonil]

1003

amino}imidazo[1,2-b]piridazin-6-il)oxi]fenil}-1,3-dimetil-1H-pirazol-5-carboxamida

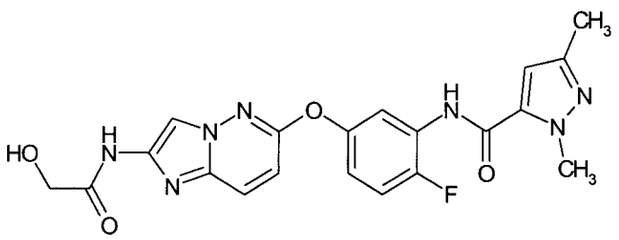


Usando clorhidrato de N-{5-[(2-aminoimidazo[1,2-b]piridazin-6-il)oxi]-2-fluorofenil}-1,3-dimetil-1H-pirazol-5-carboxamida (200 mg, 0,48 mmol), 1,1'-carbonilimidazol (233 mg, 1,44 mmol), cloruro de O-metilhidroxiamonio (120 mg, 1,44 mmol), trietilamina (0,27 mL, 1,92 mmol) y N,N-dimetilformamida (6,0 mL), y por reacción de la misma manera que en el Ejemplo 200, se obtuvo el compuesto del título (117 mg, 54%) en forma de cristales de color amarillo pálido.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 2,19 (3H, s), 3,60 (3H, s), 3,97 (3H, s), 6,84 (1H, s), 7,05 (1H, d, J = 9,6 Hz), 7,15 – 7,25 (1H, m), 7,39 (1H, t, J = 9,0 Hz), 7,50 – 7,55 (1H, m), 7,83 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 9,46 (1H, s), 9,67 (1H, s), 10,09 (1H, s).

Ejemplo 211

Producción de N-(2-fluoro-5-{[2-(glicoloilamino)imidazo[1,2-b]piridazin-6-il]oxi}fenil)-1,3-dimetil-1H-pirazol-5-carboxamida



A N-[5-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-

1004

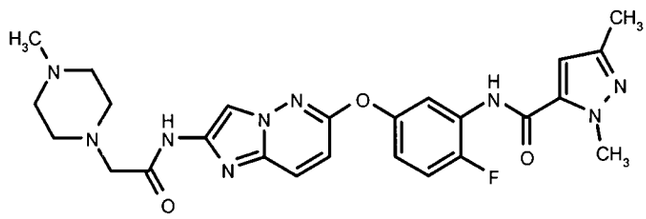
6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (507 mg, 1,13 mmol) se añadió solución metanólica al 10% de cloruro de hidrógeno (30 mL), y la mezcla se agitó a 50 °C durante 23 h. El solvente se evaporó a presión reducida. Al residuo se añadieron ácido acetoxiacético (242 mg, 2,05 mmol), clorhidrato de 1–(3–dimetilaminopropil)–3–etilcarbodiimida (336 mg, 1,75 mmol), 1–hidroxibenzotriazol (167 mg, 1,24 mmol), N–etildiisopropilamina (0,60 mL, 3,51 mmol) y N,N–dimetilformamida (10 mL), y la mezcla se agitó a temperatura ambiente durante 62 h. Se añadieron metanol (10 mL), agua (10 mL) y solución acuosa saturada de carbonato de sodio (2 mL) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró a presión reducida. Se le añadió una solución acuosa saturada de hidrógeno–carbonato de sodio 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 concentró a presión reducida. El residuo se separó y se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 0/100→100/0→metanol/acetato de etilo = 2/98) y se cristalizó en etanol para dar el compuesto del título (94 mg, 19%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,98 (3H, s), 4,05 (2 H, d, J = 6,0 Hz), 5,51 (1H, t, J = 6,0 Hz), 6,85 (1H, s), 7,11 (1H, d, J = 9,8 Hz), 7,18 – 7,27 (1H, m), 7,41 (1H, m), 7,55 (1H, dd, J = 6,4, 3,0 Hz), 8,01 (1H, s), 8,07 (1H, d, J = 9,0 Hz), 10,11 (1H, s), 10,23 (1H, s).

1005.

Ejemplo 212

Producción de diclorhidrato de N–{2–fluoro–5–[(2–{[(4–metilpiperazin–1–il)acetil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1,3–dimetil–1H–pirazol–5–carboxamida



2HCl

A N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (1,05 mg, 2,33 mmol) se añadió solución metanólica al 10% de cloruro de hidrógeno (120 mL), y la mezcla se agitó a 50 °C durante 44 h. El solvente se evaporó a presión reducida. A una mitad del residuo se añadieron ácido (4–metilpiperazin–1–il)acético (205 mg, 1,30 mmol), clorhidrato de 1–(3–dimetilaminopropil)–3–etilcarbodiimida (284 mg, 1,48 mmol), 1–hidroxibenzotriazol (167 mg, 1,24 mmol), N–etildiisopropilamina (0,60 mL, 3,51 mmol) y N,N–dimetilformamida (10 mL), y la mezcla se agitó a temperatura ambiente durante 11 h. Una solución acuosa saturada de hidrógeno–carbonato de sodio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 0/100→70/30) y la fracción objeto se concentró a presión reducida. El residuo se disolvió en

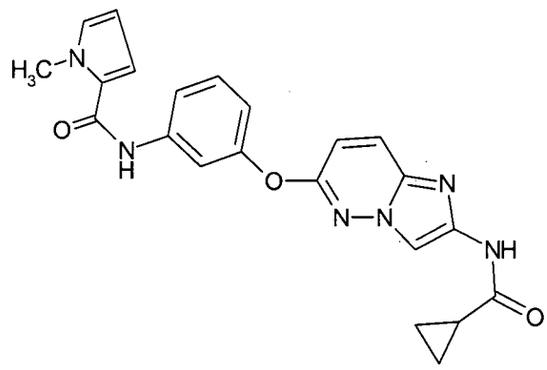
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metanol y se trató con una solución de cloruro de hidrógeno 4 N–acetato de etilo para dar el compuesto del título (43 mg, 6%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 2,78 (3H, s), 3,21 (1H, brs), 3,34 (1H, brs), 3,67 (1H, br), 3,98 (3H, s), 6,87 (1H, s), 7,13 (1H, d, J = 9,5 Hz), 7,18 – 7,27 (1H, m), 7,41 (1H, t, J = 9,7 Hz), 7,51 – 7,60 (1H, m), 8,02 (1H, s), 8,09 (1H, d, J = 9,5 Hz), 10,13 (1H, s), 11,03 (1H, s).

Ejemplo 213

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–1H–pirrol–2–carboxamida



Usando ácido 1–metil–1H–pirrol–2–carboxílico (97 mg, 0,78 mmol), tetrahidrofurano(4,0 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (135 μL, 1,55 mmol), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (133 mg, 49%) en forma de un polvo blanco.

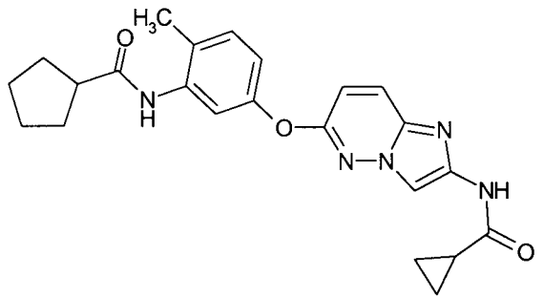
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,88 –

100 f

1,96 (1H, m), 3,85 (3H, s), 6,09 (1H, dd, J = 3,9, 2,7 Hz), 6,91 – 6,95 (1H, m), 7,01 – 7,07 (3H, m), 7,35 – 7,41 (1H, m), 7,58 – 7,62 (1H, m), 7,66 – 7,68 (1H, m), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 9,87 (1H, s), 11,09 (1H, s).

Ejemplo 214

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]ciclopentancarboxamida

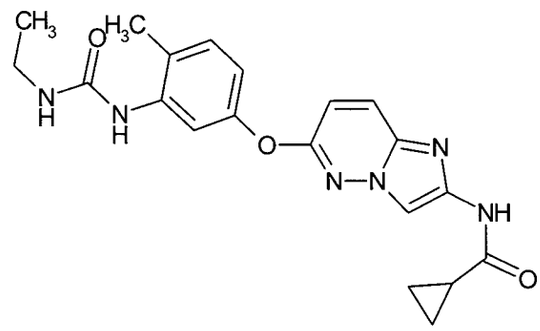


Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), N,N–dimetilacetamida (3,0 mL) y cloruro de ciclopentancarbonilo (90 μL, 0,74 mmol), y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (119 mg, 46%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,83 (4H, m), 1,48 – 1,96 (9H, m), 2,22 (3H, s), 2,82 – 2,93 (1H, m), 6,97 (1H, dd, J = 8,4, 2,6 Hz), 7,01 (1H, d, J = 9,6 Hz), 7,26 (1H, d, J = 8,4 Hz), 7,37 (1H, d, J = 2,6 Hz), 7,93 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 9,24 (1H, s), 11,07 (1H, s).

Ejemplo 215

Producción de N–[6–(3–{[(etilamino)carbonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida

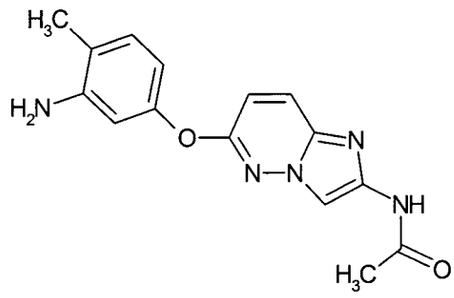


A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) en piridina (4,0 mL) se añadió isocianato de etilo (490 μL, 6,19 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. El solvente se evaporó a presión reducida y se añadió agua al residuo. La mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo/etanol y se filtró para dar el compuesto del título (142 mg, 58%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,04 (3H, t, J = 7,1 Hz), 1,86 – 1,95 (1H, m), 2,19 (3H, s), 3,02 – 3,14 (2H, m), 6,64 – 6,75 (2H, m), 6,98 (1H, d, J = 9,6 Hz), 7,16 (1H, d, J = 8,1 Hz), 7,71 (1H, s), 7,86 (1H, d, J = 2,7 Hz), 7,93 (1H, s), 8,00 (1H, d, J = 9,6 Hz), 11,07 (1H, s).

Ejemplo 216

Producción de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]acetamida



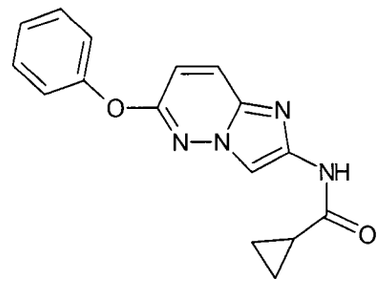
A una solución de 3–amino–4–metilfenol (1,22 g, 9,93 mmol) en N,N–dimetilformamida (25,0 mL) se añadió tert-butóxido de potasio (1,16 g, 10,3 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. A la mezcla de reacción se le añadieron N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (2,5 g, 8,28 mmol) y carbonato de potasio (0,57 g, 4,14 mmol), y la mezcla se agitó a 140 °C durante 16 h. Se añadió salmuera saturada a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo) y el residuo obtenido se lavó con hexano/acetato de etilo, y se filtró para dar el compuesto del título (1,04 g, 42%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,05 (3H, s), 2,07 (3H, s), 5,06 (2H, s), 6,28 (1H, d, J = 8,1, 2,4 Hz), 6,42 (1H, d, J = 2,4 Hz), 6,94 (1H, d, J = 9,6 Hz), 6,95 (1H, d, J = 8,1 Hz), 7,97 (1H, d, J = 8,1 Hz), 7,98 (1H, s), 10,78 (1H, s).

Ejemplo 217

Producción de N–(6–fenoxiimidazo[1,2–b]piridazin–2–

il)ciclopropancarboxamida

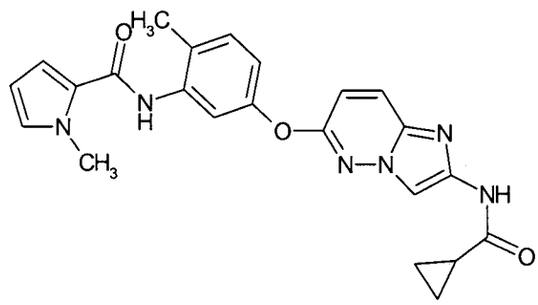


Usando fenol (69 mg, 0,73 mmol), N,N–dimetilformamida (25,0 mL), tert-butóxido de potasio (1,16 g, 10,3 mmol), N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (200 mg, 0,61 mmol) y carbonato de potasio (42 mg, 0,31 mmol), y de la misma manera que en el Ejemplo 216, se obtuvo el compuesto del título (98 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 7,03 (1H, d, J = 9,6 Hz), 7,23 – 7,29 (3H, m), 7,42 – 7,49 (2H, m), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 11,06 (1H, s).

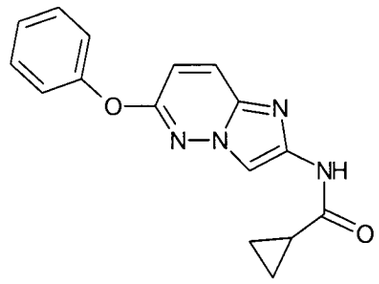
Ejemplo 218

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirrol–2–carboxamida



Usando ácido 1–metil–1H–pirrol–2–carboxílico (93 mg, 0,74 mmol), tetrahidrofurano (4,0 mL), N,N–dimetilformamida (30 μL, 0,39

il)ciclopropancarboxamida

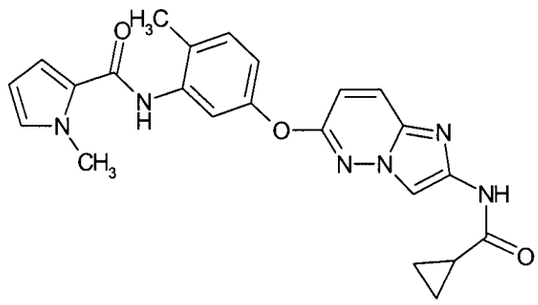


Usando fenol (69 mg, 0,73 mmol), N,N–dimetilformamida (25,0 mL), tert-butóxido de potasio (1,16 g, 10,3 mmol), N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (200 mg, 0,61 mmol) y carbonato de potasio (42 mg, 0,31 mmol), y de la misma manera que en el Ejemplo 216, se obtuvo el compuesto del título (98 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 7,03 (1H, d, J = 9,6 Hz), 7,23 – 7,29 (3H, m), 7,42 – 7,49 (2H, m), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 11,06 (1H, s).

Ejemplo 218

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirrol–2–carboxamida



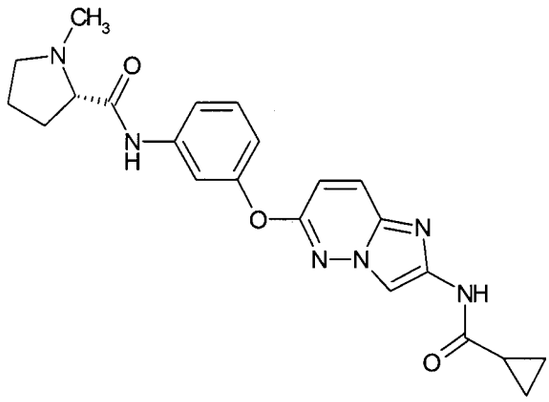
Usando ácido 1–metil–1H–pirrol–2–carboxílico (93 mg, 0,74 mmol), tetrahidrofurano (4,0 mL), N,N–dimetilformamida (30 μL, 0,39

mmol), cloruro de oxalilo (135 μL, 1,48 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (15 mg, 6%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,87 – 1,95 (1H, m), 2,25 (3H, s), 3,84 (3H, s), 6,06 – 6,09 (1H, m), 6,96 – 7,03 (3H, m), 7,03 (1H, d, J = 9,6 Hz), 7,26 – 7,32 (2H, m), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,35 (1H, s), 11,07 (1H, s).

Ejemplo 219

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–metil–L–prolinamida



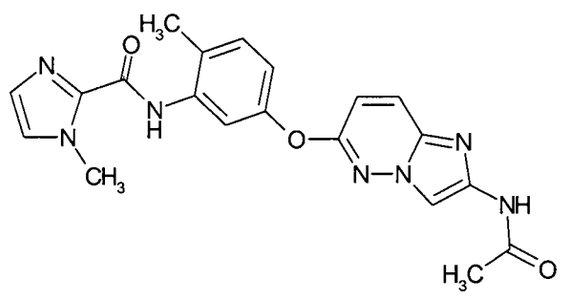
A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropilcarboxamida (200 mg, 0,65 mmol) en N,N–dimetilformamida (4,0 mL) se añadieron 1–metil–L–prolina (167 mg, 1,29 mmol), hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N'N'–tetrametiluronio (736 mg, 1,94 mmol), hidroxibenzotriazol (262 mg, 1,94 mmol) y N,N–diisopropiletilamina (338 μL, 1,94 mmol), y la

mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/etanol = 8/1), y el residuo obtenido se recristalizó en acetato de etilo para dar el compuesto del título (86 mg, 32%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,68 – 1,84 (3H, m), 1,87 – 1,95 (1H, m), 2,06 – 2,18 (1H, m), 2,25 – 2,36 (1H, m), 2,32 (3H, s), 2,85 – 2,92 (1H, m), 3,05 – 3,13 (1H, m), 6,91 – 6,95 (1H, m), 7,03 (1H, d, J = 9,8 Hz), 7,32 – 7,39 (1H, m), 7,54 – 7,58 (1H, m), 7,65 – 7,68 (1H, m), 7,95 (1H, s), 8,03 (1H, d, J = 9,8 Hz), 9,81 (1H, s), 11,08 (1H, s).

Ejemplo 220

Producción de N–(5–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–metilfenil)–1–metil–1H–imidazol–2–carboxamida



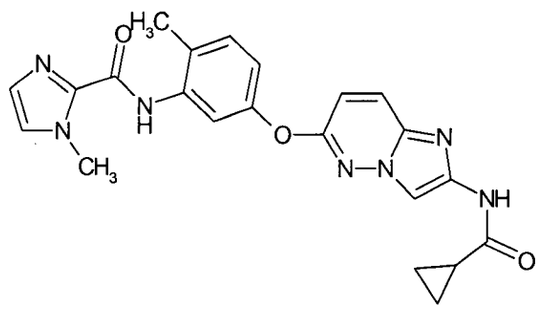
A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (150 mg, 0,50 mmol) en N,N–

dimetilformamida (3,0 mL) se añadieron ácido 1–metil–1H–imidazol–2–carboxílico (127 mg, 1,01 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (290 mg, 1,51 mmol) y 1–hidroxibenzotriazol (205 mg, 1,51 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo obtenido se recristalizó en acetato de etilo/etanol para dar el compuesto del título (115 mg, 56%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,05 (3H, s), 2,30 (3H, s), 3,97 (3H, s), 6,96 – 7,09 (3H, m), 7,33 (1H, d, J = 8,4 Hz), 7,45 (1H, s), 7,68 (1H, d, J = 2,4 Hz), 7,95 (1H, s), 8,02 (1H, d, J = 9,9 Hz), 9,77 (1H, s), 10,78 (1H, s).

Ejemplo 221

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–imidazol–2–carboxamida



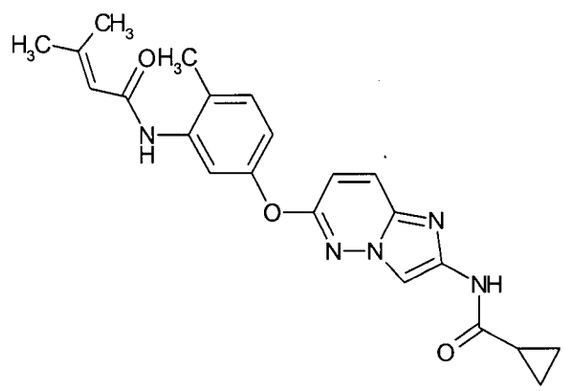
A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) en

N,N–dimetilformamida (3,0 mL) se añadieron ácido 1–metil–1H–imidazol–2–carboxílico (117 mg, 0,93 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (267 mg, 1,39 mmol) y 1–hidroxibenzotriazol (188 mg, 1,39 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo obtenido se lavó con acetato de etilo/hexano para dar el compuesto del título (66 mg, 32%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,85 – 1,96 (1H, m), 2,30 (3H, s), 3,96 (3H, s), 6,98 – 7,03 (2H, m), 7,07 (1H, d, J = 9,5 Hz), 7,32 (1H, d, J = 8,4 Hz), 7,42 (1H, s), 7,68 (1H, d, J = 2,7 Hz), 7,93 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,76 (1H, s), 11,06 (1H, s).

Ejemplo 222

Producción de N–(6–{4–metil–3–[(3–metilbut–2–enoil)amino]fenoxi}imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida



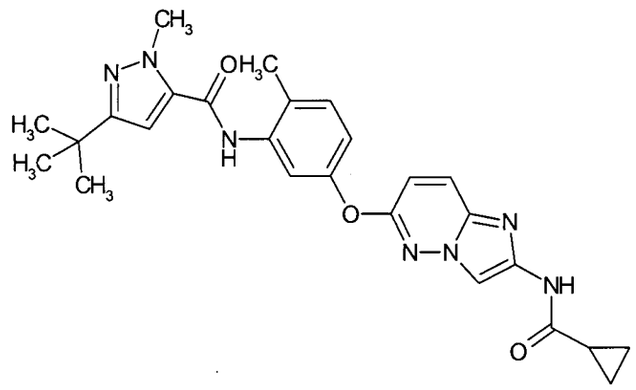
P006

Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), N,N–dimetilacetamida (2,0 mL) y cloruro de 3,3–dimetilacriloílo (83 μL, 0,74 mmol), y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (142 mg, 57%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,84 (4H, m), 1,86 (3H, s), 1,87 – 1,93 (1H, m), 2,11 (3H, s), 2,22 (3H, s), 5,99 (1H, s), 6,94 (1H, dd, J = 8,3, 2,6 Hz), 7,01 (1H, d, J = 9,6 Hz), 7,25 (1H, d, J = 8,3 Hz), 7,49 (1H, d, J = 2,6 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,14 (1H, s), 11,05 (1H, s).

Ejemplo 223

Producción de 3–tert-butil–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirazol–5–carboxamida



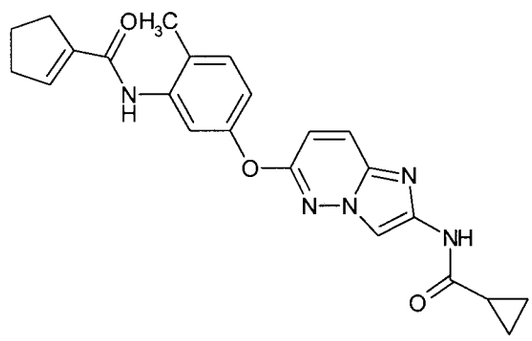
Usando ácido 3–tert-butil–1–metil–1H–pirazol–5–carboxílico (61 mg, 0,33 mmol), tetrahidrofurano (1,8 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (44 μL, 0,50 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (90 mg, 0,28 mmol) y N,N–

dimetilacetamida (1,8 mL), y de la misma manera que en el Ejemplo 119, se obtuvo el compuesto del título (55 mg, 41%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,83 (4H, m), 1,27 (9H, s), 1,86 – 1,94 (1H, m), 2,25 (3H, s), 3,99 (3H, s), 6,92 (1H, s), 7,04 (1H, d, J = 9,5 Hz), 7,09 (1H, dd, J = 8,4, 2,4 Hz), 7,25 (1H, d, J = 2,4 Hz), 7,34 (1H, d, J = 8,4 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,84 (1H, s), 11,07 (1H, s).

Ejemplo 224

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]ciclopent–1–en–1–carboxamida



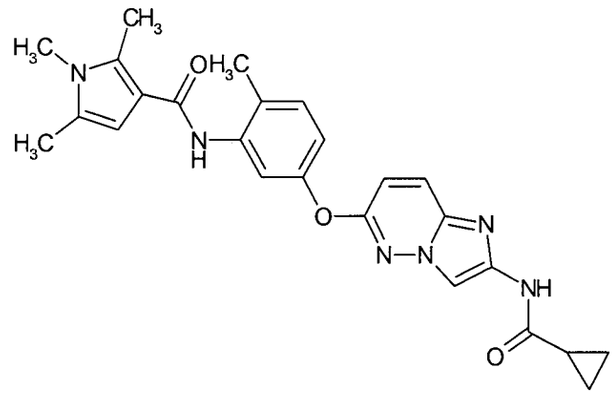
Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), N,N–dimetilacetamida (4,0 mL), ácido 1–ciclopentencarboxílico (139 mg, 1,24 mmol), hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N'N'–tetrametiluronio (704 mg, 1,86 mmol), 1–hidroxibenzotriazol (251 mg, 1,86 mmol) y N,N–diisopropiletilamina (323 μL, 1,86 mmol), y de la misma manera que en el Ejemplo 219, se obtuvo el compuesto del título (69 mg, 21%) en forma de un polvo blanco.

1018

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,84 – 1,95 (3H, m), 2,21 (3H, s), 2,40 – 2,61 (4H, m), 6,67 – 6,70 (1H, m), 7,00 – 7,04 (2H, m), 7,23 – 7,30 (2H, m), 7,91 (1H, s), 8,01 (1H, d, J = 9,3 Hz), 9,18 (1H, s), 11,06 (1H, s).

Ejemplo 225

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,2,5–trimetil–1H–pirrol–3–carboxamida



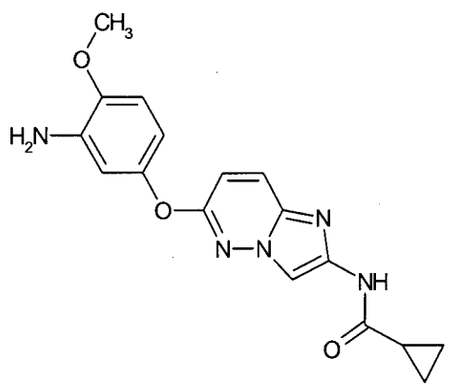
A una solución de ácido 1,2,5–trimetilpirrol–3–carboxílico (142 mg, 0,93 mmol) en tetrahidrofurano (4,0 mL) se añadieron N,N–dimetilformamida (20 µL, 0,26 mmol) y cloruro de oxalilo (108 µL, 1,24 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y trietilamina (259 µL, 1,86 mmol) en N,N–dimetilacetamida (4,0 mL), y la mezcla se agitó a 50 °C durante 16 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El

solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/3→acetato de etilo solo), se lavó con hexano/acetato de etilo y se filtró para dar el compuesto del título (68 mg, 24%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,83 (4H, m), 1,86 – 1,94 (1H, m), 2,17 (3H, s), 2,23 (3H, s), 2,44 (3H, s), 3,37 (3H, s), 6,35 (1H, s), 6,96 (1H, dd, J = 8,1, 2,4 Hz), 7,01 (1H, d, J = 9,6 Hz), 7,26 (1H, d, J = 8,1 Hz), 7,36 (1H, d, J = 2,4 Hz), 7,92 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 8,73 (1H, s), 11,05 (1H, s).

Ejemplo 226

Producción de N–[6–(3–amino–4–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



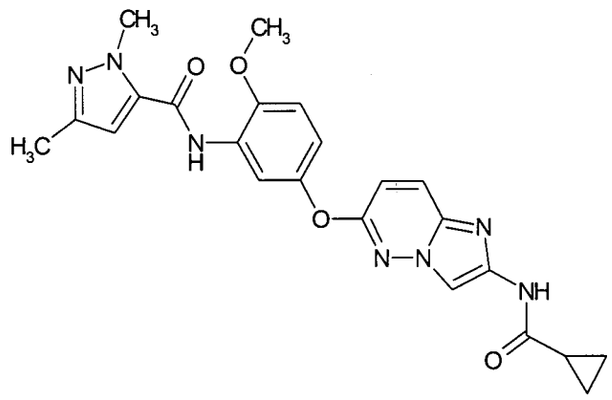
Usando 3–amino–4–metoxifenol (408 mg, 2,93 mmol), N,N–dimetilformamida (16 mL), tert-butóxido de potasio (343 mg, 3,05 mmol), N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (800 mg, 2,44 mmol) y carbonato de potasio (169 mg, 1,22 mmol), y de la misma manera que en el Ejemplo 216, se obtuvo el compuesto del título (1,04 g, 42%) en forma de un polvo color café.

1020

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,86 – 1,94 (1H, m), 3,77 (3H, s), 4,95 (2H, s), 6,33 (1H, dd, J = 8,7, 2,9 Hz), 6,46 (1H, d, J = 2,9 Hz), 6,79 (1H, d, J = 8,7 Hz), 6,91 (1H, d, J = 9,6 Hz), 7,93 (1H, s), 7,96 (1H, d, J = 9,6 Hz), 11,04 (1H, s).

Ejemplo 227

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metoxifenil]–1,3–dimetil–1H–pirazol–5–carboxamida



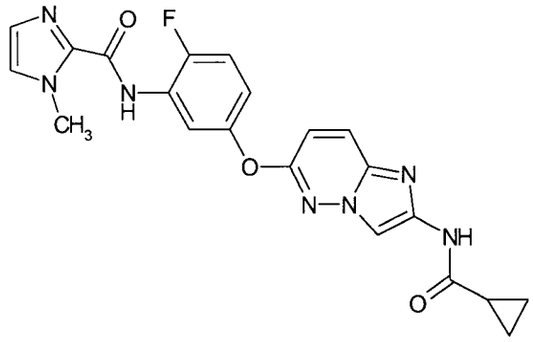
Usando N–[6–(3–amino–4–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,59 mmol), N,N–dimetilacetamida (4,0 mL) y cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (113 mg, 0,71 mmol), y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (146 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,87 – 1,96 (1H, m), 2,19 (3H, s), 3,88 (3H, s), 3,97 (3H, s), 6,82 (1H, s), 7,03 (1H, d, J = 9,6 Hz), 7,07 – 7,19 (2H, m), 7,70 (1H, d, J = 3,0 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,35 (1H, s), 11,06 (1H, s).

1024

Ejemplo 228

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–imidazol–2–carboxamida



A una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) en N,N–dimetilformamida (4,0 mL) se añadieron ácido 1–metil–1H–imidazol–2–carboxílico (154 mg, 1,22 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (351 mg, 1,83 mmol) y 1–hidroxibenzotriazol (248 mg, 1,83 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo obtenido se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo) para dar el compuesto del título (31 mg, 12%) en forma de un polvo blanco.

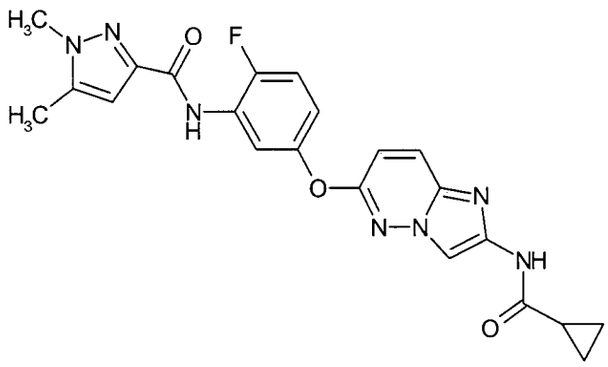
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,86 – 1,96 (1H, m), 3,97 (3H, s), 7,03 – 7,17 (3H, m), 7,37 – 7,48 (2H, m),

1022

7,88 (1H, dd, J = 6,5, 2,9 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,9 Hz), 9,91 (1H, s), 11,07 (1H, s).

Ejemplo 229

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,5–dimetil–1H–pirazol–3–carboxamida



A una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) en N,N–dimetilformamida (4,0 mL) se le añadieron 1,5–dimetil–1H–pirazol–3–carboxílico (171 mg, 1,22 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (351 mg, 1,83 mmol), 1–hidroxibenzotriazol (248 mg, 1,83 mmol) y trietilamina (256 μL, 1,83 mmol), y la mezcla se agitó a 60°C durante 36 h. Se le añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo obtenido se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/1→acetato de etilo solo) para dar el compuesto del título (72 mg, 26%) en forma de

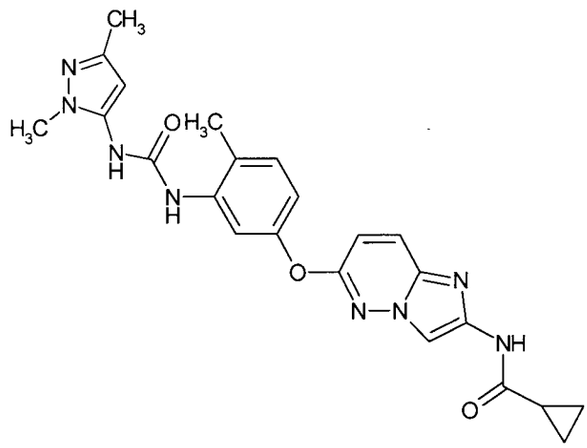
1023

un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,82 (4H, m), 1,87 – 1,96 (1H, m), 2,30 (3H, s), 3,84 (3H, s), 6,57 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,07 – 7,14 (1H, m), 7,35 – 7,43 (1H, m), 7,89 (1H, dd, J = 6,3, 3,0 Hz), 7,95 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 9,46 (1H, s), 11,08 (1H, s).

Ejemplo 230

Producción de N–{6–[3–({[(1,3–dimetil–1H–pirazol–5–il)amino]carbonil}amino)–4–metilfenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



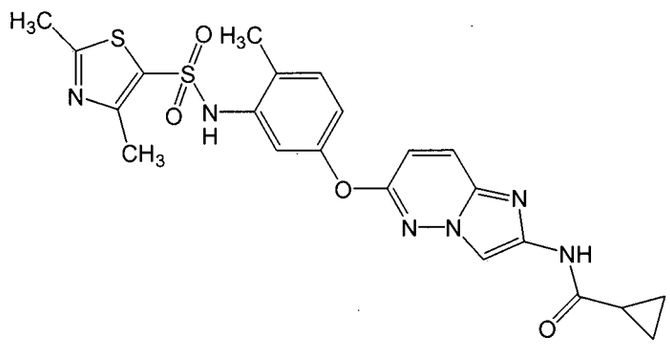
A una solución de 1,3–dimetil–1H–pirazol–5–amina (104 mg, 0,93 mmol) en N,N–dimetilformamida (4,0 mL) se añadió N,N–carbonildiimidazol (150 mg, 0,93 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. A la mezcla de reacción se añadió N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano,

se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (etanol/acetato de etilo = 1/20→1/10) para dar el compuesto del título (58 mg, 20%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,82 (4H, m), 1,87 – 1,95 (1H, m), 2,05 (3H, s), 2,27 (3H, s), 3,59 (3H, s), 5,94 (1H, s), 6,83 (1H, dd, J = 8,0, 2,6 Hz), 7,00 (1H, d, J = 9,5 Hz), 7,24 (1H, d, J = 8,4 Hz), 7,80 (1H, d, J = 2,6 Hz), 7,92 (1H, s), 8,00 (1H, d, J = 9,5 Hz), 8,25 (1H, s), 8,99 (1H, s), 11,05 (1H, s).

Ejemplo 231

Producción de N–[6–(3–{[(2,4–dimetil–1,3–tiazol–5–il)sulfonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) en piridina (4,0 mL) se añadió cloruro de 2,4–dimetil–1,3–tiazol–5–sulfonilo (157 mg, 0,74 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción, y la

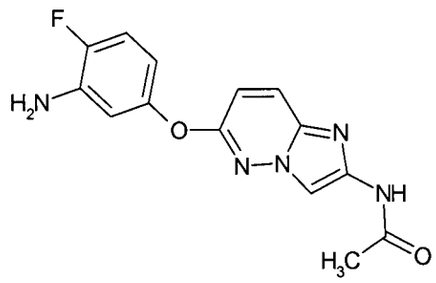
L025

mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/1→acetato de etilo solo) y se lavó con hexano/acetato de etilo para dar el compuesto del título (196 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,88 – 1,95 (1H, m), 2,07 (3H, s), 2,20 (3H, s), 2,55 (3H, s), 6,92 (1H, d, J = 2,7 Hz), 7,01 (1H, d, J = 9,8 Hz), 7,07 – 7,12 (1H, dd, J = 8,4, 2,7 Hz), 7,27 (1H, d, J = 8,4 Hz), 7,93 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 10,10 (1H, s), 11,08 (1H, s).

Ejemplo 232

Producción de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida



A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)acetamida (12 g, 39,7 mmol) en N,N–dimetilformamida (120 mL) se añadieron 3–amino–4–fluorofenol (7,6 g, 59,6 mmol) y carbonato de potasio (11,0 g, 79,5 mmol), y la mezcla se agitó a 140°C durante 12 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió

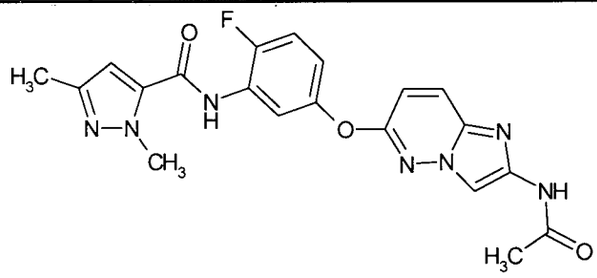
P026

agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/1→acetato de etilo solo) para dar el compuesto del título (9,5 g, 79%) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,07 (3H, s), 5,36 (2H, s), 6,30 – 6,37 (1H, m), 6,58 (1H, dd, J = 7,8, 2,7 Hz), 6,97 (1H, d, J = 9,6 Hz), 6,98 – 7,06 (1H, m), 7,99 (1H, d, J = 9,6 Hz), 8,00 (1H, s), 10,78 (1H, s).

Ejemplo 233

Producción de N–(5–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–fluorofenil)–1,3–dimetil–1H–pirazol–5–carboxamida



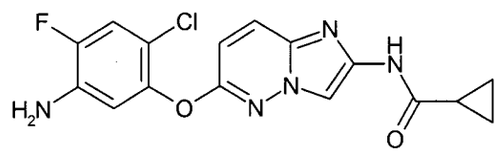
A una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (5,6 g, 18,6 mmol) en N,N–dimetilacetamida (44,8 mL) se añadió cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (3,25 g, 20,4 mmol). Tras agitar a temperatura ambiente durante 2 h, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se

filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo/etanol para dar el compuesto del título (6,1 g, 78%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,06 (3H, s), 2,19 (3H, s), 3,97 (3H, s), 6,85 (1H, s),7,07 (1H, d, J = 9,6 Hz), 7,17 – 7,25 (1H, m), 7,34 – 7,44 (1H, m), 7,50 – 7,58 (1H, m), 7,96 (1H, s), 8,04 (1H, d), 10,10 (1H, s), 10,79 (1H, s).

Ejemplo 234

Producción de N–[6–(5–amino–2–cloro–4–fluorofenoxi) imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (600 mg, 1,83 mmol) en N,N–dimetilformamida (12 mL) se le añadieron 3–amino–6–cloro–4–fluorofenol (443 mg, 2,74 mmol) y carbonato de potasio (505 mg, 3,66 mmol). De la misma manera que en el Ejemplo 232, se obtuvo el compuesto del título (372 mg, 56%) en forma de un polvo color café.

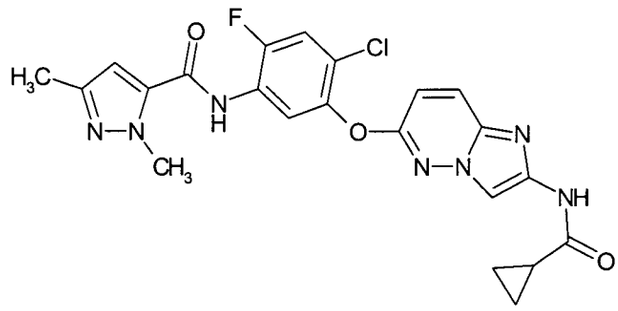
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,83 (4H, m), 1,87 – 1,95 (1H, m), 5,56 (2H, s), 6,74 (1H, d, J = 8,4 Hz), 7,07 (1H, d, J = 9,5 Hz), 7,34 (1H, d, J = 10,5 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,5 Hz), 11,07 (1H, s).

Ejemplo 235

Producción de N–[4–cloro–5–({2–[(ciclopropilcarbonil)

1028

amino]imidazo[1,2-b]piridazin-6-il}oxi)-2-fluorofenil]-1,3-dimetil-1H-pirazol-5-carboxamida

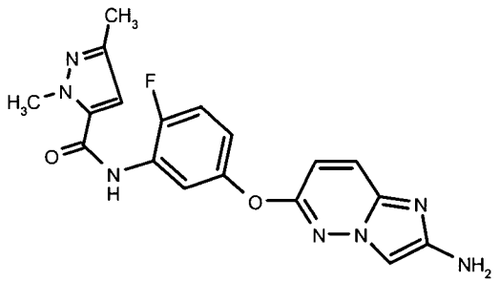


Usando N-[6-(5-amino-2-cloro-4-fluorofenoxi)imidazo[1,2-b]piridazin-2-il]ciclopropancarboxamida (200 mg, 0,55 mmol), N,N-dimetilacetamida (4,0 mL) y cloruro de 1,3-dimetil-1H-pirazol-5-carbonilo (105 mg, 0,66 mmol), y de la misma manera que en el Ejemplo 120, se obtuvo el compuesto del título (108 mg, 40%) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,78 – 0,84 (4H, m), 1,85 – 1,96 (1H, m), 2,19 (3H, s), 3,97 (3H, s), 6,84 (1H, s), 7,16 (1H, d, J = 9,6 Hz), 7,74 – 7,81 (2H, m), 7,90 (1H, s), 8,08 (1H, d, J = 9,6 Hz), 10,19 (1H, s), 11,07 (1H, s).

Ejemplo 236

Producción de clorhidrato de N-{5-[(2-aminoimidazo[1,2-b]piridazin-6-il)oxi]-2-fluorofenil}-1,3-dimetil-1H-pirazol-5-carboxamida



HCl

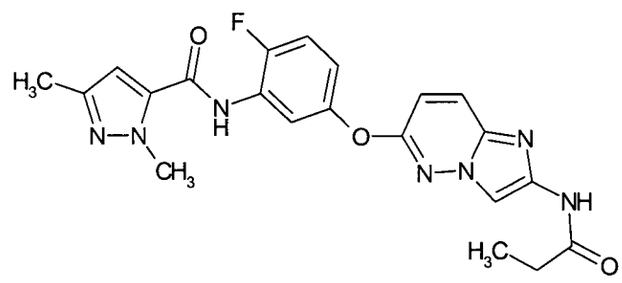
1029

A una suspensión de N–[4–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida (2,0 g, 4,72 mmol) en metanol (20 mL) se le añadió solución de ácido clorhídrico 4 N/acetato de etilo (16 mL). Tras agitar a temperatura ambiente durante 4 h, la mezcla se agitó a 50 °C durante 12 h. El solvente se evaporó a presión reducida, y éter diisopropílico/etanol (8 mL/2 mL) se añadió al residuo. La mezcla se agitó a temperatura ambiente durante 2 h. El precipitado se recogió por filtración y se lavó con éter diisopropílico para dar el compuesto del título (2,0 g, cuant.) en forma de un polvo color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 3,98 (3H, s), 6,91 (1H, s), 7,18 – 7,26 (1H, m), 7,37 (1H, d, J = 9,6 Hz), 7,39 – 7,48 (2H, m), 7,54 – 7,60 (1H, m), 8,20 (1H, d, J = 9,6 Hz), 10,24 (1H, s).

Ejemplo 237

Producción de N–(2–fluoro–5–{[2–(propionilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–

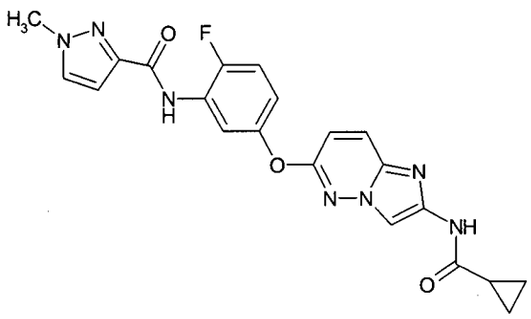
1030

carboxamida (200 mg, 0,48 mmol) en N,N–dimetilacetamida (2,0 mL) se le añadió cloruro de propionilo (49,9 μL, 0,57 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. Se le añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/1→acetato de etilo solo) y se lavó con acetato de etilo para dar el compuesto del título (78 mg, 37%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,06 (3H, t, J = 7,5 Hz), 2,19 (3H, s), 2,37 (2H, q, J = 7,5 Hz), 3,98 (3H, s), 6,85 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,18 – 7,24 (1H, m), 7,37 – 7,44 (1H, m), 7,55 (1H, dd, J = 6,3, 3,3 Hz), 7,98 (1H, s), 8,08 (1H, d, J = 9,6 Hz), 10,11 (1H, s), 10,74 (1H, s).

Ejemplo 238

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–3–carboxamida

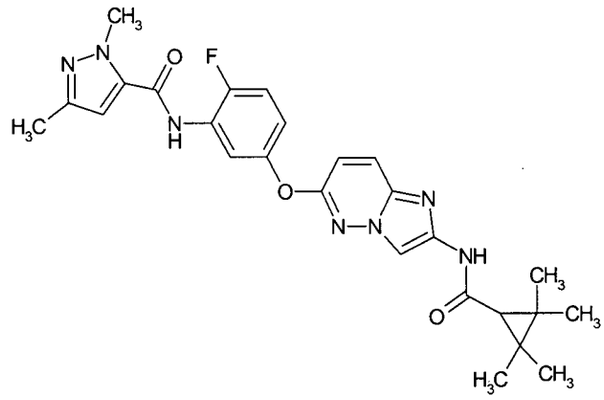


A una solución de ácido 1–metil–1H–pirazol–3–carboxílico (115 mg, 0,92 mmol) en tetrahidrofurano (4,0 mL) se le añadieron N,N–dimetilformamida (20 µL, 0,26 mmol) y cloruro de oxalilo (80 µL, 0,92 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) en N,N–dimetilacetamida (4,0 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida y etanol (10 mL) se añadió al residuo. La mezcla se agitó con calentamiento a 75 °C y se enfrió hasta temperatura ambiente, y el precipitado se recogió por filtración para dar el compuesto del título (144 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,87 – 1,97 (1H, m), 3,97 (3H, s), 6,77 (1H, d, J = 2,4 Hz), 7,06 – 7,16 (2H, m), 7,36 – 7,43 (1H, m), 7,82 – 7,89 (2H, m), 7,95 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 9,59 (1H, s), 11,08 (1H, s).

Ejemplo 239

Producción de N–{2–fluoro–5–[(2–{[(2,2,3,3–tetrametilciclopropil) carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de ácido 2,2,3,3–tetrametilciclopropancarboxílico (102 mg, 0,72 mmol) en tetrahidrofurano (4,0 mL) se añadieron N,N–dimetilformamida (20 μL, 0,26 mmol) y cloruro de oxalilo (63 μL, 0,72 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) en N,N–dimetilacetamida (4,0 mL), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/1) y se precipitó en hexano/acetato de etilo para dar el compuesto del título (46 mg, 19%) en forma de un polvo blanco.

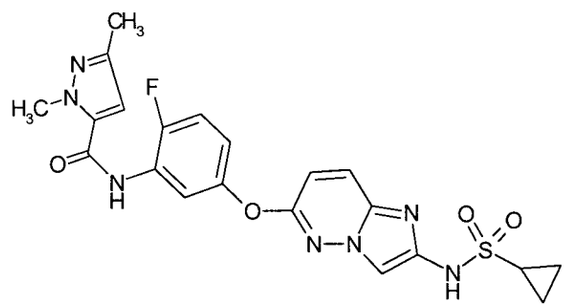
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,16 (6H, s), 1,22 (6H, s), 1,47 (1H, s), 2,19 (3H, s), 3,97 (3H, s), 6,83 (1H, s), 7,04 (1H, d, J = 9,5

L033

Hz), 7,17 – 7,22 (1H, m), 7,34 – 7,42 (1H, m), 7,51 – 7,55 (1H, m), 7,95 (1H, s), 8,01 (1H, d, J = 9,5 Hz), 10,09 (1H, s), 11,70 (1H, s).

Ejemplo 240

Producción de N–[5–({2–[(ciclopropilsulfonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida



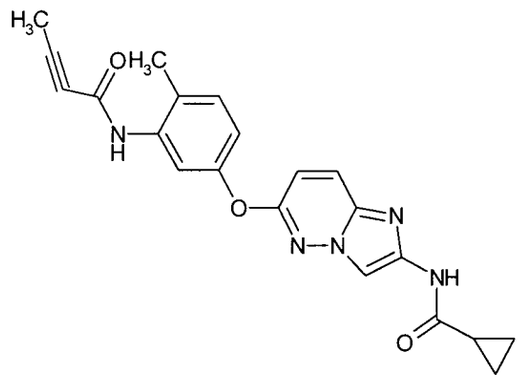
A una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (400 mg, 0,97 mmol) en 1–metil–2–pirrolidona (4,0 mL) se añadieron trietilamina (404 µL, 2,90 mmol) y cloruro de ciclopropansulfonilo (204 mg, 1,45 mmol), y la mezcla se agitó a 70 °C durante 16 h. Tras enfriar la mezcla hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo) y se precipitó en hexano/acetato de etilo para dar el compuesto del título (74 mg, 16%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,92 – 1,03 (4H, m), 2,19 (3H, s), 2,75 – 2,86 (1H, m), 3,97 (3H, s), 6,84 (1H, s), 7,10 (1H, d, J =

9,6 Hz), 7,18 – 7,25 (1H, m), 7,36 – 7,43 (1H, m), 7,52 – 7,56 (1H, m), 7,63 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,09 (1H, s), 10,30 (1H, s).

Ejemplo 241

Producción de N–{6–[3–(but–2–inoilamino)–4–metilfenoxi] imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



Usando ácido 2–butinoico (78 mg, 0,93 mmol), tetrahidrofurano (4,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (81 μL, 0,93 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 238, se obtuvo el compuesto del título (47 mg, 20%) en forma de un polvo blanco.

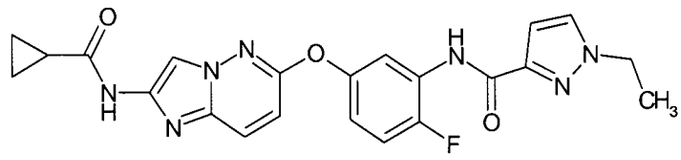
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,85 – 1,95 (1H, m), 2,03 (3H, s), 2,21 (3H, s), 6,96 – 7,04 (2H, m), 7,25 – 7,29 (2H, m), 7,92 (1H, s), 8,10 (1H, d, J = 9,3 Hz), 10,05 (1H, s), 11,05 (1H, s).

Ejemplo 242

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

1035

b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–3–carboxamida

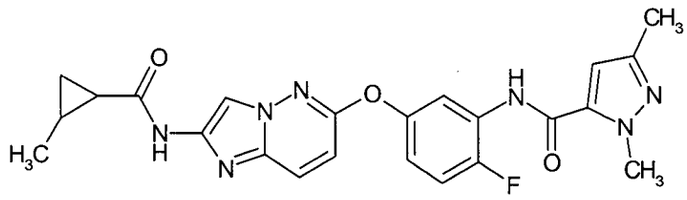


Usando ácido 1–etil–1H–pirazol–3–carboxílico (128 mg, 0,92 mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (80 μL, 0,92 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 238, se obtuvo el compuesto del título (111 mg, 40%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,44 (3H, t, J = 7,2 Hz), 1,87 – 1,97 (1H, m), 4,26 (2H, q, J = 7,2 Hz), 6,77 (1H, d, J = 2,1 Hz), 7,07 (1H, d, J = 9,6 Hz), 7,09 – 7,16 (1H, m), 7,39 (1H, dd, J = 11,4, 8,7 Hz), 7,84 (1H, dd, J = 6,5, 2,9 Hz), 7,91 – 7,96 (2H, m), 8,04 (1H, d, J = 9,6 Hz), 9,57 (1H, s), 11,07 (1H, s).

Ejemplo 243

Producción de N–{2–fluoro–5–[(2–{[(2–metilciclopropil) carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1,3–dimetil–1H–pirazol–5–carboxamida



Usando ácido 2–metilciclopropancarboxílico (72 mg, 0,72

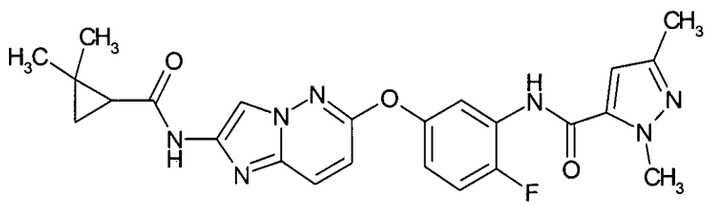
1636

mmol), tetrahidrofurano (2,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (63 μL, 0,72 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 239, se obtuvo el compuesto del título (55 mg, 25%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,72 (1H, m), 0,95 – 1,05 (1H, m), 1,06 – 1,09 (3H, m), 1,18 – 1,27 (1H, m), 1,64 – 1,73 (1H, m), 2,19 (3H, s), 3,98 (3H, s), 6,84 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,09 – 7,24 (1H, m), 7,36 – 7,43 (1H, m), 7,52 – 7,56 (1H, m), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 10,99 (1H, s).

Ejemplo 244

Producción de N–{5–[(2–{[(2,2–dimetilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida



Usando ácido 2,2–dimetilciclopropancarboxílico (82 mg, 0,72 mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (63 μL, 0,72 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–

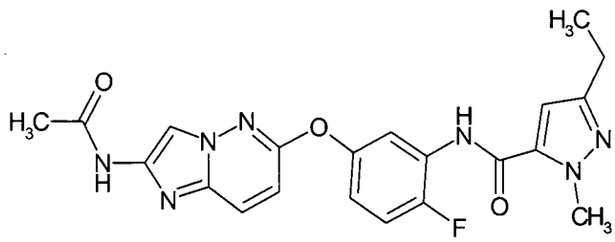
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dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 239, se obtuvo el compuesto del título (37 mg, 16%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 1,27 (2H, m), 1,12 (3H, s), 1,14 (3H, s), 1,75 – 1,84 (1H, m), 2,19 (3H, s), 3,97 (3H, s), 6,83 (1H, s), 7,05 (1H, d, J = 8,7 Hz), 7,16 – 7,24 (1H, m), 7,35 – 7,42 (1H, m), 7,50 – 7,55 (1H, m), 7,95 (1H, s), 8,03 (1H, d, J = 8,7 Hz), 10,09 (1H, s), 10,90 (1H, s).

Ejemplo 245

Producción de N–(5–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–fluorofenil)–3–etil–1–metil–1H–pirazol–5–carboxamida



Usando ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (215 mg, 1,39 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (122 μL, 1,39 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (300 mg, 1,00 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 238, se obtuvo el compuesto del título (219 mg, 50%) en forma de un polvo blanco.

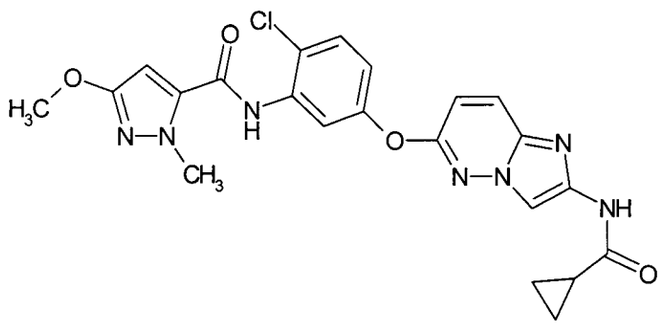
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,19 (3H, t, J = 7,5 Hz), 2,06 (3H, s), 2,55 (2H, q, J = 7,5 Hz), 3,99 (3H, s), 6,89 (1H, s), 7,07 (1H, d, J = 9,6 Hz), 7,18 – 7,25 (1H, m), 7,36 – 7,43 (1H, m), 7,52 – 7,56

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(1H, m), 7,95 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 10,10 (1H, s), 10,78 (1H, s).

Ejemplo 246

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida

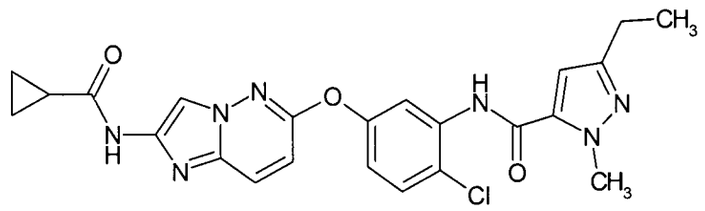


Usando ácido 3–metoxi–1–metil–1H–pirazol–5–carboxílico (191 mg, 1,22 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (107 μL, 1,22 mmol), N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,87 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 238, se obtuvo el compuesto del título (259 mg, 62%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,87 (4H, m), 1,86 – 1,99 (1H, m), 3,79 (3H, s), 3,91 (3H, s), 6,47 (1H, s), 7,09 (1H, d, J = 9,9 Hz), 7,23 – 7,28 (1H, m), 7,49 – 7,53 (1H, m), 7,62 (1H, d, J = 8,7 Hz), 7,94 (1H, s), 8,05 (1H, d, J = 9,9 Hz), 10,05 (1H, s), 11,07 (1H, s).

Ejemplo 247

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–etil–1–metil–1H–pirazol–5–carboxamida

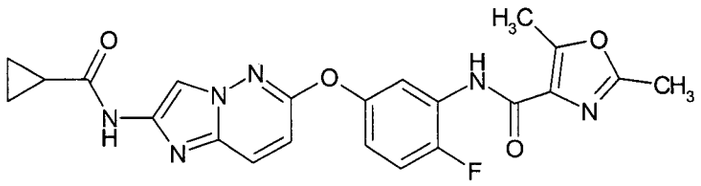


Usando ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (188 mg, 1,22 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 µL, 0,39 mmol), cloruro de oxalilo (107 µL, 1,22 mmol), N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,87 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 238, se obtuvo el compuesto del título (268 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,19 (3H, t, J = 7,7 Hz), 1,84 – 1,97 (1H, m), 2,55 (2H, q, J = 7,7 Hz), 3,99 (3H, s), 6,88 (1H, s), 7,09 (1H, d, J = 9,6 Hz), 7,25 (1H, dd, J = 8,7, 2,9 Hz), 7,53 (1H, d, J = 2,9 Hz), 7,62 (1H, d, J = 8,7 Hz), 7,95 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,00 (1H, s), 11,07 (1H, s).

Ejemplo 248

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,5–dimetil–1,3–oxazol–4–carboxamida

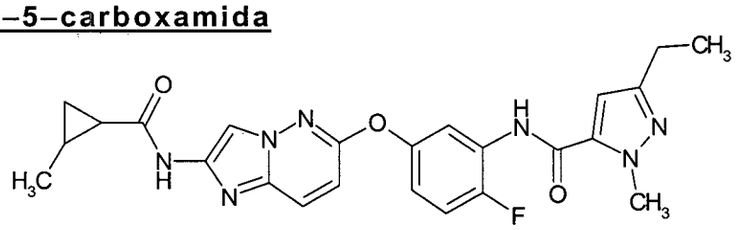


A una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) en N,N–dimetilacetamida (4,0 mL) se añadió cloruro de 2,5–dimetil–1,3–oxazol–4–carbonilo (127 mg, 0,79 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió agua a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con etanol para dar el compuesto del título (198 mg, 72%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,86 – 1,97 (1H, m), 2,45 (3H, s), 2,55 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,08 – 7,15 (1H, m), 7,35 – 7,42 (1H, m), 7,87 (1H, dd, J = 6,5, 2,9 Hz), 7,93 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,48 (1H, s), 11,06 (1H, s).

Ejemplo 249

Producción de 3–etil–N–{2–fluoro–5–[(2–{[(2–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1–metil–1H–pirazol–5–carboxamida



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A una solución de ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (158 mg, 1,03 mmol) en tetrahidrofurano (3,8 mL) se añadieron N,N–dimetilformamida (20 µL, 0,26 mmol) y cloruro de oxalilo (90 µL, 1,03 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida (250 mg, 0,73 mmol) en N,N–dimetilacetamida (5,0 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo) y se recristalizó en hexano/acetato de etilo para dar el compuesto del título (201 mg, 57%) en forma de un polvo blanco.

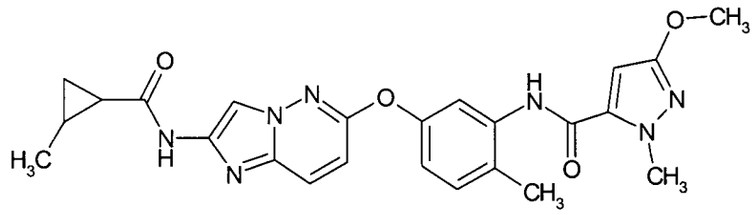
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,71 (1H, m), 0,95 – 1,04 (1H, m), 1,06 – 1,10 (3H, m), 1,19 (3H, t, J = 7,7 Hz), 1,17 – 1,29 (1H, m), 1,61 – 1,72 (1H, m), 2,57 (2H, q, J = 7,7 Hz), 3,98 (3H, s), 6,89 (1H, s), 7,06 (1H, d, J = 9,3 Hz), 7,18 – 7,22 (1H, m), 7,35 – 7,42 (1H, m), 7,50 – 7,53 (1H, m), 7,92 (1H, s), 8,03 (1H, d, J = 9,3 Hz), 10,10 (1H, s), 10,98 (1H, s).

Ejemplo 250

Producción de 3–metoxi–1–metil–N–{2–metil–5–[(2–{[(2–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–

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il)oxi]fenil}–1H–pirazol–5–carboxamida

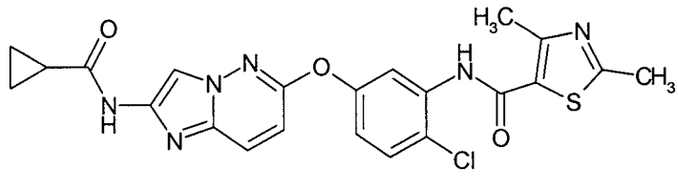


Usando ácido 3–metoxi–1–metil–1H–pirazol–5–carboxílico (194 mg, 1,24 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (109 μL, 1,22 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida (300 mg, 0,89 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (291 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,71 (1H, m), 0,95 – 1,04 (1H, m), 1,06 – 1,09 (3H, m), 1,19 –1,26 (1H, m), 1,62 – 1,72 (1H, m), 2,24 (3H, s), 3,79 (3H, s), 3,91 (3H, s), 6,45 (1H, s), 7,03 (1H, d, J = 9,3 Hz), 7,09 (1H, dd, J = 8,3, 2,6 Hz), 7,25 (1H, d, J = 2,6 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,91 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,84 (1H, s), 10,97 (1H, s).

Ejemplo 251

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida

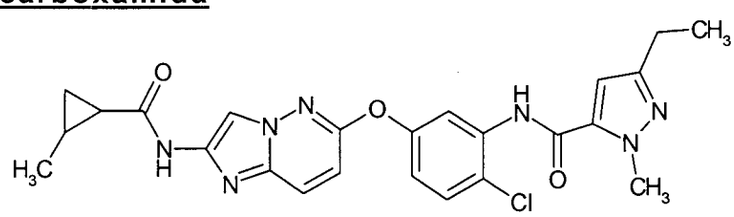


Usando ácido 2,4–dimetil–1,3–tiazol–5–carboxílico (192 mg, 1,22 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (107 μL, 1,22 mmol), N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,87 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (206 mg, 49%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,82 (4H, m), 1,83 – 1,97 (1H, m), 2,59 (3H, s), 2,64 (3H, s), 7,08 (1H, d, J = 9,5 Hz), 7,20 – 7,24 (1H, m), 7,59 – 7,63 (2H,m), 7,94 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 9,78 (1H, s), 11,07 (1H, s).

Ejemplo 252

Producción de N–{2–cloro–5–[(2–{[(2–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–etil–1–metil–1H–pirazol–5–carboxamida



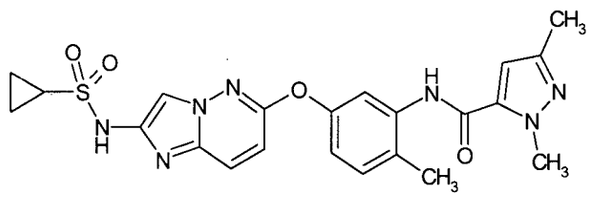
Usando ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (181 mg, 1,17 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (102 μL, 1,17 mmol), N–[6–(3–

amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida (300 mg, 0,84 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (207 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,73 (1H, m), 0,97 – 1,04 (1H, m), 1,05 – 1,09 (3H, m), 1,16 – 1,25 (1H, m), 1,19 (3H, t, J = 7,5 Hz), 1,62 –1,73 (1H, m), 2,55 (2H, q, J = 7,5 Hz), 3,99 (3H, s), 6,88 (1H, s), 7,08 (1H, d, J = 9,5 Hz), 7,21 – 7,27 (1H, m), 7,53 (1H, d, J = 3,0 Hz), 7,62 (1H, d, J = 8,7 Hz), 7,94 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 10,00 (1H, s), 10,99 (1H, s).

Ejemplo 253

Producción de N–[5–({2–[(ciclopropilsulfonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



A una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–fluorofenil}–1,3–dimetil–1H–pirazol–5–carboxamida (400 mg, 0,97 mmol) en 1–metil–2–pirrolidona (4,0 mL) se le añadieron trietilamina (404 μL, 2,90 mmol) y cloruro de ciclopropansulfonilo (204 mg, 1,45 mmol), y la mezcla se agitó a 70°C durante 16 h. Después de enfriar hasta temperatura ambiente, se añadió agua a la mezcla de reacción, y la mezcla se extrajo con

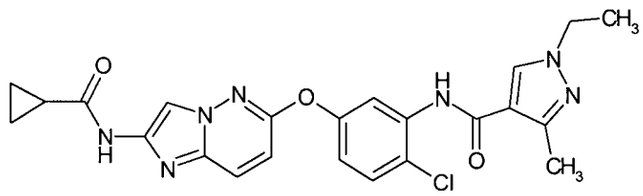
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acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo solo) y se recristalizó en hexano/acetato de etilo para dar el compuesto del título (74 mg, 16%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,84 – 1,03 (4H, m), 2,19 (3H,s), 2,25 (3H, s), 2,72 – 2,86 (1H, m), 3,97 (3H, s), 6,80 (1H, s), 7,05 – 7,12 (2H, m), 7,26 – 7,29 (1H, m), 7,34 (1H, d, J = 8,4 Hz), 7,61 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 9,79 (1H, s), 10,29 (1H, s).

Ejemplo 254

Producción de N–[2–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–etil–3–metil–1H–pirazol–4–carboxamida



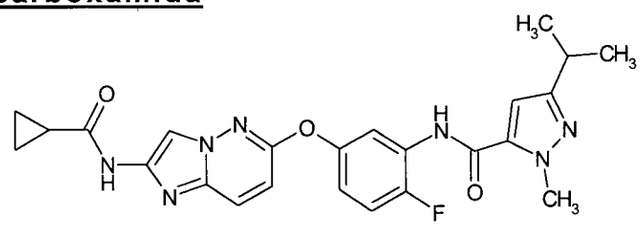
Usando ácido 1–etil–3–metil–1H–pirazol–4–carboxílico (188 mg, 1,22 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (107 μL, 1,22 mmol), N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,87 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (135 mg, 33%) en forma de un polvo blanco. Punto de fusión 200 °C.

1046

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,83 (4H, m), 1,38 (3H, t, J = 7,2 Hz), 1,78 –1,96 (1H, m), 2,35 (3H, s), 4,09 (2H, q, J = 7,2 Hz), 7,08 (1H, d, J = 9,6 Hz), 7,15 (1H, dd, J = 8,9, 3,0 Hz), 7,62 (1H, d, J = 8,9 Hz), 7,65 (1H, d, J = 3,0 Hz), 7,95 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 8,36 (1H, s), 9,30 (1H, s), 11,06 (1H, s).

Ejemplo 255

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–isopropil–1–metil–1H–pirazol–5–carboxamida



A una solución de ácido 3–isopropil–1–metil–1H–pirazol–5–carboxílico (144 mg, 0,86 mmol) en tetrahidrofurano (3,0 mL) se añadieron N,N–dimetilformamida (30 μL, 0,39 mmol) y cloruro de oxalilo (75 μL, 0,86 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) en N,N–dimetilacetamida (4,0 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano, se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El

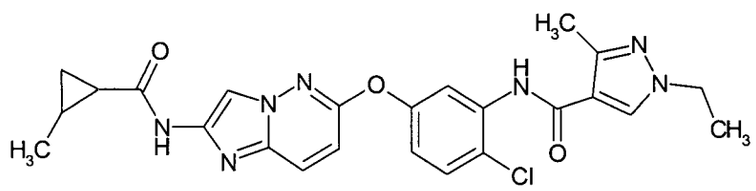
L047

solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo para dar el compuesto del título (216 mg, 74%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,21 (6H, d, J = 6,6 Hz), 1,85 – 1,96 (1H, m), 2,83 –2,96 (1H, m), 3,98 (3H, s), 6,91 (1H, s), 7,06 (1H, d, J = 9,3 Hz), 7,17 – 7,22 (1H, m), 7,35 – 7,42 (1H, m), 7,50 – 7,54 (1H, m), 7,93 (1H, s), 8,03 (1H, d, J = 9,3 Hz), 10,10 (1H, s), 11,06 (1H, s).

Ejemplo 256

Producción de N–{2–cloro–5–[(2–{[(2–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1–etil–3–metil–1H–pirazol–4–carboxamida



Usando ácido 1–etil–3–metil–1H–pirazol–4–carboxílico (181 mg, 1,17 mmol), tetrahidrofurano (4,5 mL), N,N–dimetilformamida (30 μL, 0,39 mmol), cloruro de oxalilo (102 μL, 1,17 mmol), N–[6–(3–amino–4–clorofenoxi)imidazo[1,2–b]piridazin–2–il]–2–metilciclopropancarboxamida (300 mg, 0,84 mmol) y N,N–dimetilacetamida (6,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (118 mg, 28%) en forma de un polvo blanco.

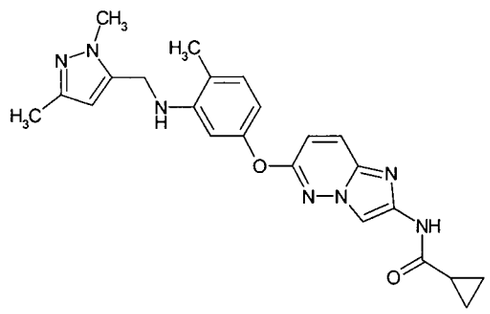
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,61 – 0,69 (1H, m), 0,96 –

1048

1,04 (1H, m), 1,06 – 1,10 (3H, m), 1,18 – 1,29 (1H, m), 1,38 (3H, t, J = 7,2 Hz), 1,62 –1,71 (1H, m), 2,35 (3H, s), 4,09 (2H, q, J = 7,2 Hz), 7,07 (1H, d, J = 9,6 Hz), 7,15 (1H, dd, J = 8,9, 3,2 Hz), 7,58 (1H, d, J = 8,9 Hz), 7,64 (1H, d, J = 3,2 Hz), 7,93 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 8,36 (1H, s), 9,30 (1H, s), 10,99 (1H, s).

Ejemplo 257

Producción de N–[6–(3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (210 mg, 0,64 mmol), 3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}–4–metilfenol (220 mg, 0,96 mmol), carbonato de potasio (220 mg, 1,6 mmol) y N,N–dimetilformamida (1,5 mL) se agitó bajo irradiación de microondas a 150 °C durante 40 min. El solvente se evaporó a presión reducida, Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo, la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida,

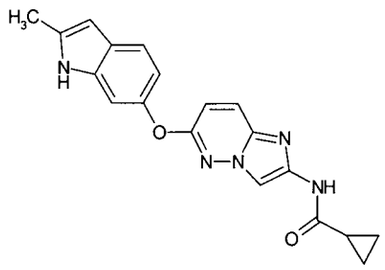
1049

y el residuo se purificó por cromatografía en columna de gel de sílice (metanol/acetato de etilo = 0/100→5/95) para dar el compuesto del título (200 mg, 72%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,84 (4H, m), 1,87 – 1,96 (1H, m), 2,00 (3H, s), 2,11 (3H, s), 3,68 (3H, s), 4,26 (2H, d, J = 5,7 Hz), 5,64 (1H, t, J = 5,7 Hz), 5,80 (1H, s), 6,34 (1H, dd, J = 7,9, 2,3 Hz), 6,40 (1H, d, J = 2,3 Hz), 6,89 (1H, d, J = 9,8 Hz), 7,01 (1H, d, J = 8,5 Hz), 7,91 – 8,01 (2H, m), 11,07 (1H, s).

Ejemplo 258

Producción de N–{6–[(2–metil–1H–indol–6–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



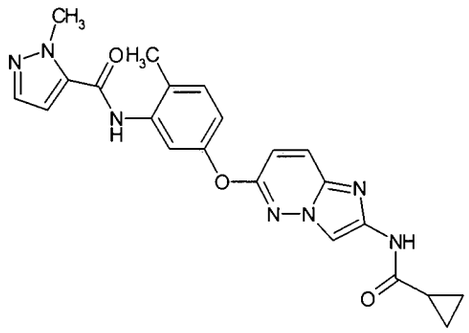
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (360 mg, 1,1 mmol), 2–metil–1H–indol–6–ol (320 mg, 2,2 mmol), carbonato de potasio (450 mg, 3,3 mmol) y N,N–dimetilformamida (4 mL) se agitó a 120 °C durante 24 h. El solvente se evaporó a presión reducida, Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida,

y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→90/10) para dar el compuesto del título (140 mg, 36%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,84 – 1,97 (1H, m), 2,39 (3H, s), 6,15 (1H, s), 6,81 (1H, dd, J = 8,5, 2,1 Hz), 6,96 (1H, d, J = 9,8 Hz), 7,13 (1H, d, J = 2,1 Hz), 7,42 (1H, d, J = 8,5 Hz), 7,90 (1H, s), 7,97 (1H, d, J = 9,8 Hz), 11,00 (1H, s), 11,04 (1H, s).

Ejemplo 259

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirazol–5–carboxamida



A una solución de ácido 1–metil–1H–pirazol–5–carboxílico (106 mg, 0,84 mmol) en tetrahidrofurano (5 mL) se añadieron N,N–dimetilformamida (1 gota), cloruro de oxalilo (91 μL, 1,0 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. El solvente se evaporó a presión reducida, y el cloruro de 1–metil–1H–pirazol–5–carbonilo obtenido se disolvió en N,N–dimetilacetamida (2 mL). Esto se añadió a una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (210

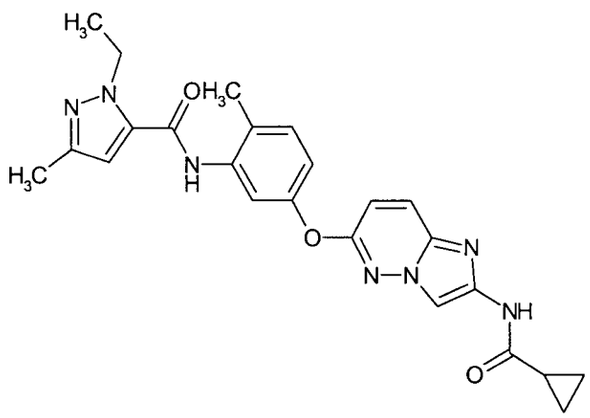
1651

mg, 0,65 mmol) en N,N–dimetilacetamida (5 mL), y la mezcla se agitó a temperatura ambiente durante 30 min. A la mezcla se añadieron acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno–carbonato de sodio, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→90/10) para dar el compuesto del título (230 mg, 83%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,87 – 1,97 (1H, m), 2,25 (3H, s), 4,05 (3H, s), 7,00 – 7,07 (2H, m), 7,11 (1H, dd, J = 8,3, 2,3 Hz), 7,28 (1H, d, J = 2,7 Hz), 7,36 (1H, d, J = 8,3 Hz), 7,53 (1H, d, J = 2,3 Hz), 7,93 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,91 (1H, s), 11,07 (1H, s).

Ejemplo 260

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–etil–3–metil–1H–pirazol–5–carboxamida



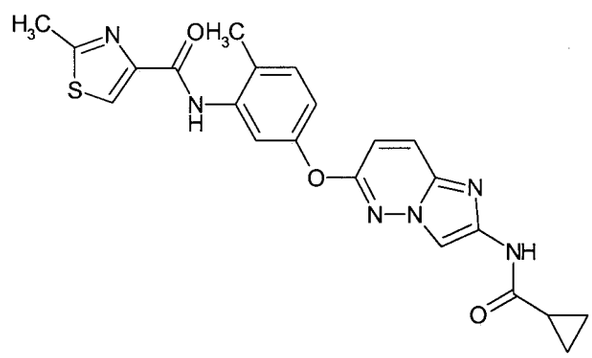
1052

De la misma manera que en el Ejemplo 259 y usando ácido 1–etil–3–metil–1H–pirazol–5–carboxílico (130 mg, 0,84 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (91 µL, 1,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (210 mg, 0,65 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (220 mg, 75%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,83 (4H, m), 1,26 (3H, t, J = 7,1 Hz), 1,84 – 1,95 (1H, m), 2,18 (3H, s), 2,23 (3H, s), 4,39 (2H, q, J = 7,1 Hz), 6,78 (1H, s), 7,02 (1H, d, J = 9,6 Hz), 7,08 (1H, dd, J = 8,2, 2,7 Hz), 7,26 (1H, d, J = 2,7 Hz), 7,32 (1H, d, J = 8,2 Hz), 7,91 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 9,79 (1H, s), 11,05 (1H, s).

Ejemplo 261

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2–metil–1,3–tiazol–4–carboxamida



Una mezcla de ácido 2–metil–1,3–tiazol–4–carboxílico (120 mg, 0,84 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (210 mg, 0,65 mmol), 1–

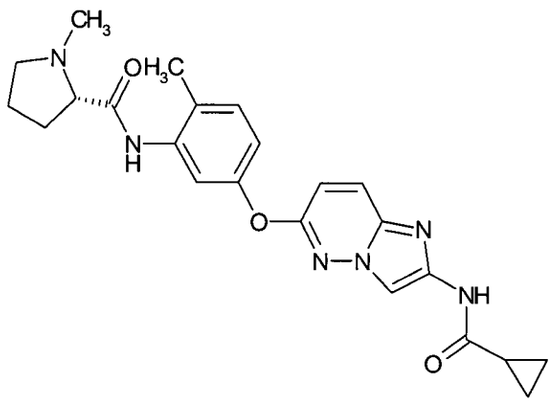
1053

hidroxibenzotriazol (110 mg, 0,84 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (160 mg, 0,84 mmol), trietilamina (85 mg, 0,84 mmol) y N,N–dimetilformamida (5 mL) se agitó a temperatura ambiente durante 16 h. El solvente se evaporó a presión reducida, Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→100/0) para dar el compuesto del título (180 mg, 62%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,82 (4H, m), 1,82 – 1,94 (1H, m), 2,27 (3H, s), 2,72 (3H, s), 6,95 – 7,07 (2H, m), 7,32 (1H, d, J = 8,8 Hz), 7,65 (1H, d, J = 2,7 Hz), 7,93 (1H, s), 8,01 (1H, d, J = 9,6 Hz), 8,25 (1H, s), 9,73 (1H, s), 11,06 (1H, s).

Ejemplo 262

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–L–prolinamida



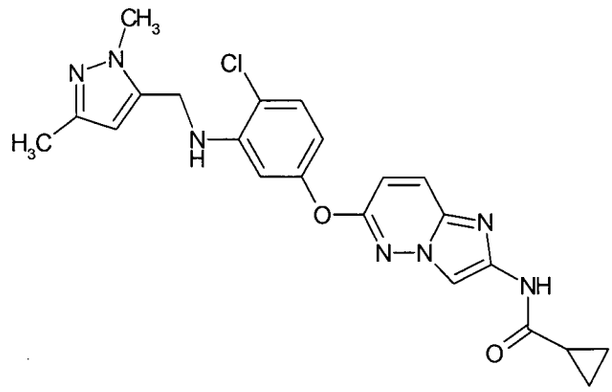
1054

Una mezcla de 1–metil–L–prolina (170 mg, 1,3 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (210 mg, 0,65 mmol), 1–hidroxibenzotriazol (175 mg, 1,3 mmol), hexafluorofosfato de O–(benzotriazol–1–il)–N,N,N',N'–tetrametiluronio (490 mg, 1,3 mmol), N,N–diisopropiletilamina (330 mg, 2,6 mmol) y N,N–dimetilformamida (15 mL) se agitó a temperatura ambiente durante 18 h, y luego a 40 °C durante 4 h. El solvente se evaporó a presión reducida, Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo, la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (metanol/acetato de etilo = 0/100→10/90) para dar el compuesto del título (15 mg, 5%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,69 – 1,86 (3H, m), 1,87 – 1,99 (1H, m), 2,11 – 2,22 (1H, m), 2,23 (3H, s), 2,38 (1H, d, J = 8,0 Hz), 2,43 (3H, s), 2,95 (1H, dd, J = 10,0, 4,7 Hz), 3,16 (1H, dd, J = 7,4, 4,7 Hz), 6,95 (1H, dd, J = 8,3, 2,7 Hz), 7,02 (1H, d, J = 9,5 Hz), 7,29 (1H, d, J = 8,3 Hz), 7,77 (1H, d, J = 2,7 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,61 (1H, s), 11,07 (1H, s).

Ejemplo 263

Producción de N–[6–(4–cloro–3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



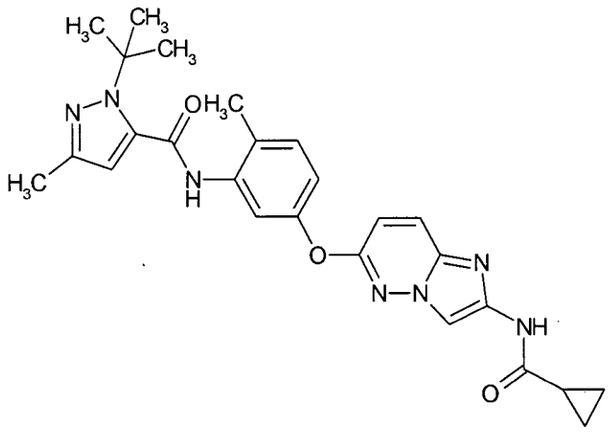
De la misma manera que en el Ejemplo 257 y usando N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (210 mg, 0,65 mmol), 4–cloro–3–{[(1,3–dimetil–1H–pirazol–5–il)metil]amino}fenol(240 mg, 0,97 mmol), carbonato de potasio (220 mg, 1,6 mmol) y N,N–dimetilformamida (1,5 mL) como materiales de partida, se obtuvo el compuesto del título (180 mg, 61%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,86 – 1,91 (1H, m), 1,98 (3H, s), 3,68 (3H, s), 4,35 (2H, d, J = 6,1 Hz), 5,78 (1H, s), 6,11 (1H, t, J = 6,1 Hz), 6,46 (1H, dd, J = 8,7, 2,7 Hz), 6,61 (1H, d, J = 2,7 Hz), 6,96 (1H, d, J = 9,5 Hz), 7,30 (1H, d, J = 8,7 Hz), 7,93 – 8,03 (2H, m), 11,06 (1H, s).

Ejemplo 264

Producción de 1–tert-butil–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–metil–1H–pirazol–5–carboxamida

1056



A una solución de N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (210 mg, 0,65 mmol) en N,N–dimetilacetamida (5 mL) se añadió una solución de cloruro de 1–tert-butil–3–metil–1H–pirazol–5–carbonilo (160 mg, 0,78 mmol) en N,N–dimetilacetamida (1 mL), y la mezcla se agitó a temperatura ambiente durante 30 min. acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno–carbonato de sodio se añadieron a la mezcla, la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→90/10) para dar el compuesto del título (14 mg, 4%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,88 (4H, m), 1,60 (9H, s), 1,86 – 1,98 (1H, m), 2,19 (3H, s), 2,27 (3H, s), 6,45 (1H, s), 6,99 – 7,15 (2H, m), 7,27 – 7,41 (2H, m), 7,91 – 7,97 (1H, m), 8,02 (1H, d, J = 9,8 Hz), 10,05 (1H, s), 11,05 (1H, s).

Organizacion y
Digitalizacion CSA Ltda

Patente de invención 09-2290

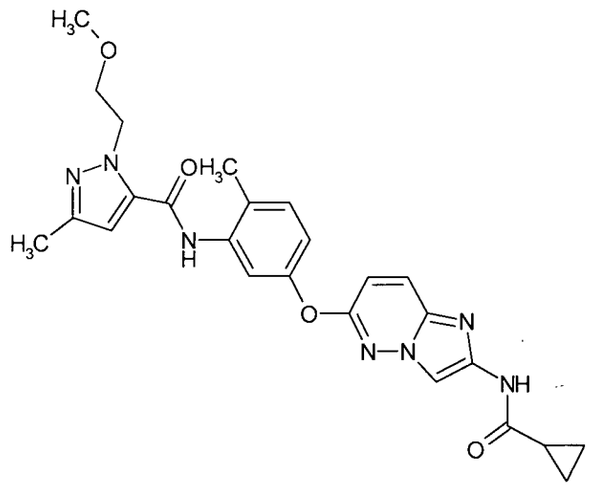
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1057

Ejemplo 265

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando 1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxílico (150 mg, 0,80 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (83 µL, 0,97 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (230 mg, 77%) en forma de un sólido de color verde pálido.

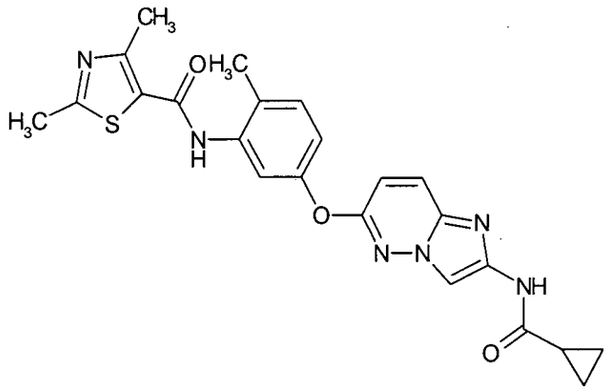
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,85 – 1,98 (1H, m), 2,20 (3H, s), 2,25 (3H, s), 3,17 (3H, s), 3,62 (2H, t, J = 5,5 Hz), 4,56 (2H, t, J = 5,5 Hz), 6,76 (1H, s), 7,04 (1H, d, J = 9,5 Hz), 7,10 (1H, dd, J = 8,3, 2,3 Hz), 7,26 (1H, d, J = 2,3 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,93 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,82 (1H,

1058

s), 11,05 (1H, s).

Ejemplo 266

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2,4–dimetil–1,3–tiazol–5–carboxamida

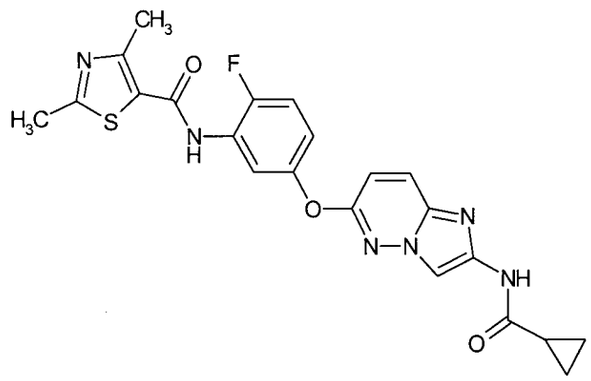


De la misma manera que en el Ejemplo 261 y usando ácido 2,4–dimetil–1,3–tiazol–5–carboxílico (130 mg, 0,80 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), 1–hidroxibenzotriazol (110 mg, 0,80 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (150 mg, 0,80 mmol), trietilamina (94 mg, 0,93 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (120 mg, 41%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,84 (4H, m), 1,86 – 1,97 (1H, m), 2,26 (3H, s), 2,57 (3H, s), 2,64 (3H, s), 7,03 (1H, d, J = 9,5 Hz), 7,08 (1H, dd, J = 8,3, 2,3 Hz), 7,30 – 7,37 (2H, m), 7,93 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,62 (1H, s), 11,06 (1H, s).

Ejemplo 267

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–tiazol–5–carboxamida



De la misma manera que en el Ejemplo 261 y usando ácido 2,4–dimetil–1,3–tiazol–5–carboxílico (190 mg, 1,2 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), 1–hidroxibenzotriazol (170 mg, 1,2 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (240 mg, 1,2 mmol), N,N–diisopropiletilamina (240 mg, 1,9 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (93 mg, 32%) en forma de un sólido de color amarillo pálido.

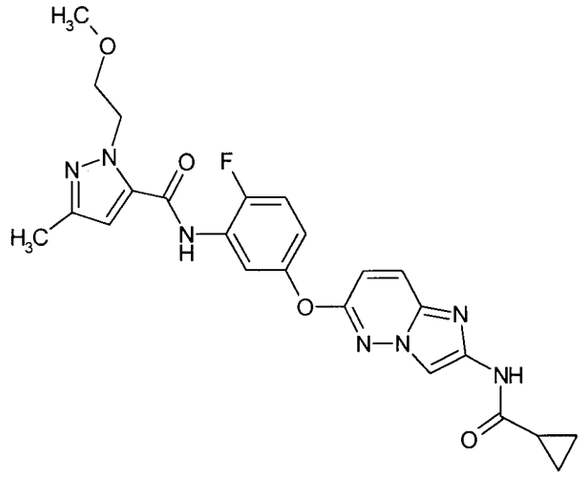
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,86 – 1,97 (1H, m), 2,56 (3H, s), 2,65 (3H, s), 7,07 (1H, d, J = 9,8 Hz), 7,14 – 7,23 (1H, m), 7,33 – 7,44 (1H, m), 7,58 (1H, dd, J = 6,2, 2,8 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,8 Hz), 9,94 (1H, s), 11,06 (1H, s).

Ejemplo 268

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

P060

b]piridazin–6–il}oxi)–2–fluorofenil]–1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxamida



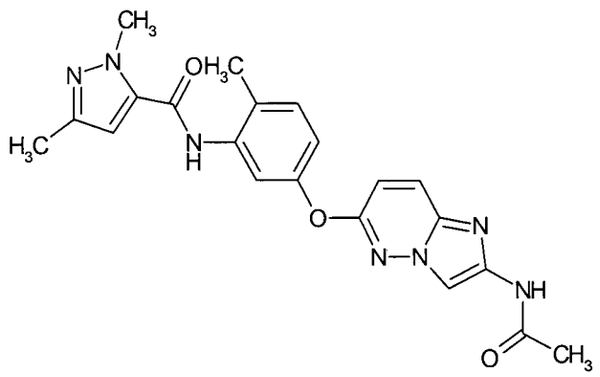
De la misma manera que en el Ejemplo 259 y usando ácido 1–(2–metoxietil)–3–metil–1H–pirazol–5–carboxílico (150 mg, 0,80 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (83 µL, 0,97 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (230 mg, 77%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,82 (4H, m), 1,85 – 1,97 (1H, m), 2,19 (3H, s), 3,30 (3H, s), 3,63 (2H, t, J = 5,7 Hz), 4,56 (2H, t, J = 5,7 Hz), 6,81 (1H, s), 7,07 (1H, d, J = 9,5 Hz), 7,17 – 7,25 (1H, m), 7,35 – 7,44 (1H, m), 7,54 (1H, dd, J = 6,2, 2,8 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,5 Hz), 10,12 (1H, s), 11,06 (1H, s).

Ejemplo 269

Producción de N–(5–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida

L661

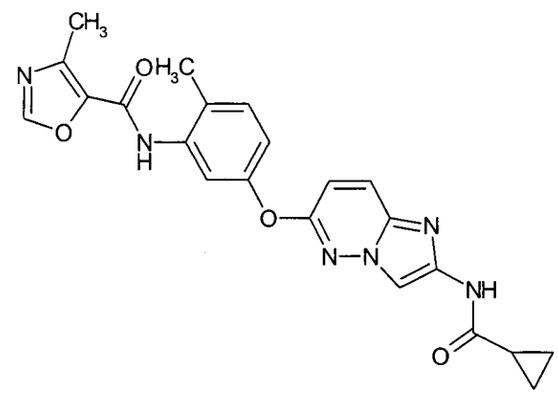


De la misma manera que en el Ejemplo 264 y usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (840 mg, 2,8 mmol), cloruro de 1,3–dimetil–1H–pirazol–5–carbonilo (540 mg, 3,4 mmol) y N,N–dimetilacetamida (35 mL), se obtuvo el compuesto del título (910 mg, 77%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,05 (3H, s), 2,18 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,04 (1H, d, J = 9,8 Hz), 7,10 (1H, dd, J = 8,3, 2,7 Hz), 7,28 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,95 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 9,79 (1H, s), 10,78 (1H, s).

Ejemplo 270

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metil–1,3–oxazol–5–carboxamida

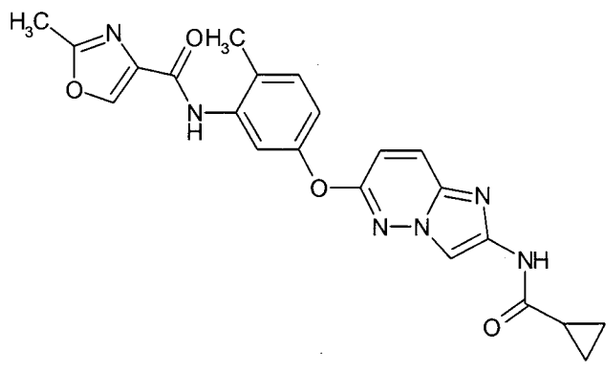


De la misma manera que en el Ejemplo 259 y usando ácido 4–metil–1,3–oxazol–5–carboxílico (77 mg, 0,60 mmol), tetrahidrofurano (10 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (62 µL, 0,72 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (170 mg, 83%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,86 – 1,98 (1H, m), 2,25 (3H, s), 2,41 (3H, s), 7,04 (1H, d, J = 9,5 Hz), 7,09 (1H, dd, J = 8,1, 2,5 Hz), 7,29 – 7,39 (2H, m), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 8,51 (1H, s), 9,82 (1H, s), 11,06 (1H, s).

Ejemplo 271

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2–metil–1,3–oxazol–4–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 2–metil–1,3–oxazol–4–carboxílico (77 mg, 0,60 mmol), tetrahidrofurano (10 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (62 µL, 0,72 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–

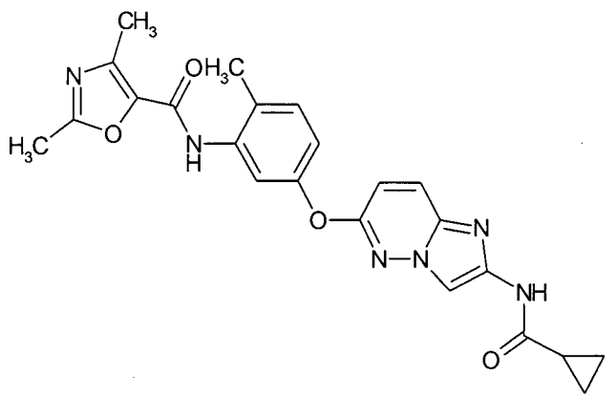
L063

2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (150 mg, 74%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,87 – 1,96 (1H, m), 2,27 (3H, s), 2,51 (3H, s), 6,99 – 7,07 (2H, m), 7,32 (1H, d, J = 8,7 Hz), 7,54 (1H, d, J = 2,7 Hz), 7,94 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 8,62 (1H, s), 9,54 (1H, s), 11,06 (1H, s).

Ejemplo 272

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2,4–dimetil–1,3–oxazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 2,4–dimetil–1,3–oxazol–5–carboxílico (85 mg, 0,60 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (62 μL, 0,72 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (170 mg, 81%) en forma de

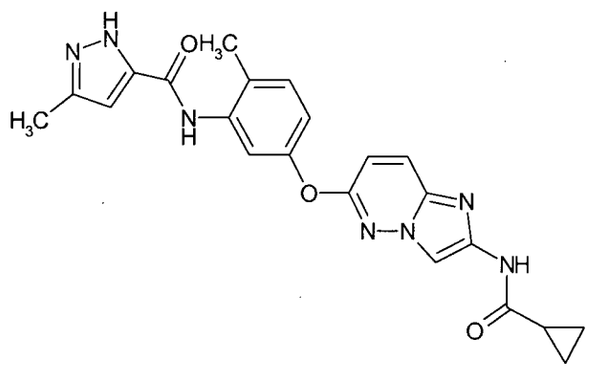
P064

un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,86 – 1,98 (1H, m), 2,24 (3H, s), 2,34 (3H, s), 2,48 (3H, s), 7,03 (1H, d, J = 9,5 Hz), 7,08 (1H, dd, J = 8,3, 2,7 Hz), 7,29 (1H, d, J = 2,7 Hz), 7,33 (1H, d, J = 8,3 Hz), 7,94 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,70 (1H, s), 11,06 (1H, s).

Ejemplo 273

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–metil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 261 y usando ácido 3–metil–1H–pirazol–5–carboxílico (160 mg, 1,2 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol), 1–hidroxibenzotriazol (170 mg, 1,2 mmol), clorhidrato de 1–etil–3–(3–dimetilaminopropil)carbodiimida (240 mg, 1,2 mmol), trietilamina (190 mg, 1,9 mmol) y N,N–dimetilformamida (3 mL) como materiales de partida, se obtuvo el compuesto del título (190 mg, 70%) en forma de un sólido blanco.

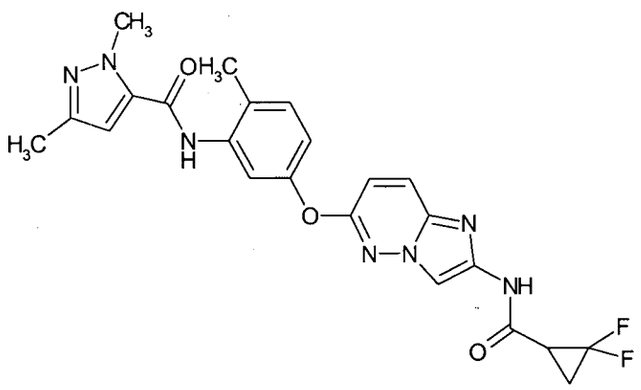
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,84 (4H, m), 1,87 –

1065

1,97 (1H, m), 2,29 (6H, s), 6,49 (1H, s), 6,99 (1H, dd, J = 8,3, 2,7 Hz), 7,03 (1H, d, J = 9,5 Hz), 7,31 (1H, d, J = 8,3 Hz), 7,68 (1H, d, J = 2,7 Hz), 7,94 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,36 (1H, s), 11,06 (1H, s), 13,09 (1H, s).

Ejemplo 274

Producción de N–{5–[(2–{[(2,2–difluorociclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 2,2–difluorociclopropancarboxílico (88 mg, 0,60 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (74 µL, 0,86 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (250 mg, 0,60 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (210 mg, 73%) en forma de un sólido blanco.

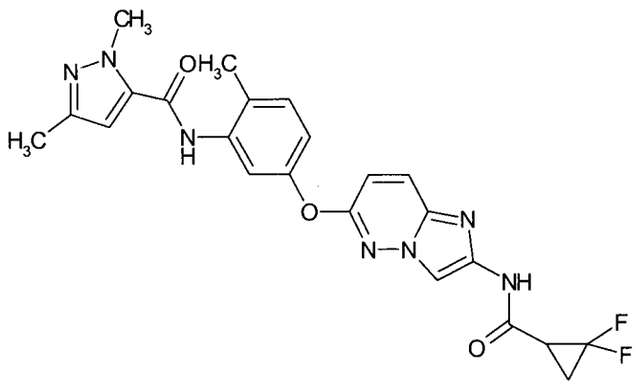
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,95 – 2,09 (2H, m), 2,19 (3H, s), 2,25 (3H, s), 2,86 – 2,96 (1H, m), 3,98 (3H, s), 6,81 (1H, s), 7,05

L066

1,97 (1H, m), 2,29 (6H, s), 6,49 (1H, s), 6,99 (1H, dd, J = 8,3, 2,7 Hz), 7,03 (1H, d, J = 9,5 Hz), 7,31 (1H, d, J = 8,3 Hz), 7,68 (1H, d, J = 2,7 Hz), 7,94 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,36 (1H, s), 11,06 (1H, s), 13,09 (1H, s).

Ejemplo 274

Producción de N–{5–[(2–{[(2,2–difluorociclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 2,2–difluorociclopropancarboxílico (88 mg, 0,60 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (74 µL, 0,86 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (250 mg, 0,60 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (210 mg, 73%) en forma de un sólido blanco.

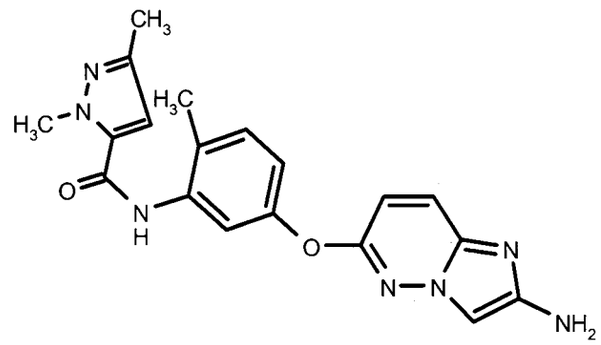
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,95 – 2,09 (2H, m), 2,19 (3H, s), 2,25 (3H, s), 2,86 – 2,96 (1H, m), 3,98 (3H, s), 6,81 (1H, s), 7,05

1667

– 7,13 (2H, m), 7,29 (1H, d, J = 2,3 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,96 (1H, s), 8,06 (1H, d, J = 9,8 Hz), 9,79 (1H, s), 11,29 (1H, s).

Ejemplo 275

Producción de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida



HCl

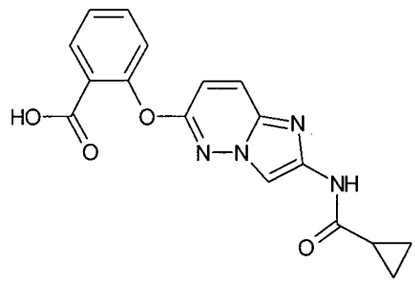
A una suspensión de N–(5–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida (310 mg, 0,73 mmol) en metanol (10 mL) se añadió ácido clorhídrico 4 N/acetato de etilo (10 mL, 40 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo/tetrahidrofurano, y luego con éter dietílico para dar el compuesto del título (240 mg, 78%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,18 (3H, s), 2,27 (3H, s), 3,97 (3H, s), 6,90 (1H, s), 7,12 (1H, dd, J = 8,3, 2,3 Hz), 7,29 – 7,41 (3H, m), 7,45 (1H, s), 8,20 (1H, d, J = 9,5 Hz), 9,94 (1H, s).

Ejemplo 276

1068

Producción de ácido 2-({2-[(ciclopropilcarbonil) amino]imidazo[1,2-b]piridazin-6-il}oxi)benzoico



A una solución de salicilato de etilo (1010 mg, 6,1 mmol) en N,N-dimetilformamida (8 mL) se le añadió tert-butóxido de potasio (840 mg, 6,4 mmol) a 0 °C, y la mezcla se agitó a 0 °C durante 5 min y a temperatura ambiente durante 25 min. A la mezcla de reacción se le añadieron N-(6-yodoimidazo[1,2-b]piridazin-2-il)ciclopropancarboxamida (1,0 g, 3,1 mmol) y carbonato de potasio (420 mg, 3,1 mmol), y la mezcla se agitó a 100 °C durante 24 h. El solvente se evaporó a presión reducida, se añadieron acetato de etilo/tetrahidrofurano y agua al residuo. La capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→90/10) para dar 2-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)benzoato de etilo (200 mg, 18%) en forma de un sólido blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,74 – 0,83 (4H, m), 1,00 (3H, t, J = 7,2 Hz), 1,83 – 1,97 (1H, m), 4,08 (2H, q, J = 7,2 Hz), 7,09 (1H,

L669

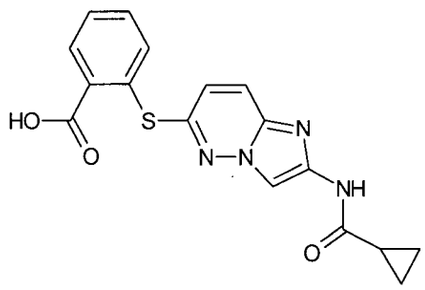
d, J = 9,5 Hz), 7,39 – 7,51 (2H, m), 7,69 – 7,76 (1H, m), 7,80 (1H, s), 7,95 (1H, dd, J = 7,8, 1,7 Hz), 8,03 (1H, d, J = 9,5 Hz), 11,02 (1H, s).

A una solución de 2–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoato de etilo (200 mg, 0,54 mmol) en tetrahidrofurano (10 mL) se añadió solución acuosa 4 N de hidróxido de sodio (1,5 mL), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió ácido clorhídrico 6 N (1,5 mL) y acetato de etilo se añadieron a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (130 mg, 73%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,83 (4H, m), 1,84 – 1,96 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,35 – 7,46 (2H, m), 7,66 – 7,73 (1H, m), 7,81 (1H, s), 7,94 (1H, dd, J = 7,7, 1,7 Hz), 8,00 (1H, d, J = 9,6 Hz), 11,02 (1H, s).

Ejemplo 277

Producción de ácido 2–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}tio)benzoico



Una mezcla de 2–mercaptobenzoato de metilo (1030 mg, 6,1 mmol), N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (1,0 g, 3,1 mmol), carbonato de potasio (1050 mg, 7,6 mmol) y N,N–dimetilformamida (10 mL) se agitó a 80 °C durante 7 h. La mezcla se evaporó a presión reducida, y Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo. La capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→90/10) para dar 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoato de metilo (200 mg, 18%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,89 (4H, m), 1,90 – 2,00 (1H, m), 3,85 (3H, s), 7,16 (1H, d, J = 9,5 Hz), 7,28 (1H, d, J = 8,0 Hz), 7,39 – 7,46 (1H, m), 7,48 – 7,55 (1H, m), 7,90 – 8,00 (2H, m), 8,21 (1H, s), 11,21 (1H, s).

De la misma manera que en el Ejemplo 276 y usando 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoato de metilo (390 mg, 1,1 mmol) y solución acuosa 4 N de hidróxido de sodio (2 mL) como materiales de partida, se obtuvo el compuesto del título (340 mg, 92%) en forma de un sólido de color amarillo pálido.

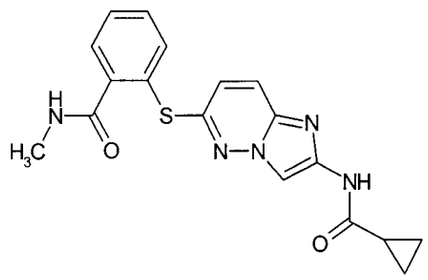
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,91 (4H, m), 1,88 – 2,02 (1H, m), 7,15 – 7,21 (2H, m), 7,38 (1H, t, J = 6,8 Hz), 7,43 –

1071

7,50 (1H, m), 7,89 – 8,01 (2H, m), 8,22 (1H, s), 11,21 (1H, s).

Ejemplo 278

Producción de 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)–N–metilbenzamida



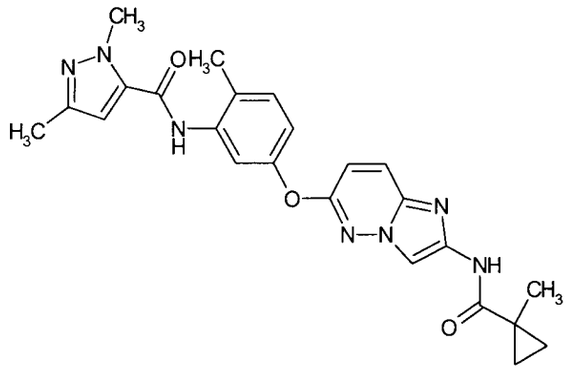
Una mezcla de ácido 2–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (120 mg, 0,35 mmol), una solución de metilamina en tetrahidrofurano (2M, 1 mL, 2,0 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (200 mg, 0,53 mmol) y N,N–dimetilformamida (4 mL) se agitó a temperatura ambiente durante 5 h. La mezcla se evaporó a presión reducida, Se añadieron acetato de etilo/tetrahidrofurano y agua al residuo, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→90/10) para dar el compuesto del título (45 mg, 41%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,88 (4H, m), 1,89 – 1,97 (1H, m), 2,71 (3H, d, J = 4,5 Hz), 6,97 (1H, d, J = 9,5 Hz), 7,38

– 7,46 (3H, m), 7,49 – 7,56 (1H, m), 7,88 (1H, d, J = 9,5 Hz), 8,15 (1H, s), 8,40 (1H, t, J = 4,5 Hz), 11,15 (1H, s).

Ejemplo 279

Producción de 1,3–dimetil–N–{2–metil–5–[(2–{[(1–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1H–pirazol–5–carboxamida



A una solución de ácido 1–metilciclopropancarboxílico (97 mg, 0,97 mmol) en tetrahidrofurano (1,5 mL) se añadieron N,N–dimetilformamida (1 gota) y cloruro de oxalilo (83 µL, 0,97 mmol), y la mezcla se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se añadió a una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) en N,N–dimetilacetamida (5 mL), y la mezcla se agitó a temperatura ambiente durante 1 h. acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno–carbonato de sodio se añadieron a la mezcla, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio anhidro, y

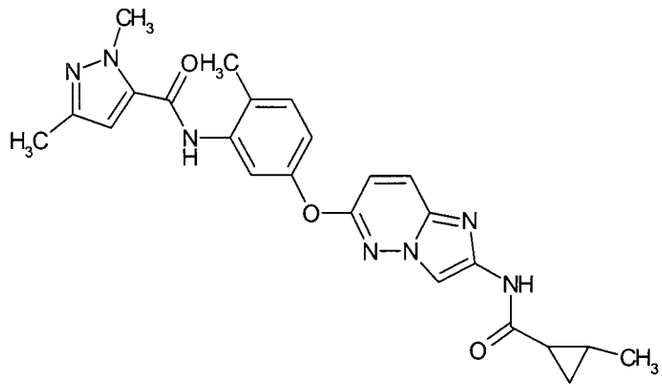
1073

se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→100/0) para dar el compuesto del título (105 mg, 74%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,60 – 0,68 (2H, m), 1,09 – 1,15 (2H, m), 1,40 (3H, s), 2,19 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,05 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,7, 2,4 Hz), 7,28 (1H, d, J = 2,4 Hz), 7,35 (1H, d, J = 8,7 Hz), 7,98 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 9,80 (1H, s), 10,15 (1H, s).

Ejemplo 280

Producción de 1,3–dimetil–N–{2–metil–5–[(2–{[(2–metilciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 279 y usando ácido 2–metilciclopropancarboxílico (97 mg, 0,97 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (83 μL, 0,97 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–dimetilacetamida (5 mL) como materiales de

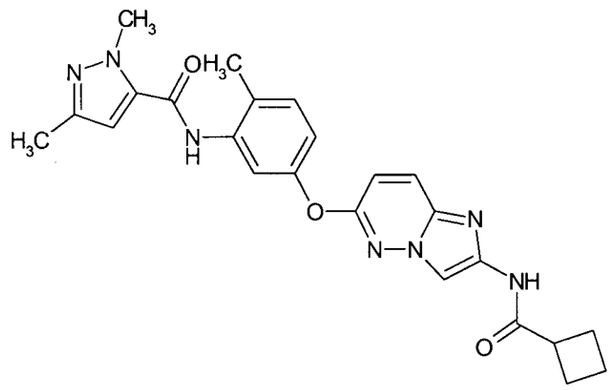
1074

partida, se obtuvo el compuesto del título (155 mg, 70%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,58 – 0,69 (1H, m), 0,93 – 1,04 (1H, m), 1,04 – 1,12 (3H, m), 1,17 – 1,28 (1H, m), 1,61 – 1,71 (1H, m), 2,20 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,03 (1H, d, J = 9,5 Hz), 7,09 (1H, dd, J = 8,3, 2,7 Hz), 7,27 (1H, d, J = 2,7 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,92 (1H, s), 8,02 (1H, d, J = 9,5 Hz), 9,79 (1H, s), 10,97 (1H, s).

Ejemplo 281

Producción de N–[5–({2–[(ciclobutilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 264 y usando clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol), cloruro de ciclobutancarbonilo (86 mg, 0,73 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (170 mg, 76%) en forma de un sólido blanco.

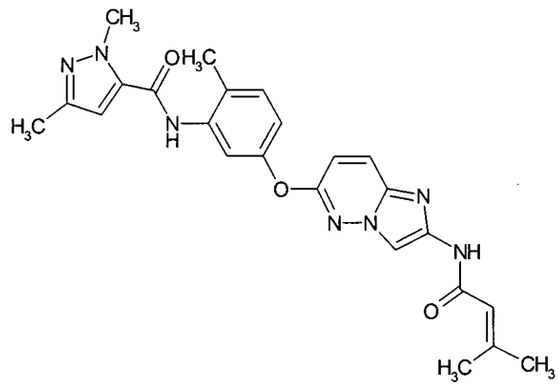
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,73 – 1,98 (3H, m), 2,01 –

2078.

2,22 (4H, m), 2,19 (3H, s), 2,25 (3H, s), 3,99 (3H, s), 6,81 (1H, s), 7,04 (1H, d, J = 9,8 Hz), 7,10 (1H, dd, J = 8,7, 2,4 Hz), 7,28 (1H, d, J = 2,4 Hz), 7,35 (1H, d, J = 8,7 Hz), 7,96 – 8,06 (2H, m), 9,81 (1H, s), 10,64 (1H, s).

Ejemplo 282

Producción de 1,3–dimetil–N–[2–metil–5–({2–[(3–metilbut–2–enoil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 264 y usando clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol), cloruro de 3–metilbut–2–enoílo (81 μL, 0,73 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (150 mg, 68%) en forma de un sólido de color amarillo pálido.

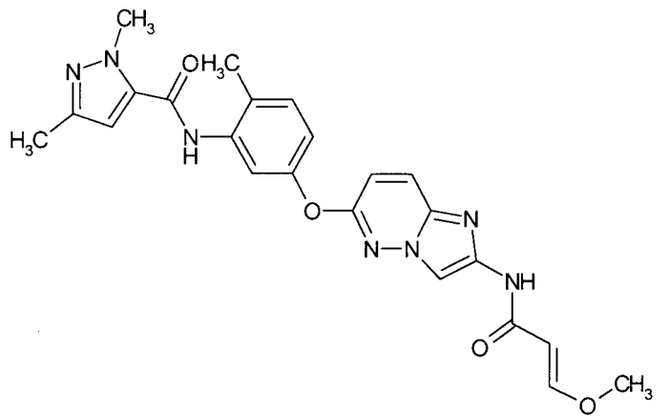
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,85 (3H, s), 2,17 (3H, d, J = 0,8 Hz), 2,19 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 5,98 (1H, s), 6,81 (1H, s), 7,03 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,5, 2,4 Hz), 7,28

1076

(1H, d, J = 2,4 Hz), 7,35 (1H, d, J = 8,5 Hz), 7,96 – 8,05 (2H, m), 9,81 (1H, s), 10,69 (1H, s).

Ejemplo 283

Producción de N–{5–[(2–{[(2E)–3–metoxiprop–2–enoil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida



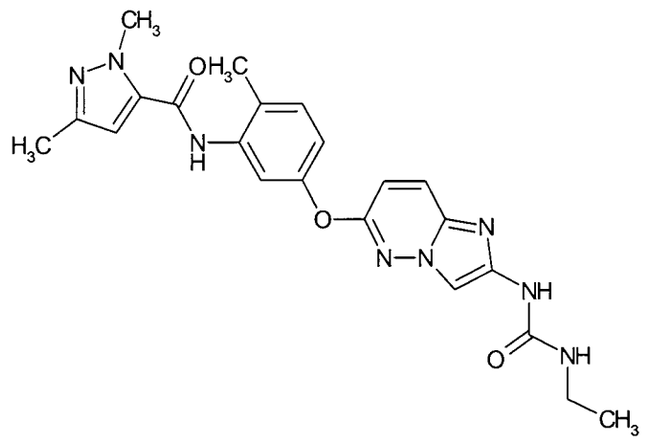
De la misma manera que en el Ejemplo 279 y usando ácido (2E)–3–metoxiacrílico (99 mg, 0,97 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (83 μL, 0,97 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (63 mg, 28%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 2,25 (3H, s), 3,68 (3H, s), 3,98 (3H, s), 5,68 (1H, d, J = 12,2 Hz), 6,83 (1H, s), 7,04 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,7, 2,6 Hz), 7,27 (1H, d, J = 2,6 Hz), 7,35 (1H, d, J = 8,7 Hz), 7,54 (1H, d, J = 12,2 Hz), 7,96 –

8,07 (2H, m), 9,84 (1H, s), 10,61 (1H, s).

Ejemplo 284

Producción de N–{5–[(2–{[(etilamino)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida

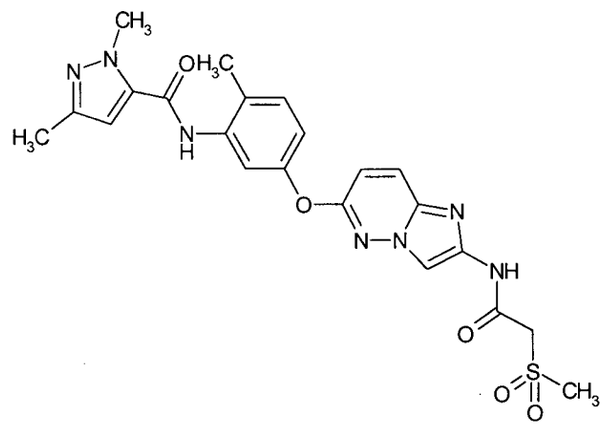


A una solución de clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) en piridina (3 mL) se le añadió isocianato de etilo (380 μL, 4,8 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadieron acetato de etilo/tetrahidrofurano y agua a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→100/0) para dar el compuesto del título (160 mg, 72%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,05 (3H, t, J = 7,2 Hz), 2,20 (3H, s), 2,24 (3H, s), 3,06 – 3,18 (2H, m), 3,98 (3H, s), 6,47 – 6,55 (1H, m), 6,81 (1H, s), 6,97 (1H, d, J = 9,6 Hz), 7,08 (1H, dd, J = 8,7, 2,6 Hz), 7,26 (1H, d, J = 2,6 Hz), 7,34 (1H, d, J = 8,7 Hz), 7,70 (1H, s), 7,95 (1H, d, J = 9,6 Hz), 8,99 (1H, s), 9,80 (1H, s).

Ejemplo 285

Producción de 1,3–dimetil–N–{2–metil–5–[(2–{[(metilsulfonil) acetil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–1H–pirazol–5–carboxamida



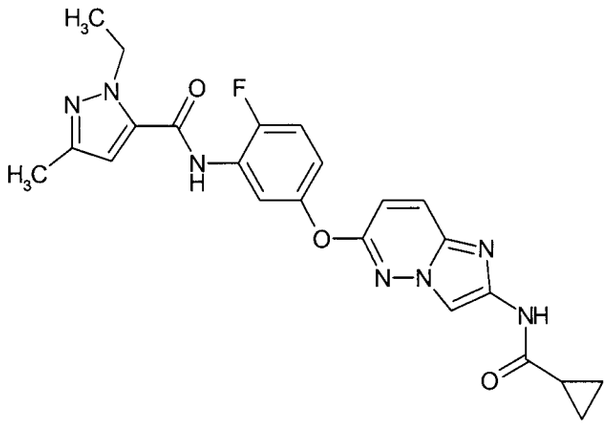
De la misma manera que en el Ejemplo 279 y usando ácido (metilsulfonil)acético (100 mg, 0,73 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (63 μL, 0,73 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (91 mg, 38%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,20 (3H, s), 2,25 (3H, s), 3,17

(3H, s), 3,99 (3H, s), 4,37 (2H, s), 6,81 (1H, s), 7,07 – 7,14 (2H, m), 7,29 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,7 Hz), 8,01 (1H, s), 8,08 (1H, d, J = 9,5 Hz), 9,79 (1H, s), 11,26 (1H, s).

Ejemplo 286

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 1–etil–3–metil–1H–pirazol–5–carboxílico (120 mg, 0,79 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (89 µL, 1,0 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (150 mg, 53%) en forma de un sólido blanco.

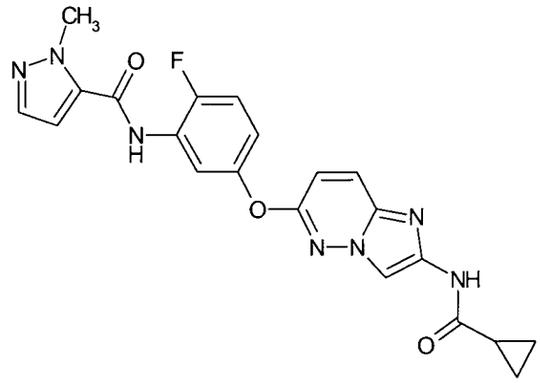
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,29 (3H, t, J = 7,0 Hz), 1,86 – 1,97 (1H, m), 2,21 (3H, s), 4,40 (2H, q, J = 7,0 Hz), 6,83 (1H, s), 7,07 (1H, d, J = 9,5 Hz), 7,16 – 7,25 (1H, m), 7,34

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– 7,45 (1H, m), 7,54 (1H, dd, J = 6,4, 3,0 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,5 Hz), 10,08 (1H, s), 11,06 (1H, s).

Ejemplo 287

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida



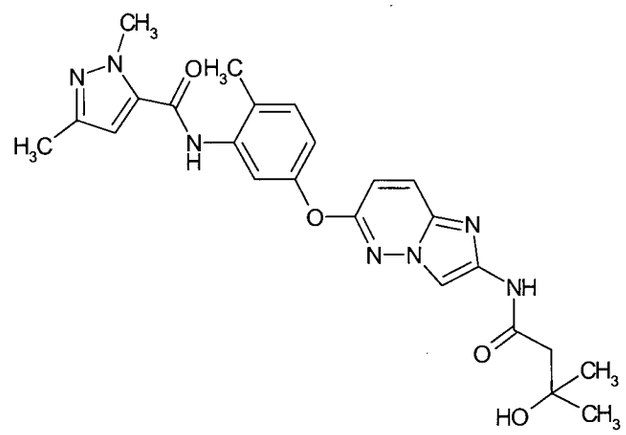
De la misma manera que en el Ejemplo 259 y usando ácido 1–metil–1H–pirazol–5–carboxílico (100 mg, 0,79 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (89 µL, 1,0 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (180 mg, 68%) en forma de un sólido blanco. Punto de fusión 253 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,87 – 1,98 (1H, m), 4,06 (3H, s), 7,07 (1H, d, J = 7,2 Hz), 7,09 (1H, s), 7,17 – 7,26 (1H, m), 7,34 – 7,46 (1H, m), 7,50 – 7,56 (2H, m), 7,94 (1H, s), 8,04 (1H, d, J = 9,8 Hz), 10,19 (1H, s), 11,06 (1H, s).

Ejemplo 288

1081

Producción de N–[5–({2–[(3–hidroxi–3–metilbutanoil)amino] imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida



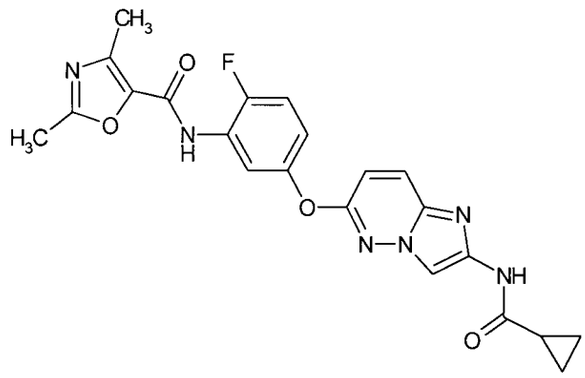
De la misma manera que en el Ejemplo 278 y usando ácido ácido 3–hidroxi–3–metilbutanoico (74 mg, 0,63 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (240 mg, 0,63 mmol), N,N–diisopropiletilamina (190 mg, 1,5 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (150 mg, 66%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,19 (6H, s), 2,19 (3H, s), 2,25 (3H, s), 2,48 (2H, s), 3,98 (3H, s), 4,76 (1H, s), 6,81 (1H, s), 6,99 – 7,14 (2H, m), 7,28 (1H, d, J = 2,3 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,94 – 8,06 (2H, m), 9,79 (1H, s), 10,58 (1H, s).

Ejemplo 289

1082

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–oxazol–5–carboxamida



De la misma manera que en el Ejemplo 259 y usando ácido 2,4–dimetil–1,3–oxazol–5–carboxílico (84 mg, 0,59 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (61 μL, 0,71 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (140 mg, 67%) en forma de un sólido blanco. Punto de fusión 202°C.

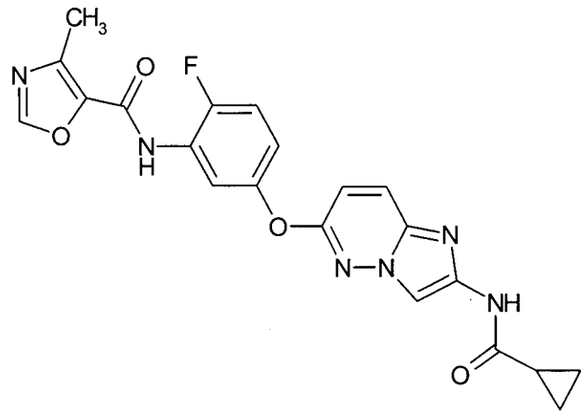
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,84 – 1,98 (1H, m), 2,35 (3H, s), 2,48 (3H, s), 7,07 (1H, d, J = 9,6 Hz), 7,14 – 7,23 (1H, m), 7,39 (1H, dd, J = 10,0, 9,0 Hz), 7,56 (1H, dd, J = 6,4, 3,0 Hz), 7,95 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 9,95 (1H, s), 11,07 (1H, s).

Ejemplo 290

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–4–metil–1,3–oxazol–5–

1083

carboxamida



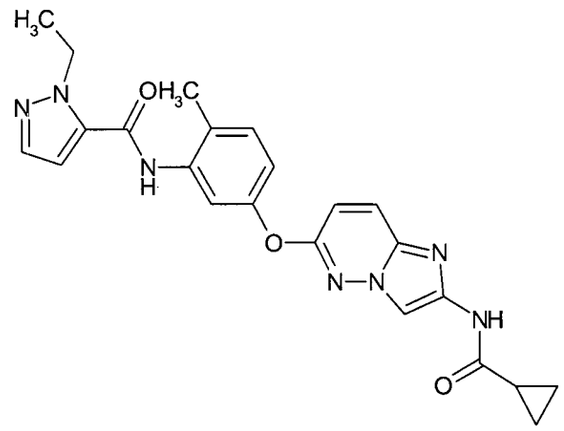
De la misma manera que en el Ejemplo 259 y usando ácido 4–metil–1,3–oxazol–5–carboxílico (76 mg, 0,59 mmol), tetrahidrofurano (10 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (61 µL, 0,71 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como material de partida, se obtuvo el compuesto del título (170 mg, 84%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,86 (4H, m), 1,85 – 1,97 (1H, m), 2,41 (3H, s), 7,07 (1H, d, J = 9,4 Hz), 7,16 – 7,25 (1H, m), 7,40 (1H, dd, J = 10,0, 9,0 Hz), 7,57 (1H, dd, J = 6,4, 3,0 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,4 Hz), 8,54 (1H, s), 10,10 (1H, s), 11,07 (1H, s).

Ejemplo 291

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–etil–1H–pirazol–5–carboxamida

1084



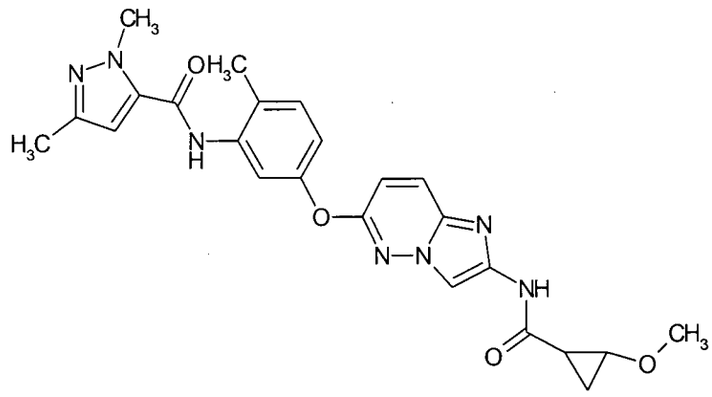
De la misma manera que en el Ejemplo 259 y usando ácido 1–etil–1H–pirazol–5–carboxílico (110 mg, 0,80 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (83 μL, 0,97 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (210 mg, 75%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,32 (3H, t, J = 7,2 Hz), 1,86 – 1,96 (1H, m), 2,25 (3H, s), 4,50 (2H, q, J = 7,2 Hz), 7,02 – 7,07 (2H, m), 7,11 (1H, dd, J = 8,3, 2,4 Hz), 7,28 (1H, d, J = 2,4 Hz), 7,36 (1H, d, J = 8,3 Hz), 7,54 (1H, d, J = 2,1 Hz), 7,93 (1H, s), 8,03 (1H, d, J = 10,0 Hz), 9,92 (1H, s), 11,10 (1H, s).

Ejemplo 292

Producción de N–{5–[(2–{[(2–metoxiciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida

1085.

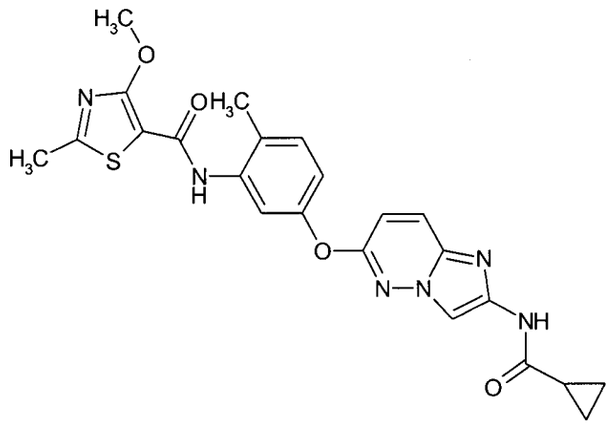


De la misma manera que en el Ejemplo 278 y usando ácido 2–metoxiciclopropancarboxílico (86 mg, 0,74 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,49 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (280 mg, 0,74 mmol), N,N–diisopropiletilamina (190 mg, 1,5 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (83 mg, 35%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,09 – 1,20 (2H, m), 2,03 – 2,13 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 3,30 (3H, s), 3,40 – 3,49 (1H, m), 3,97 (3H, s), 6,81 (1H, s), 7,04 (1H, d, J = 9,8 Hz), 7,09 (1H, dd, J = 8,3, 2,7 Hz), 7,28 (1H, d, J = 2,7 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,91 (1H, s), 8,03 (1H, d, J = 9,8 Hz), 9,79 (1H, s), 11,09 (1H, s).

Ejemplo 293

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metoxi–2–metil–1,3–tiazol–5–carboxamida



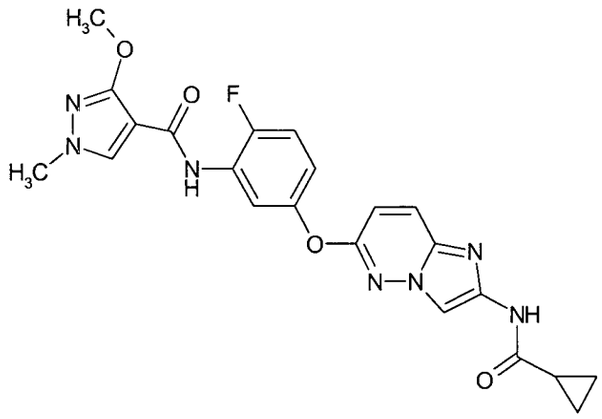
De la misma manera que en el Ejemplo 259 y usando ácido 4–metoxi–2–metil–1,3–tiazol–5–carboxílico (120 mg, 0,70 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (120 µL, 1,4 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (120 mg, 53%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,88 – 1,98 (1H, m), 2,32 (3H, s), 2,65 (3H, s), 4,18 (3H, s), 6,96 (1H, dd, J = 8,3, 2,7 Hz), 7,03 (1H, d, J = 9,8 Hz), 7,33 (1H, d, J = 8,3 Hz), 7,93 (1H, s), 7,97 (1H, d, J = 2,7 Hz), 8,02 (1H, d, J = 9,8 Hz), 9,05 (1H, s), 11,06 (1H, s).

Ejemplo 294

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–4–carboxamida

1087

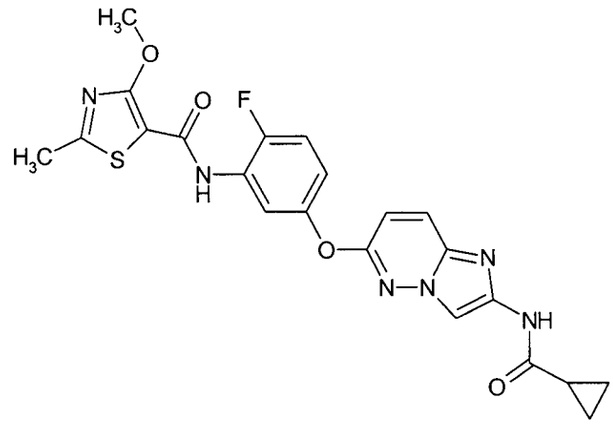


De la misma manera que en el Ejemplo 259 y usando ácido 3–metoxi–1–metil–1H–pirazol–4–carboxílico (93 mg, 0,60 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (61 μL, 0,72 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (59 mg, 28%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,86 – 1,97 (1H, m), 3,75 (3H, s), 4,01 (3H, s), 6,97 – 7,09 (2H, m), 7,33 – 7,44 (1H, m), 7,94 (1H, s), 8,04 (1H, d, J = 9,8 Hz), 8,11 – 8,19 (2H, m), 8,94 (1H, d, J = 2,7 Hz), 11,07 (1H, s).

Ejemplo 295

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–4–metoxi–2–metil–1,3–tiazol–5–carboxamida



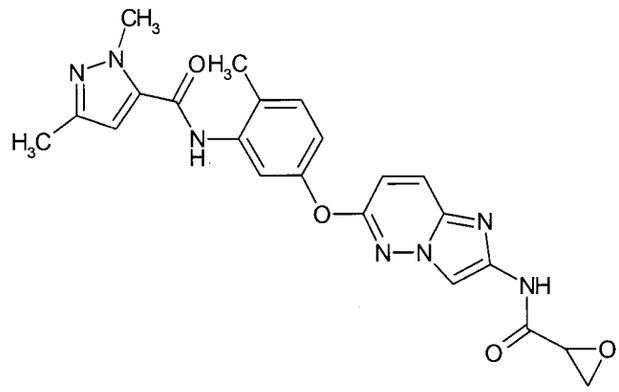
De la misma manera que en el Ejemplo 259 y usando ácido 4–metoxi–2–metil–1,3–tiazol–5–carboxílico (100 mg, 0,60 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (61 μL, 0,72 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (89 mg, 40%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,84 (4H, m), 1,88 – 1,96 (1H, m), 2,64 – 2,68 (3H, m), 4,18 (3H, s), 7,03 – 7,12 (2H, m), 7,42 (1H, dd, J = 10,6, 9,1 Hz), 7,93 (1H, s), 8,01 – 8,09 (2H, m), 9,27 (1H, s), 11,06 (1H, s).

Ejemplo 296

Producción de 1,3–dimetil–N–[2–metil–5–({2–[(oxirano–2–ilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–pirazol–5–carboxamida

P089



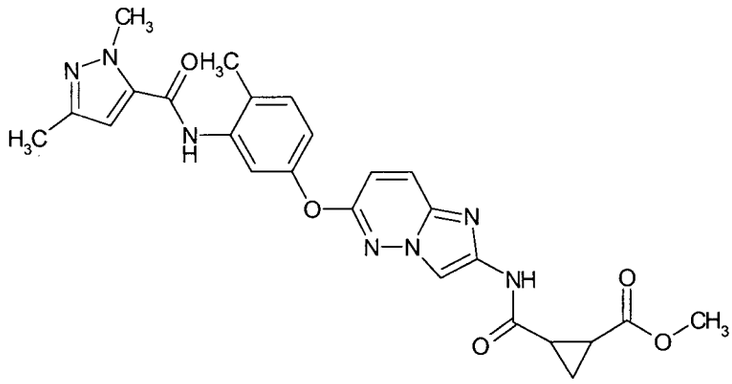
De la misma manera que en el Ejemplo 279 y usando ácido oxiran–2–carboxílico (54 mg, 0,62 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (53 μL, 0,62 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (170 mg, 0,41 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (96 mg, 52%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,19 (3H, s), 2,25 (3H, s), 2,88 – 2,99 (2H, m), 3,64 – 3,70 (1H, m), 3,97 (3H, s), 6,81 (1H, s), 7,04 – 7,16 (2H, m), 7,29 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,99 (1H, s), 8,07 (1H, d, J = 9,8 Hz), 9,79 (1H, br. s), 11,30 (1H, br. s).

Ejemplo 297

Producción de 2–({[6–(3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]amino}carbonil)ciclopropancarboxilato de metilo

1696



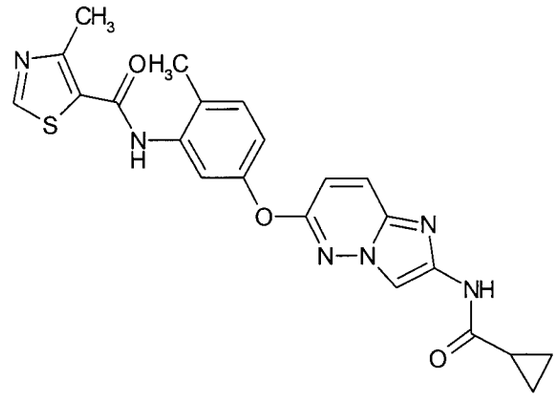
De la misma manera que en el Ejemplo 279 y usando ácido 2–(metoxicarbonil)ciclopropancarboxílico (140 mg, 0,78 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (69 µL, 0,8 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (250 mg, 0,6 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (75 mg, 25%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,19 – 1,29 (2H, m), 1,39 – 1,47 (1H, m), 2,19 (3H, s), 2,24 (3H, s), 2,25 – 2,33 (1H, m), 3,51 (3H, s), 3,97 (3H, s), 6,80 (1H, s), 7,04 (1H, d, J = 9,8 Hz), 7,09 (1H, dd, J = 8,3, 2,7 Hz), 7,27 (1H, d, J = 2,7 Hz), 7,34 (1H, d, J = 8,3 Hz), 7,90 (1H, s), 8,03 (1H, d, J = 9,8 Hz), 9,79 (1H, s), 11,10 (1H, s).

Ejemplo 298

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metil–1,3–tiazol–5–carboxamida

1091



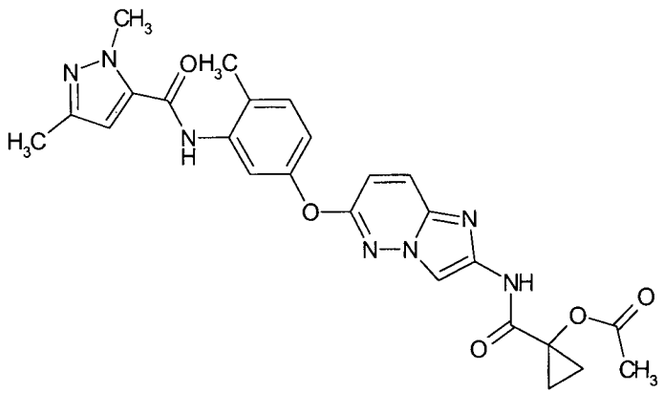
De la misma manera que en el Ejemplo 259 y usando ácido 4–metil–1,3–tiazol–5–carboxílico (86 mg, 0,60 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (100 µL, 1,2 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (170 mg, 80%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,85 – 1,97 (1H, m), 2,26 (3H, s), 2,65 (3H, s), 7,04 (1H, d, J = 9,8 Hz), 7,09 (1H, dd, J = 8,3, 2,7 Hz), 7,30 – 7,39 (2H, m), 7,94 (1H, s), 8,03 (1H, d, J = 9,8 Hz), 9,12 (1H, s), 9,80 (1H, s), 11,06 (1H, s).

Ejemplo 299

Producción de acetato de 1–({[6–(3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]amino}carbonil)ciclopropilo

L092



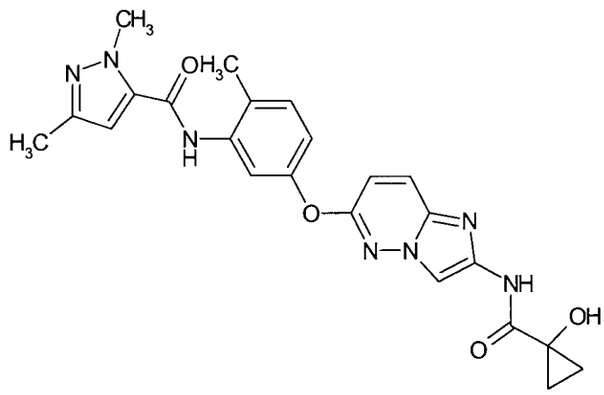
De la misma manera que en el Ejemplo 279 y usando ácido 1–acetoxiciclopropancarboxílico (90 mg, 0,63 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (54 μL, 0,63 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (200 mg, 0,48 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (180 mg, 74%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,11 – 1,19 (2H, m), 1,42 – 1,48 (2H, m), 2,10 (3H, s), 2,19 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,06 (1H, d, J = 9,8 Hz), 7,10 (1H, dd, J = 8,3, 2,7 Hz), 7,28 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,99 (1H, s), 8,03 (1H, d, J = 9,8 Hz), 9,79 (1H, br. s), 10,87 (1H, br. s).

Ejemplo 300

Producción de N–{5–[(2–{[(1–hidroxiciclopropil)carbonil]amino}imidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida

L093



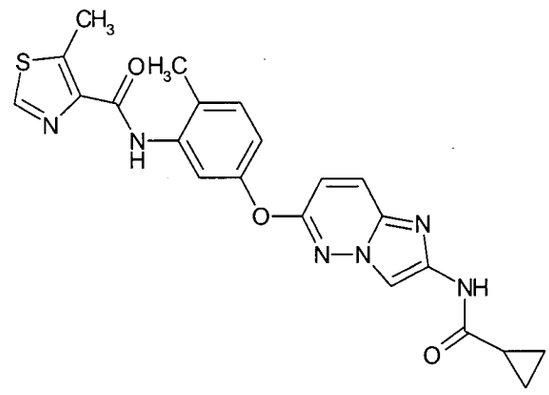
A una solución de acetato de 1–({[6–(3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]amino}carbonil)ciclopropilo (130 mg, 0,25 mmol) en tetrahidrofurano (2 mL) se le añadió solución acuosa 1 N de hidróxido de sodio (2 mL), y la mezcla se agitó a temperatura ambiente durante 2 h. Se añadieron ácido clorhídrico 1 N (2,5 mL) y acetato de etilo se añadieron a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (99 mg, 86%) en forma de un sólido de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,96 – 1,03 (2H, m), 1,13 – 1,22 (2H, m), 2,19 (3H, s), 2,26 (3H, s), 3,97 (3H, s), 6,63 (1H, br. s), 6,81 (1H, s), 7,03 – 7,14 (2H, m), 7,29 (1H, d, J = 2,7 Hz), 7,35 (1H, d, J = 8,3 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,8 Hz), 9,79 (2H, br. s).

Ejemplo 301

1094

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–5–metil–1,3–tiazol–4–carboxamida



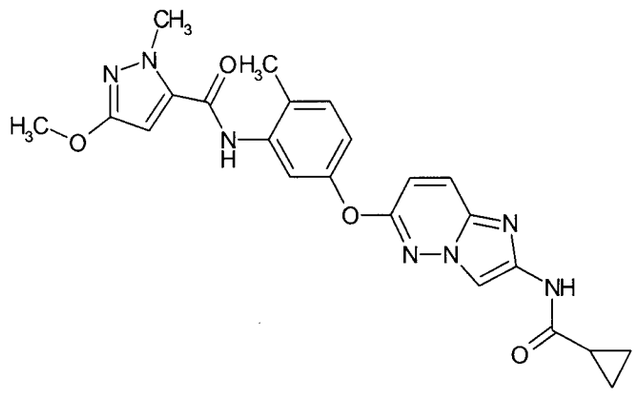
De la misma manera que en el Ejemplo 259 y usando ácido 5–metil–1,3–tiazol–4–carboxílico (74 mg, 0,52 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 μL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (130 mg, 0,40 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (110 mg, 60%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,85 – 1,96 (1H, m), 2,31 (3H, s), 2,78 (3H, s), 6,96 – 7,09 (2H, m), 7,34 (1H, d, J = 8,7 Hz), 7,79 (1H, d, J = 2,4 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 10,2 Hz), 9,02 (1H, s), 9,79 (1H, s), 11,07 (1H, s).

Ejemplo 302

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida

1095



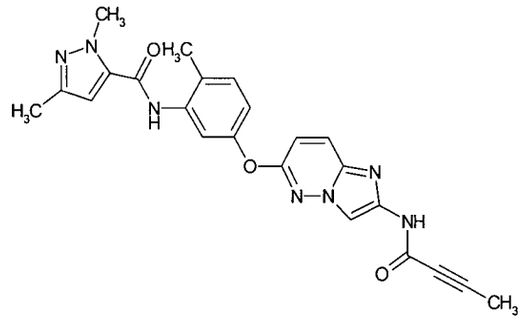
De la misma manera que en el Ejemplo 259 y usando ácido 3–metoxi–1–metil–1H–pirazol–5–carboxílico (80 mg, 0,52 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 µL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (130 mg, 0,40 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (160 mg, 85%) en forma de un sólido blanco. Punto de fusión 224 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,86 – 1,97 (1H, m), 2,24 (3H, s), 3,80 (3H, s), 3,90 (3H, s), 6,46 (1H, s), 7,04 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,7, 2,6 Hz), 7,26 (1H, d, J = 2,6 Hz), 7,35 (1H, d, J = 8,7 Hz), 7,93 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,86 (1H, s), 11,07 (1H, s).

Ejemplo 303

Producción de N–(5–{[2–(but–2–inoilamino)imidazo[1,2–b]piridazin–6–il]oxi}–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida

1096

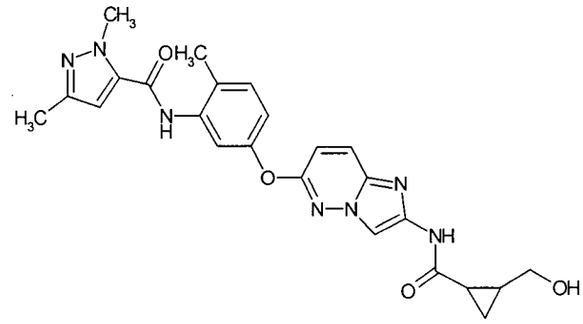


De la misma manera que en el Ejemplo 279 y usando ácido but–2–inoico (46 mg, 0,54 mmol), tetrahidrofurano (1,5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (47 µL, 0,54 mmol), clorhidrato de N–{5–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]–2–metilfenil}–1,3–dimetil–1H–pirazol–5–carboxamida (150 mg, 0,36 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (60 mg, 37%) como un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,03 (3H, s), 2,19 (3H, s), 2,25 (3H, s), 3,98 (3H, s), 6,81 (1H, s), 7,03 – 7,14 (2H, m), 7,28 (1H, d, J = 2,4 Hz), 7,35 (1H, d, J = 8,5 Hz), 7,94 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 9,81 (1H, br. s), 11,48 (1H, br. s).

Ejemplo 304

Producción de N–(5–{[2–({[2–(hidroximetil)ciclopropil]carbonil}amino)imidazo[1,2–b]piridazin–6–il]oxi}–2–metilfenil)–1,3–dimetil–1H–pirazol–5–carboxamida



L097

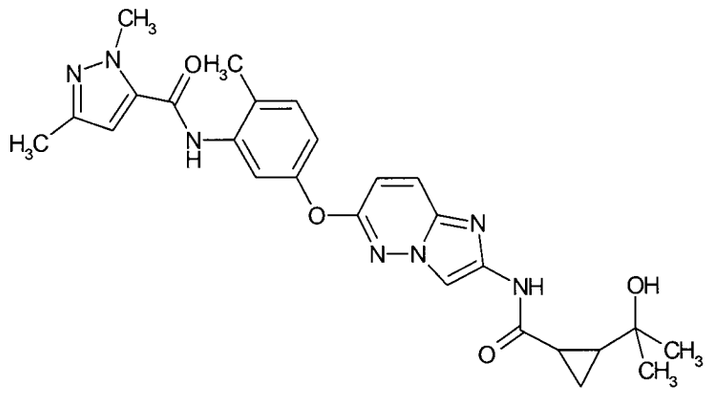
A una suspensión de cloruro de calcio (135 mg, 1,1 mmol) en tetrahidrofurano/etanol (2/1, 1 mL) se añadió una solución de borhidruro de sodio (92 mg, 2,2 mmol) y 2-({[6-(3-{[(1,3-dimetil-1H-pirazol-5-il)carbonil]amino}-4-metilfenoxi)imidazo[1,2-b]piridazin-2-il]amino}carbonil)ciclopropancarboxilato de metilo (180 mg, 0,37 mmol) en tetrahidrofurano/etanol (2/1, 1 mL), y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadieron solución acuosa saturada de cloruro de amonio y acetato de etilo a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→100/0, y luego metanol/acetato de etilo = 0/100→5/95) para dar el compuesto del título (35 mg, 20%) en forma de un sólido blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,83 – 1,04 (2H, m), 1,37 – 1,49 (1H, m), 1,94 – 2,05 (1H, m), 2,19 (3H, s), 2,25 (3H, s), 3,41 – 3,53 (1H, m), 3,56 – 3,66 (1H, m), 3,97 (3H, s), 4,44 (1H, t, J = 5,2 Hz), 6,81 (1H, s), 7,03 (1H, d, J = 9,6 Hz), 7,09 (1H, dd, J = 8,5, 2,6 Hz), 7,27 (1H, d, J = 2,6 Hz), 7,34 (1H, d, J = 8,5 Hz), 7,95 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 9,80 (1H, s), 10,99 (1H, s).

Ejemplo 305

Producción de N-(5-{[2-({[2-(1-hidroxi-1-metiletil)ciclopropil]carbonil}amino)imidazo[1,2-b]piridazin-6-il]oxi}-2-metilfenil)-1,3-dimetil-1H-pirazol-5-carboxamida

1098



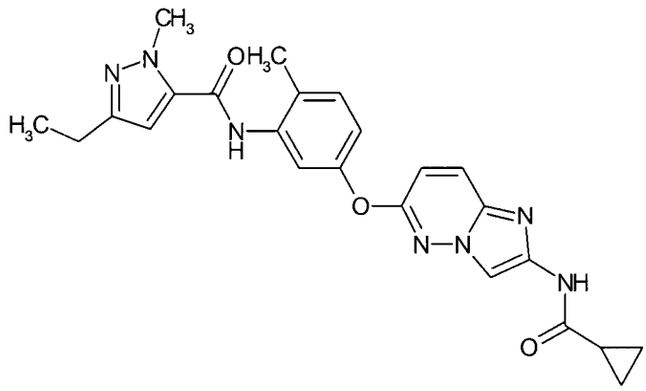
A una solución de 2–({[6–(3–{[(1,3–dimetil–1H–pirazol–5–il)carbonil]amino}–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]amino}carbonil)ciclopropanecarboxilato de metilo (250 mg, 0,49 mmol) en tetrahidrofurano (5 mL) se añadió una solución de yodo(metil)magnesio en éter dietílico (2 M, 540 µL, 1,1 mmol) a 0 °C, y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadieron ácido clorhídrico 0,5 N (3 mL) y acetato de etilo a la mezcla de reacción, y la capa acuosa se extrajo con acetato de etilo (×3). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se lavó con acetato de etilo/hexano para dar el compuesto del título (190 mg, 78%) en forma de un sólido de color verde pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,35 – 1,46 (1H, m), 1,67 (3H, s), 1,69 – 1,78 (1H, m), 2,06 – 2,23 (2H, m), 2,30 (3H, s), 2,34 (3H, s), 3,70 (3H, s), 4,12 (3H, s), 6,43 (1H, s), 6,85 (1H, d, J = 9,6 Hz), 6,97 (1H, dd, J = 8,3, 2,4 Hz), 7,24 – 7,28 (1H, m), 7,58 (1H, s), 7,73 (1H, d, J = 9,6 Hz), 7,94 (1H, m), 8,13 (1H, s), 8,97 (1H, s).

L099

Ejemplo 306

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–etil–1–metil–1H–pirazol–5–carboxamida



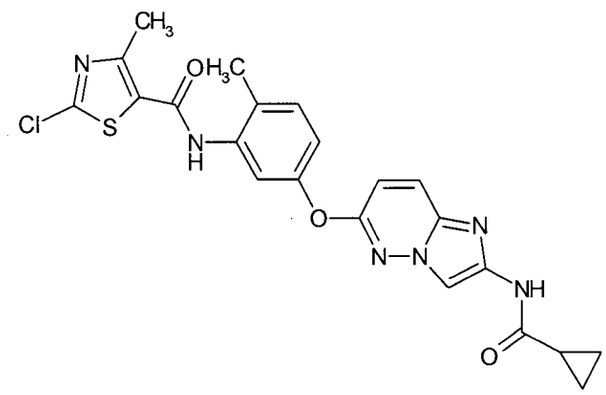
De la misma manera que en el Ejemplo 259 y usando ácido 3–etil–1–metil–1H–pirazol–5–carboxílico (120 mg, 0,80 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 µL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (190 mg, 68%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,19 (3H, t, J = 7,8 Hz), 1,87 – 1,97 (1H, m), 2,25 (3H, s), 2,57 (2H, q, J = 7,8 Hz), 3,99 (3H, s), 6,85 (1H, s), 7,04 (1H, d, J = 9,5 Hz), 7,10 (1H, d, J = 8,3 Hz), 7,27 (1H, s), 7,35 (1H, d, J = 8,3 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,81 (1H, s), 11,06 (1H, s).

Ejemplo 307

Producción de 2–cloro–N–[5–({2–[(ciclopropilcarbonil)amino]

imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–4–metil–1,3–tiazol–5–carboxamida

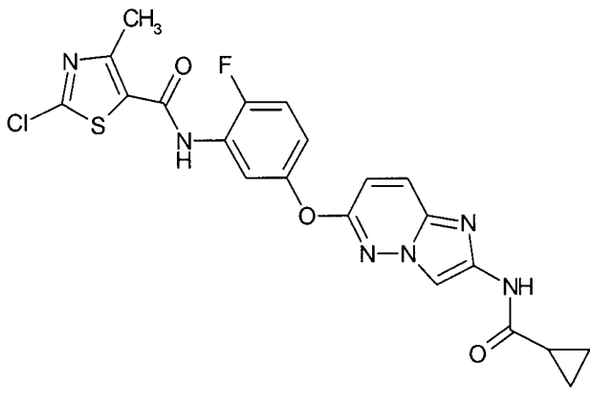


De la misma manera que en el Ejemplo 259 y usandoácido 2–cloro–4–metil–1,3–tiazol–5–carboxílico (140 mg, 0,80 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 μL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (270 mg, 91%) en forma de un sólido de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,86 – 1,96 (1H, m), 2,25 (3H, s), 2,58 (3H, s), 7,04 (1H, d, J = 9,5 Hz), 7,10 (1H, dd, J = 8,3, 2,3 Hz), 7,31 – 7,38 (2H, m), 7,93 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,86 (1H, s), 11,06 (1H, s).

Ejemplo 308

Producción de 2–cloro–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–4–metil–1,3–tiazol–5–carboxamida



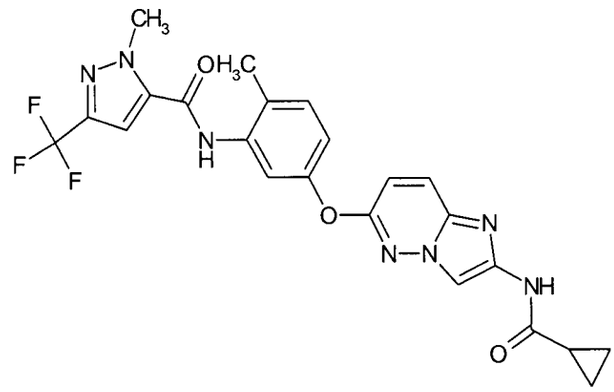
De la misma manera que en el Ejemplo 259 y usando ácido 2–cloro–4–metil–1,3–tiazol–5–carboxílico (140 mg, 0,80 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (140 μL, 1,6 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (230 mg, 78%) en forma de un sólido de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,85 – 1,97 (1H, m), 2,58 (3H, s), 7,08 (1H, d, J = 9,4 Hz), 7,17 – 7,26 (1H, m), 7,41 (1H, dd, J = 10,0, 9,0 Hz), 7,59 (1H, dd, J = 6,3, 2,9 Hz), 7,94 (1H, s), 8,05 (1H, d, J = 9,4 Hz), 10,23 (1H, s), 11,08 (1H, s).

Ejemplo 309

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–3–(trifluorometil)–1H–pirazol–5–carboxamida

1102

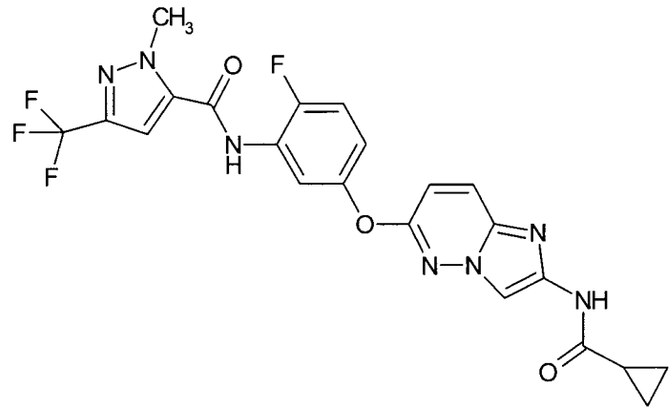


De la misma manera que en el Ejemplo 259 y usando ácido 1–metil–3–(trifluorometil)–1H–pirazol–5–carboxílico (160 mg, 0,80 mmol), tetrahidrofurano (5mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 µL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (240 mg, 76%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,86 (4H, m), 1,86 – 1,97 (1H, m), 2,27 (3H, s), 4,15 (3H, s), 7,05 (1H, d, J = 9,6 Hz), 7,13 (1H, dd, J = 8,3, 2,6 Hz), 7,30 (1H, d, J = 2,6 Hz), 7,37 (1H, d, J = 8,3 Hz), 7,49 (1H, s), 7,94 (1H, s), 8,04 (1H, d, J = 9,6 Hz), 10,13 (1H, s), 11,08 (1H, s).

Ejemplo 310

Producción de N–[5–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–3–(trifluorometil)–1H–pirazol–5–carboxamida



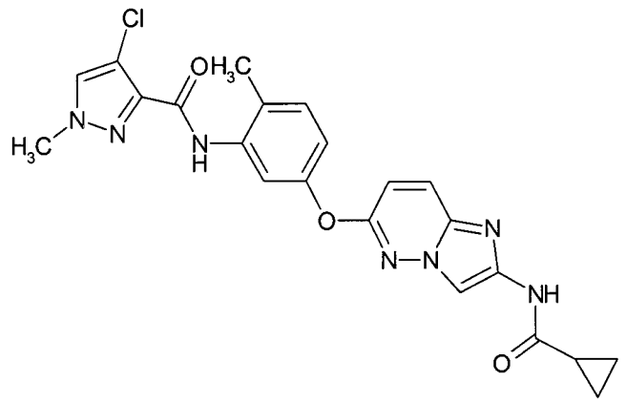
De la misma manera que en el Ejemplo 259 y usando ácido 1–metil–3–(trifluorometil)–1H–pirazol–5–carboxílico (150 mg, 0,79 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (140 µL, 1,6 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (240 mg, 77%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,85 (4H, m), 1,85 – 1,97 (1H, m), 4,15 (3H, s), 7,09 (1H, d, J = 9,4 Hz), 7,21 – 7,28 (1H, m), 7,39 – 7,47 (1H, m), 7,54 (1H, s), 7,58 (1H, dd, J = 6,3, 2,9 Hz), 7,95 (1H, s), 8,05 (1H, d, J = 9,4 Hz), 10,45 (1H, s), 11,08 (1H, s).

Ejemplo 311

Producción de 4–cloro–N–[5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirazol–3–carboxamida

LL04

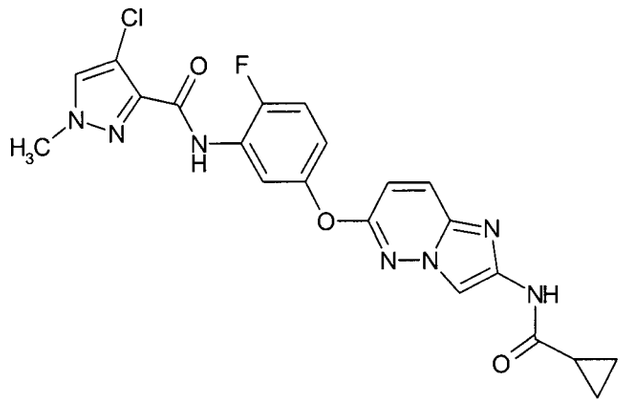


De la misma manera que en el Ejemplo 259 y usando ácido 4–cloro–1–metil–1H–pirazol–3–carboxílico (130 mg, 0,80 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 µL, 2,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,62 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (235 mg, 82%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,84 (4H, m), 1,87 – 1,96 (1H, m), 2,27 (3H, s), 3,93 (3H, s), 6,99 – 7,08 (2H, m), 7,32 (1H, d, J = 8,7 Hz), 7,52 (1H, d, J = 2,6 Hz), 7,95 (1H, s), 8,03 (1H, d, J = 10,2 Hz), 8,12 (1H, s), 9,54 (1H, s), 11,07 (1H, s).

Ejemplo 312

Producción de 4–cloro–N–[5–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–3–carboxamida



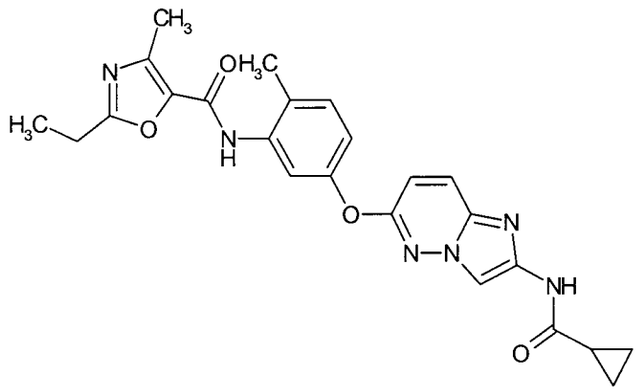
De la misma manera que en el Ejemplo 259 y usando ácido 4–cloro–1–metil–1H–pirazol–3–carboxílico (130 mg, 0,79 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (170 µL, 2,0 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,61 mmol) y N,N–dimetilacetamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (230 mg, 80%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,86 – 1,97 (1H, m), 3,94 (3H, s), 7,08 (1H, d, J = 9,6 Hz), 7,10 – 7,18 (1H, m), 7,39 (1H, dd, J = 10,4, 9,0 Hz), 7,80 (1H, dd, J = 6,5, 2,9 Hz), 7,95 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 8,14 (1H, s), 9,68 (1H, s), 11,08 (1H, s).

Ejemplo 313

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida

1106.

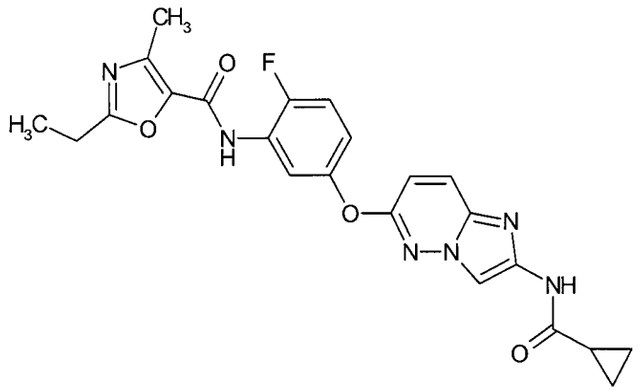


De la misma manera que en el Ejemplo 259 y usando ácido 2–etil–4–metil–1,3–oxazol–5–carboxílico (230 mg, 1,5 mmol), tetrahidrofurano (6 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (520 μL, 6,0 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (400 mg, 1,2 mmol) y N,N–dimetilacetamida (10 mL) como materiales de partida, se obtuvo el compuesto del título (390 mg, 69%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,29 (3H, t, J = 7,6 Hz), 1,92 (1H, m), 2,24 (3H, s), 2,36 (3H, s), 2,81 (2H, q, J = 7,6 Hz), 7,04 (1H, d, J = 9,5 Hz), 7,08 (1H, dd, J = 8,3, 2,7 Hz), 7,26 – 7,37 (2H, m), 7,94 (1H, s), 8,03 (1H, d, J = 9,5 Hz), 9,71 (1H, s), 11,07 (1H, s).

Ejemplo 314

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida



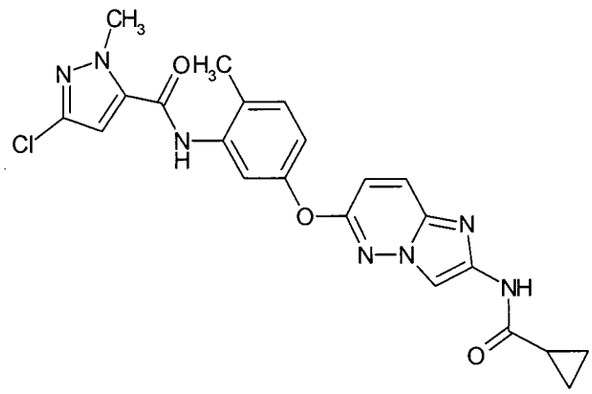
De la misma manera que en el Ejemplo 259 y usando ácido 2–etil–4–metil–1,3–oxazol–5–carboxílico (230 mg, 1,5 mmol), tetrahidrofurano (6 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (520 µL, 6,0 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (400 mg, 1,2 mmol) y N,N–dimetilacetamida (10 mL) como materiales de partida, se obtuvo el compuesto del título (400 mg, 70%) en forma de un sólido blanco. Punto de fusión 228 °C.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,29 (3H, t, J = 7,6 Hz), 1,83 – 1,95 (1H, m), 2,36 (3H, s), 2,82 (2H, q, J = 7,6 Hz), 7,07 (1H, d, J = 9,8 Hz), 7,16 – 7,25 (1H, m), 7,33 – 7,44 (1H, m), 7,56 (1H, dd, J = 6,2, 2,8 Hz), 7,94 (1H, s), 8,04 (1H, d, J = 9,8 Hz), 9,95 (1H, s), 11,07 (1H, s).

Ejemplo 315

Producción de 3–cloro–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1–metil–1H–pirazol–5–carboxamida

1108

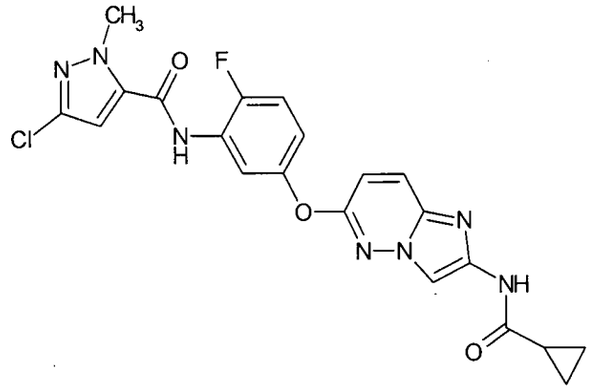


De la misma manera que en el Ejemplo 259 y usando ácido 3–cloro–1–metil–1H–pirazol–5–carboxílico (60 mg, 0,37 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (130 µL, 1,5 mmol), N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,31 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (110 mg, 74%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,01 – 0,15 (4H, m), 1,14 – 1,27 (1H, m), 1,54 (3H, s), 1,80 (3H, s), 6,27 – 6,46 (3H, m), 6,58 (1H, d, J = 2,4 Hz), 6,65 (1H, d, J = 8,5 Hz), 7,22 (1H, s), 7,33 (1H, d, J = 9,6 Hz), 9,30 (1H, br. s), 10,37 (1H, s).

Ejemplo 316

Producción de 3–cloro–N–[5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida

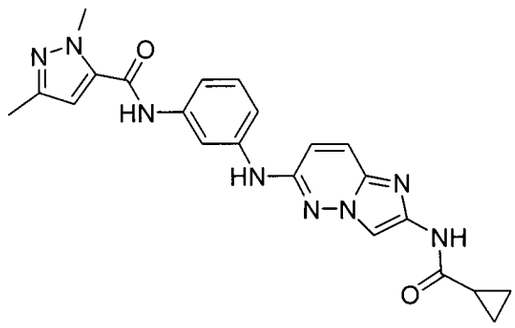


De la misma manera que en el Ejemplo 259 y usando ácido 3–cloro–1–metil–1H–pirazol–5–carboxílico (59 mg, 0,37 mmol), tetrahidrofurano (5 mL), N,N–dimetilformamida (1 gota), cloruro de oxalilo (130 µL, 1,5 mmol), N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,31 mmol) y N,N–dimetilacetamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (100 mg, 71%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,85 (4H, m), 1,84 – 1,97 (1H, m), 4,03 (3H, s), 7,02 – 7,14 (2H, m), 7,19 – 7,28 (1H, m), 7,37 – 7,47 (1H, m), 7,56 (1H, dd, J = 6,3, 2,9 Hz), 7,94 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,33 (1H, br. s), 11,08 (1H, s).

Ejemplo 317

Producción de N–[3–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}amino)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida



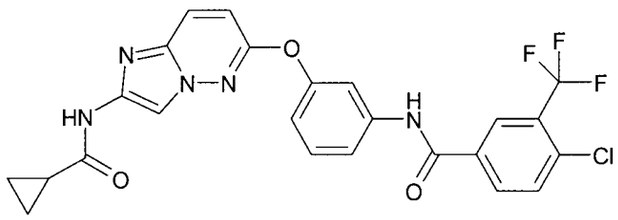
Una mezcla de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (330 mg, 1,0 mmol), N–(3–aminofenil)–1,3–dimetil–1H–pirazol–5–carboxamida (280 mg, 1,2 mmol), tris(dibencilidenacetona)dipaladio (0) (46 mg, 0,050 mmol), 2–diciclohexilfosfino–2',4',6'–tri–isopropil–1,1'–bifenilo (48 mg, 0,10 mmol), tert-butóxido de potasio (170 mg, 1,5 mmol) y ter–butanol se calentó a reflujo durante 2 días. acetato de etilo/tetrahidrofurano y solución acuosa saturada de hidrógeno–carbonato de sodio se añadieron a la mezcla, la capa acuosa se extrajo con acetato de etilo/tetrahidrofurano (×4). La capa orgánica combinada se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El filtrado se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→100/0) para dar el compuesto del título (37 mg, 9%) en forma de un sólido color café.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,88 (4H, m), 1,86 – 1,98 (1H, m), 2,22 (3H, s), 4,01 (3H, s), 6,85 (1H, s), 6,89 (1H, d, J = 9,6 Hz), 7,24 – 7,36 (2H, m), 7,45 – 7,53 (1H, m), 7,75 (1H, d, J = 9,6 Hz), 8,00 (1H, s), 8,21 (1H, s), 9,37 (1H, s), 10,15 (1H, s), 10,93

(1H, s).

Ejemplo 318

Producción de 4–cloro–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



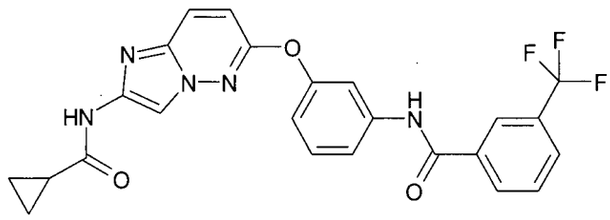
A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol) en N,N–dimetilformamida (6,0 mL) se añadieron ácido 4–cloro–3–(trifluorometil)benzoico (73 mg, 0,32 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,34 mmol) y 1–hidroxibenzotriazol (46 mg, 0,34 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→80/20) y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (130 mg, 77%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,64 – 0,93 (4H, m), 1,79 – 2,04 (1H, m), 6,99 – 7,13 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,59 –

7,69 (1H, m), 7,71 (1H, t, J = 2,1 Hz), 7,93 (1H, d, J = 8,4 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,24 (1H, dd, J = 8,4, 2,1 Hz), 8,37 (1H, d, J = 2,1 Hz), 10,64 (1H, s), 11,09 (1H, s).

Ejemplo 319

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,26 mmol), ácido 3–(trifluorometil)benzoico (54 mg, 0,29 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (55 mg, 0,29 mmol), 1–hidroxibenzotriazol (39 mg, 0,29 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (86 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,89 (4 H, m), 1,84 – 2,03 (1 H, m), 6,98 – 7,15 (2 H, m), 7,46 (1 H, t, J = 8,1 Hz), 7,60 – 7,70 (1 H, m), 7,73 (1 H, t, J = 2,1 Hz), 7,79 (1 H, t, J = 7,8 Hz), 7,91 – 8,02 (2 H, m), 8,06 (1 H, d, J = 9,6 Hz), 8,19 – 8,34 (2 H, m), 10,59 (1 H, s), 11,09 (1 H, s).

Ejemplo 320

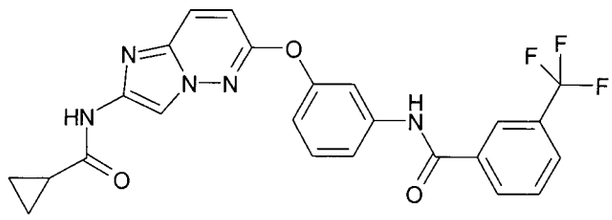
Producción de 3–(1–ciano–1–metiletil)–N–[3–({2–

P113

7,69 (1H, m), 7,71 (1H, t, J = 2,1 Hz), 7,93 (1H, d, J = 8,4 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,24 (1H, dd, J = 8,4, 2,1 Hz), 8,37 (1H, d, J = 2,1 Hz), 10,64 (1H, s), 11,09 (1H, s).

Ejemplo 319

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



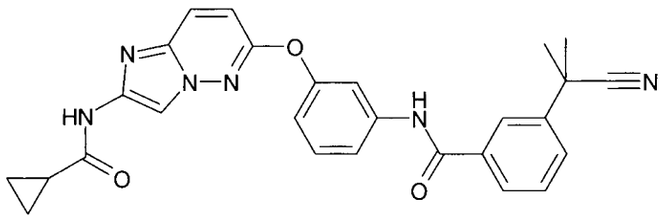
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,26 mmol), ácido 3–(trifluorometil)benzoico (54 mg, 0,29 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (55 mg, 0,29 mmol), 1–hidroxibenzotriazol (39 mg, 0,29 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (86 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,89 (4 H, m), 1,84 – 2,03 (1 H, m), 6,98 – 7,15 (2 H, m), 7,46 (1 H, t, J = 8,1 Hz), 7,60 – 7,70 (1 H, m), 7,73 (1 H, t, J = 2,1 Hz), 7,79 (1 H, t, J = 7,8 Hz), 7,91 – 8,02 (2 H, m), 8,06 (1 H, d, J = 9,6 Hz), 8,19 – 8,34 (2 H, m), 10,59 (1 H, s), 11,09 (1 H, s).

Ejemplo 320

Producción de 3–(1–ciano–1–metiletil)–N–[3–({2–

[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida

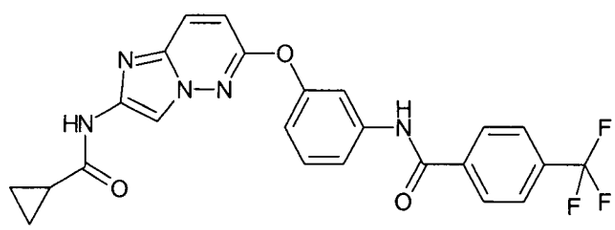


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol), ácido 3–(1–ciano–1–metiletil)benzoico (62 mg, 0,33 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,34 mmol), 1–hidroxibenzotriazol (46 mg, 0,34 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (120 mg, 77%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,74 (6H, s), 1,83 – 1,98 (1H, m), 6,99 – 7,04 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,54 – 7,69 (2H, m), 7,69 – 7,80 (2H, m), 7,92 (1H, dt, J = 7,8, 1,2 Hz), 7,98 (1H, s), 8,00 – 8,10 (2H, m), 10,45 (1H, s), 11,09 (1H, s).

Ejemplo 321

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–4–(trifluorometil)benzamida

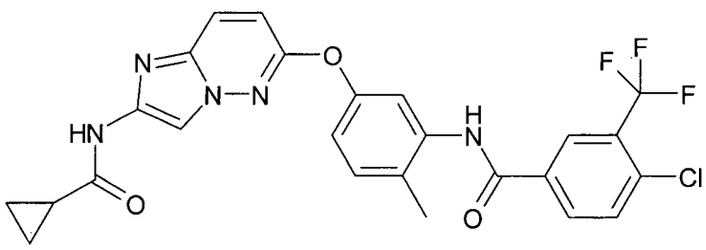


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol), ácido 4–(trifluorometil)benzoico (63 mg, 0,33 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,34 mmol), 1–hidroxibenzotriazol (46 mg, 0,34 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (110 mg, 68%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,62 – 0,94 (4H, m), 1,76 – 2,06 (1H, m), 6,99 – 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,63 – 7,71 (1H, m), 7,74 (1H, t, J = 2,1 Hz), 7,92 (2H, d, J = 8,2 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,13 (2H, d, J = 8,2 Hz), 10,60 (1H, s), 11,09 (1H, s).

Ejemplo 322

Producción de 4–cloro–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–(trifluorometil)benzamida



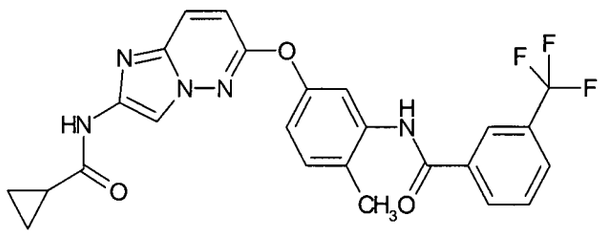
Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,25 mmol), ácido 4–cloro–3–(trifluorometil)benzoico (57 mg, 0,25 mmol), clorhidrato de N–[3–

(dimetilamino)propil]–N'–etilcarbodiimida (50 mg, 0,26 mmol), 1–hidroxibenzotriazol (35 mg, 0,26 mmol) y N,N–dimetilformamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (83 mg, 63%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,84 – 1,97 (1H, m), 2,26 (3H, s), 7,05 (1H, d, J = 9,6 Hz), 7,12 (1H, dd, J = 8,4, 2,7 Hz), 7,30 (1H, d, J = 2,7 Hz), 7,36 (1H, d, J = 8,4 Hz), 7,86 – 7,97 (2H, m), 8,03 (1H, d, J = 9,6 Hz), 8,25 (1H, dd, J = 8,4, 1,8 Hz), 8,39 (1H, d, J = 1,8 Hz), 10,26 (1H, s), 11,07 (1H, s).

Ejemplo 323

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–3–(trifluorometil)benzamida

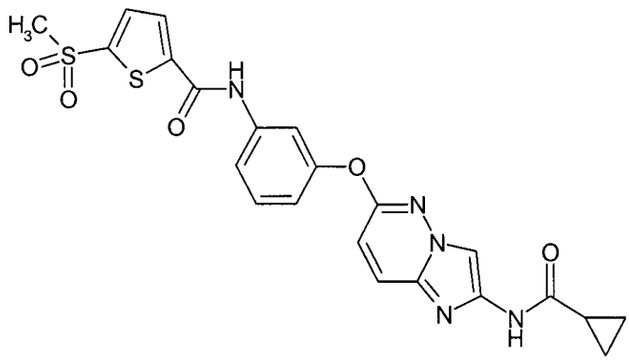


Usando N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,25 mmol), ácido ácido 3–(trifluorometil)benzoico (57 mg, 0,25 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (50 mg, 0,26 mmol), 1–hidroxibenzotriazol (35 mg, 0,26 mmol) y N,N–dimetilformamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (83 mg, 63%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,85 – 1,99 (1H, m), 2,27 (3H, s), 7,05 (1H, d, J = 9,6 Hz), 7,11 (1H, dd, J = 8,4, 2,4 Hz), 7,31 (1H, d, J = 2,4 Hz), 7,36 (1H, d, J = 8,6 Hz), 7,78 (1H, t, J = 7,8 Hz), 7,90 – 8,00 (2H, m), 8,03 (1H, d, J = 9,6 Hz), 8,20 – 8,36 (2H, m), 10,21 (1H, s), 11,07 (1H, s).

Ejemplo 324

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–(metilsulfonil)tiofen–2–carboxamida



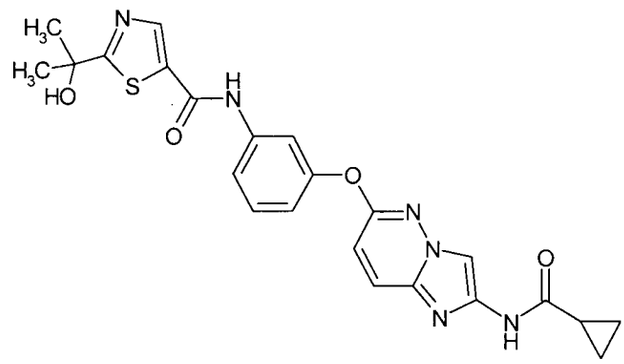
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol), ácido 5–(metilsulfonil)tiofen–2–carboxílico (47 mg, 0,33 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,34 mmol), 1–hidroxibenzotriazol (46 mg, 0,34 mmol) y N,N–dimetilformamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (41 mg, 26%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,82 – 1,98 (1H, m), 3,41 (3H, s), 6,99 – 7,14 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,58 – 7,65 (1H, m), 7,66 (1H, t, J = 2,1 Hz), 7,88 (1H, d, J = 4,2

Hz), 7,97 (1H, s), 8,03 – 8,09 (2H, m), 10,66 (1H, s), 11,09 (1H, s).

Ejemplo 325

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–(1–hidroxi–1–metiletil)–1,3–tiazol–5–carboxamida



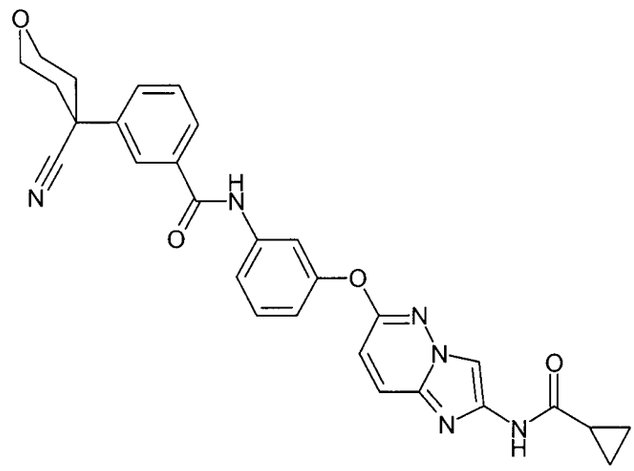
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol), ácido 2–(1–hidroxi–1–metiletil)–1,3–tiazol–5–carboxílico (96 mg, 0,51 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (95 mg, 0,50 mmol), 1–hidroxibenzotriazol (67 mg, 0,50 mmol) y N,N–dimetilformamida (8,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (99 mg, 43%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,85 (4H, m), 1,51 (6H, s), 1,85 – 1,98 (1H, m), 6,17 (1H, s), 6,98 – 7,04 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,44 (1H, t, J = 8,1 Hz), 7,54 – 7,68 (2H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,43 (1H, s), 10,42 (1H, s), 11,09 (1H, s).

Ejemplo 326

LLL9

Producción de 3-(4-cianotetrahidro-2H-piran-4-il)-N-[3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)fenil]benzamida



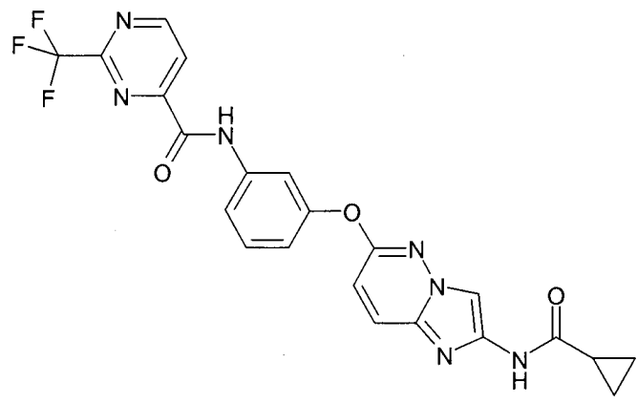
Usando N-[6-(3-aminofenoxi)imidazo[1,2-b]piridazin-2-il]ciclopropancarboxamida (150 mg, 0,49 mmol), ácido 3-(4-cianotetrahidro-2H-piran-4-il)benzoico (120 mg, 0,51 mmol), clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida (95 mg, 0,50 mmol), 1-hidroxibenzotriazol (67 mg, 0,50 mmol), trietilamina (130 μL, 0,97 mmol) y N,N-dimetilformamida (8,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (150 mg, 58%) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,67 - 0,92 (4H, m), 1,85 - 1,98 (1H, m), 2,10 - 2,23 (4H, m), 3,58 - 3,79 (2H, m), 3,86 - 4,15 (2H, m), 6,95 - 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,52 - 7,70 (2H, m), 7,71 (1H, t, J = 2,1 Hz), 7,76 - 7,85 (1H, m), 7,92 - 8,00 (2H, m), 8,02 - 8,12 (2H, m), 10,44 (1H, s),

11,09 (1H, s).

Ejemplo 327

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–(trifluorometil)pirimidin–4–carboxamida

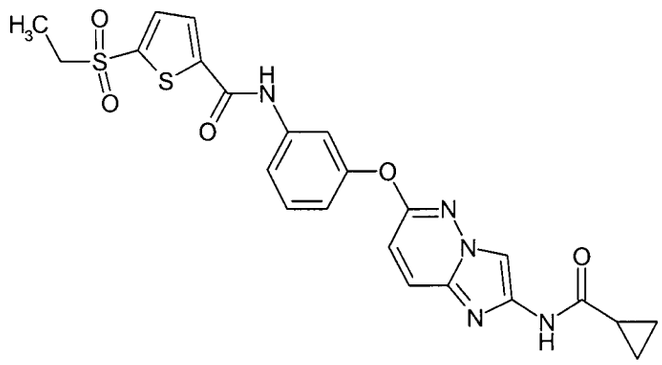


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol), ácido 2–(trifluorometil)pirimidin–4–carboxílico (150 mg, 0,83 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (100 mg, 0,53 mmol), 1–hidroxibenzotriazol (72 mg, 0,53 mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (130 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,88 (4H, m), 1,84 – 1,98 (1H, m), 7,04 – 7,15 (2H, m), 7,49 (1H, t, J = 8,1 Hz), 7,72 – 7,86 (2H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,36 (1H, d, J = 4,8 Hz), 9,35 (1H, d, J = 4,8 Hz), 10,82 (1H, s), 11,09 (1H, s).

Ejemplo 328

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–(etilsulfonil)tiofen–2–carboxamida



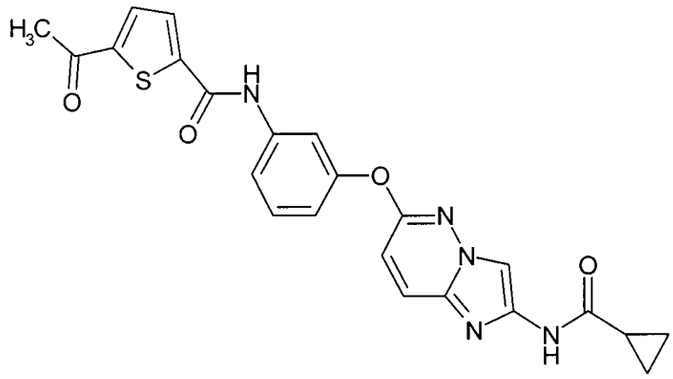
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol), ácido 5–(etilsulfonil)tiofen–2–carboxílico (110 mg, 0,50 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (98 mg, 0,51 mmol), 1–hidroxibenzotriazol (69 mg, 0,51 mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (180 mg, 71%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,19 (3H, t, J = 7,2 Hz), 1,86 – 1,98 (1H, m), 3,47 (2H, q, J = 7,2 Hz), 7,01 – 7,12 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,58 – 7,64 (1H, m), 7,66 (1H, t, J = 2,1 Hz), 7,86 (1H, d, J = 3,9 Hz), 7,97 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,09 (1H, d, J = 3,9 Hz), 10,66 (1H, s), 11,09 (1H, s).

Ejemplo 329

Producción de 5–acetil–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]tiofen–2–carboxamida

P 122

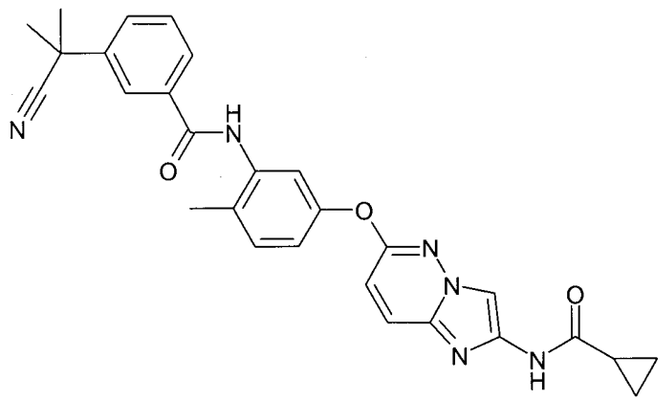


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol), ácido 5–acetiltiofen–2–carboxílico (85 mg, 0,50 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (98 mg, 0,51 mmol), 1–hidroxibenzotriazol (69 mg, 0,51 mmol) y N,N–dimetilformamida (6,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (110 mg, 48%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,86 – 1,98 (1H, m), 2,58 (3H, s), 7,00 – 7,13 (2H, m), 7,45 (1H, t, J = 8,1 Hz), 7,59 – 7,66 (1H, m), 7,67 (1H, t, J = 2,1 Hz), 7,96 – 8,01 (2H, m), 8,02 – 8,11 (2H, m), 10,55 (1H, s), 11,09 (1H, s).

Ejemplo 330

Producción de 3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]benzamida



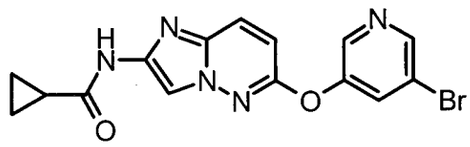
A una solución de ácido 3–(1–ciano–1–metiletil)benzoico (560 mg, 2,97 mmol) en tetrahidrofurano (15 mL) se añadieron cloruro de oxalilo (320 µL, 3,71 mmol) y N,N–dimetilformamida (2 gotas), y la mezcla se agitó a temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, y el residuo se disolvió en N–metilpirrolidona (15 mL). Se añadió N–[6–(3–amino–4–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (800 mg, 2,47 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se diluyó con ácido clorhídrico 1 N, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 50/50→100/0) para dar un aceite incoloro. El aceite se disolvió acetato de etilo, y se añadió éter diisopropílico para permitir la precipitación para dar el compuesto del título (220 mg, 18%) en forma de un sólido blanco.

P 124

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,86 (4H, m), 1,74 (6H, s), 1,84 – 1,98 (1H, m), 2,27 (3H, s), 7,05 (1H, d, J = 9,6 Hz), 7,10 (1H, dd, J = 8,4, 2,7 Hz), 7,31 (1H, d, J = 2,7 Hz), 7,36 (1H, d, J = 8,4 Hz), 7,59 (1H, t, J = 7,8 Hz), 7,70 – 7,80 (1H, m), 7,91 – 7,99 (2H, m), 8,00 – 8,11 (2H, m), 10,04 (1H, s), 11,07 (1H, s).

Ejemplo 331

Producción de N–{6–[(5–bromopiridin–3–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



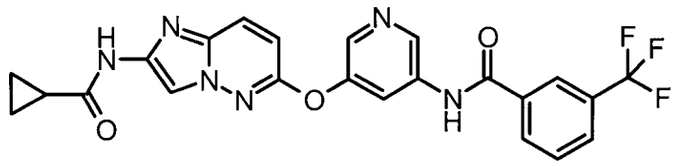
A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (1,7 g, 5,0 mmol) en N,N–dimetilformamida (20 mL) se añadieron 5–bromopiridin–3–ol (1,7 g, 10 mmol) y carbonato de potasio (1,7 g, 13 mmol), y la mezcla se agitó a 140 °C durante 8 h. Tras enfriar la mezcla hasta temperatura ambiente, la mezcla se diluyó con agua, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 50/50→100/0), y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (1,6 g, 85%) en forma de un polvo amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,67 – 0,90 (4H, m), 1,85 –

1,98 (1H, m), 7,16 (1H, m), 7,98 (1H, s), 8,08 (1H, d, J = 9,6 Hz), 8,19 – 8,25 (1H, m), 8,61 – 8,67 (2H, m), 11,09 (1H, s).

Ejemplo 332

Producción de N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)piridin–3–il]–3–(trifluorometil)benzamida



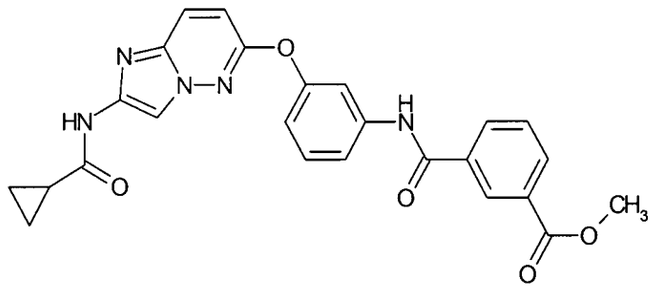
A una solución de N–{6–[(5–bromopiridin–3–il)oxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (200 mg, 0,53 mmol), 3–(trifluorometil)benzamida (160 mg, 0,91 mmol), trans–1,2–diaminociclohexano (15 mg, 0,13 mmol) y carbonato de potasio (220 mg, 1,6 mmol) en 1,4–dioxano (3,0 mL) se añadió yoduro de cobre (I) (25 mg, 0,13 mmol) bajo una atmósfera de argón, y la mezcla se agitó a 110 °C durante 60 h. La mezcla de reacción se enfrió, y se diluyó con tetrahidrofurano/acetato de etilo al 20%. La mezcla se lavó con agua, solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 60/40→100/0) y se precipitó en acetato de etilo/hexano para dar el compuesto del título (110 mg, 42%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,84 – 1,98 (1H, m), 7,17 (1H, d, J = 9,6 Hz), 7,81 (1H, t, J = 7,8 Hz), 7,96 –

8,04 (2H, m), 8,10 (1H, d, J = 9,6 Hz), 8,20 (1H, t, J = 2,4 Hz), 8,23 – 8,35 (2H, m), 8,38 (1H, d, J = 2,4 Hz), 8,85 (1H, d, J = 2,4 Hz), 10,83 (1H, s), 11,10 (1H, s).

Ejemplo 333

Producción de 3–({[3–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)fenil]amino}carbonil)benzoato de metilo

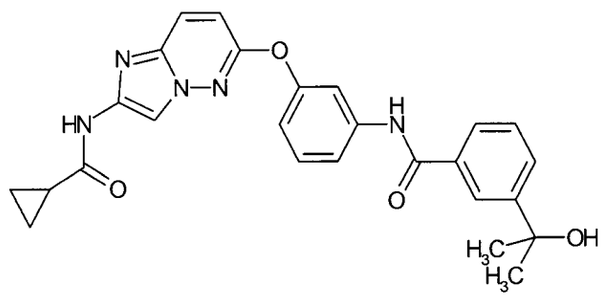


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (250 mg, 0,81 mmol), ácido 3–(metoxicarbonil)benzoico (150 mg, 0,83 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (160 mg, 0,84 mmol), 1–hidroxibenzotriazol (110 mg, 0,81 mmol) y N,N–dimetilformamida (8,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (270 mg, 72%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,84 – 1,98 (1H, m), 3,91 (3H, s), 6,97 – 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,63 – 7,79 (3H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,12 – 8,19 (1H, m), 8,19 – 8,26 (1H, m), 8,52 (1H, t, J = 1,5 Hz), 10,59 (1H, s), 11,09 (1H, s).

Ejemplo 334

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(1–hidroxi–1–metiletil)benzamida



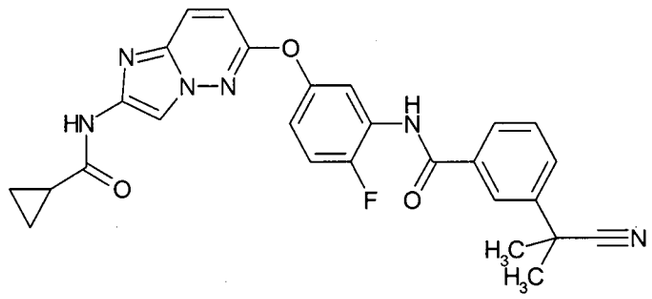
A una solución de 3–({[3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]amino}carbonil)benzoato de metilo en tetrahidrofurano (5,0 mL) se añadió gota a gota una solución de bromuro de metilmagnesio 1,4 M en tetrahidrofurano/tolueno (0,76 mL, 1,1 mmol) bajo enfriamiento con hielo. Después de la adición gota a gota, la mezcla de reacción se agitó a temperatura ambiente durante 12 h, y se agregó agua (10 mL). Se añadieron ácido clorhídrico 1 N (5,0 mL) se añadió a la mezcla, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 40/60→100/0) y se precipitó en éter diisopropílico/hexano para dar el compuesto del título (19 mg, 19%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,46 (6H,

s), 1,85 – 1,97 (1H, m), 5,14 (1H, s), 6,96 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,37 – 7,50 (2H, m), 7,67 (2H, m), 7,73 (1H, t, J = 2,1 Hz), 7,75 – 7,81 (1H, m), 7,98 (1H, s), 8,01 (1H, t, J = 1,5 Hz), 8,05 (1H, d, J = 9,6 Hz), 10,35 (1H, s), 11,09 (1H, s).

Ejemplo 335

Producción de 3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]benzamida



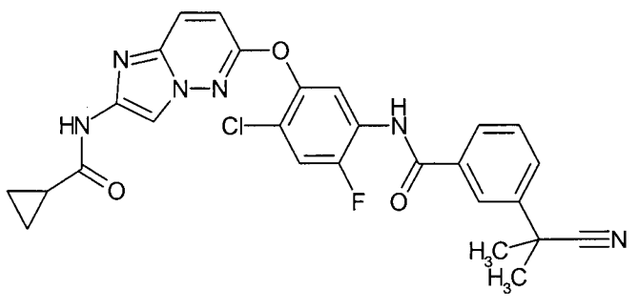
A una solución de ácido 3–(1–ciano–1–metiletil)benzoico (100 mg, 0,55 mmol) en tetrahidrofurano (2,0 mL) se añadieron cloruro de oxalilo (59 μL, 0,69 mmol) y N,N–dimetilformamida (1 gota), y la mezcla se agitó a temperatura ambiente durante 2 h. El solvente se evaporó a presión reducida, y el residuo se disolvió en N–metilpirrolidona (2 mL). Se añadió N–[6–(3–amino–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) a la mezcla, y la mezcla se agitó a temperatura ambiente durante 10 h. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre

sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 40/60→100/0), y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (140 mg, 62%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,74 (6H, s), 1,85 – 1,98 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,15 – 7,26 (1H, m), 7,34 – 7,48 (1H, m), 7,52 – 7,65 (2H, m), 7,71 – 7,82 (1H, m), 7,89 – 7,98 (2H, m), 8,01 – 8,12 (2H, m), 10,32 (1H, s), 11,07 (1H, s).

Ejemplo 336

Producción de N–[4–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(1–ciano–1–metiletil)benzamida



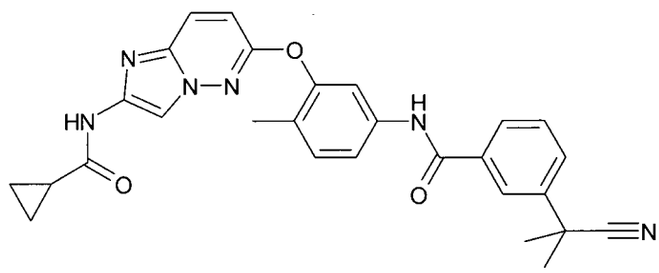
Usando ácido 3–(1–ciano–1–metiletil)benzoico (100 mg, 0,55 mmol), cloruro de oxalilo (59 μL, 0,69 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N–[6–(5–amino–2–cloro–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (170 mg, 0,46 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (170 mg, 70%) en forma de un polvo blanco.

P130

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,66 – 0,91 (4H, m), 1,74 (6H, s), 1,86 – 1,98 (1H, m), 7,18 (1H, d, J = 9,6 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,71 – 7,86 (3H, m), 7,89 – 7,99 (2H, m), 8,04 – 8,16 (2H, m), 10,42 (1H, s), 11,08 (1H, s).

Ejemplo 337

Producción de 3–(1–ciano–1–metiletil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]benzamida



Usando N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol), ácido 3–(1–ciano–1–metiletil)benzoico (92 mg, 0,49 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (94 mg, 0,49 mmol), 1–hidroxibenzotriazol (66 mg, 0,49 mmol) y N,N–dimetilformamida (7,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (160 mg, 70%) en forma de un polvo blanco.

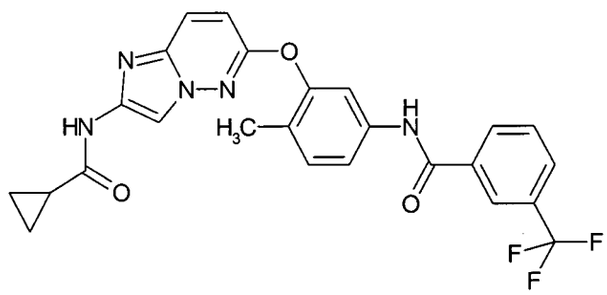
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,84 (4H, m), 1,73 (6H, s), 1,85 – 1,98 (1H, m), 2,15 (3H, s), 7,08 (1H, d, J = 9,6 Hz), 7,34 (1H, d, J = 8,4 Hz), 7,54 – 7,66 (3H, m), 7,70 – 7,78 (1H, m), 7,86 – 7,96 (2H, m), 8,01 (1H, t, J = 1,8 Hz), 8,05 (1H, d, J = 9,6 Hz), 10,37

1131

(1H, s), 11,07 (1H, s).

Ejemplo 338

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]–3–(trifluorometil)benzamida



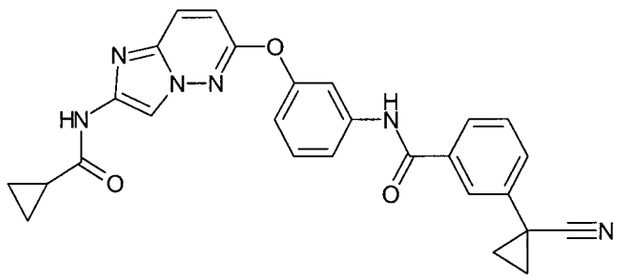
Usando N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol), ácido 3–(trifluorometil)benzoico (93 mg, 0,49 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (94 mg, 0,49 mmol), 1–hidroxibenzotriazol (66 mg, 0,49 mmol) y N,N–dimetilformamida (7,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (166 mg, 72%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,89 (4H, m), 1,82 – 2,02 (1H, m), 2,16 (3H, s), 7,08 (1H, d, J = 9,6 Hz), 7,35 (1H, d, J = 8,4 Hz), 7,55 – 7,69 (2H, m), 7,77 (1H, t, J = 7,8 Hz), 7,91 – 8,00 (2H, m), 8,06 (1H, d, J = 9,6 Hz), 8,19 – 8,31 (2H, m), 10,51 (1H, s), 11,07 (1H, s).

Ejemplo 339

Producción de 3–(1–cianociclopropil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–

il}oxi)fenil]benzamida

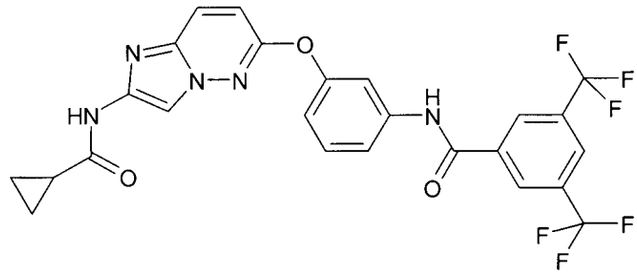


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (170 mg, 0,55 mmol), ácido 3–(1–cianociclopropil)benzoico (100 mg, 0,55 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (110 mg, 0,55 mmol), 1–hidroxibenzotriazol (74 mg, 0,55 mmol) y N,N–dimetilformamida (10 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (122 mg, 47%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,58 – 0,92 (4H, m), 1,55 – 1,68 (2H, m), 1,77 – 1,86 (2H, m), 1,86 – 1,99 (1H, m), 7,00 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,44 (1H, t, J = 8,1 Hz), 7,50 – 7,61 (2H, m), 7,61 – 7,68 (1H, m), 7,71 (1H, t, J = 2,1 Hz), 7,81 (1H, s), 7,84 – 7,91 (1H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,42 (1H, s), 11,09 (1H, s).

Ejemplo 340

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3,5–bis(trifluorometil)benzamida

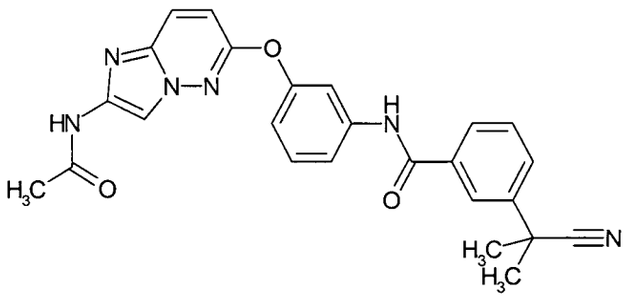


Usando ácido 3,5–bis(trifluorometil)benzoico (120 mg, 0,45 mmol), cloruro de oxalilo (48 μL, 0,56 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (120 mg, 0,37 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (63 mg, 31%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,86 (4H, m), 1,85 – 1,98 (1H, m), 7,01 – 7,15 (2H, m), 7,48 (1H, t, J = 8,1 Hz), 7,63 – 7,69 (1H, m), 7,71 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 8,38 (1H, s), 8,59 (2H, s), 10,77 (1H, s), 11,09 (1H, s).

Ejemplo 341

Producción de N–(3–{[2–(acetilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(1–ciano–1–metiletil)benzamida



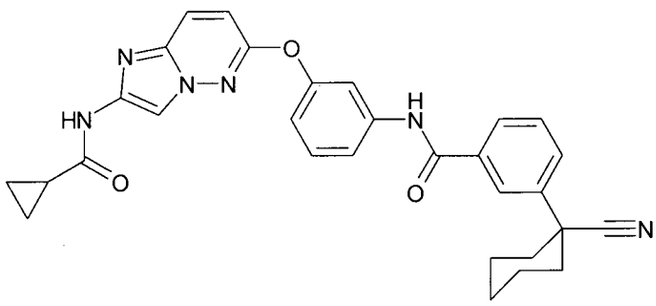
Usando ácido 3–(1–ciano–1–metiletil)benzoico (160 mg, 0,85

mmol), cloruro de oxalilo (90 μL, 1,1 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (4,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (200 mg, 0,71 mmol) y N–metilpirrolidona (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (220 mg, 69%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,74 (6H, s), 2,07 (3H, s), 6,97 – 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,63 – 7,69 (1H, m), 7,70 – 7,80 (2H, m), 7,88 – 7,96 (1H, m), 8,00 (1H, s), 8,02 (1H, t, J = 1,8 Hz), 8,05 (1H, d, J = 9,6 Hz), 10,45 (1H, s), 10,80 (1H, s).

Ejemplo 342

Producción de 3–(1–cianociclohexil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida



Usando ácido 3–(1–cianociclohexil)benzoico (100 mg, 0,45 mmol), cloruro de oxalilo (48 μL, 0,56 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi) imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (120 mg, 0,37 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de

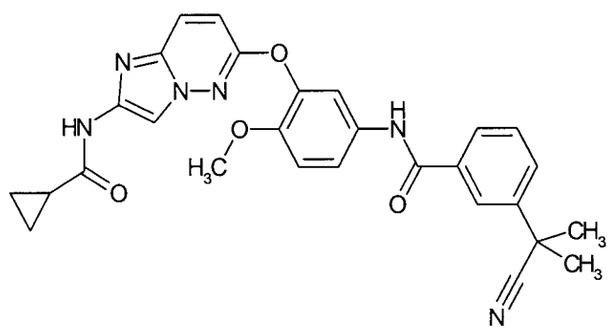
1135

la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (150 mg, 78%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,85 (4H, m), 1,22 – 1,41 (1H, m), 1,54 – 1,98 (8H, m), 2,05 – 2,20 (2H, m), 6,97 – 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,63 – 7,69 (1H, m), 7,72 (1H, t, J = 2,1 Hz), 7,74 – 7,80 (1H, m), 7,89 – 7,96 (1H, m), 7,98 (1H, s), 8,01 – 8,10 (2H, m), 10,44 (1H, s), 11,09 (1H, s).

Ejemplo 343

Producción de 3–(1–ciano–1–metiletil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]benzamida



Usando N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,44 mmol), ácido 3–(1–ciano–1–metiletil)benzoico (88 mg, 0,46 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (87 mg, 0,46 mmol), 1–hidroxibenzotriazol (62 mg, 0,46 mmol) y N,N–dimetilformamida (10 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (160 mg, 71%) en

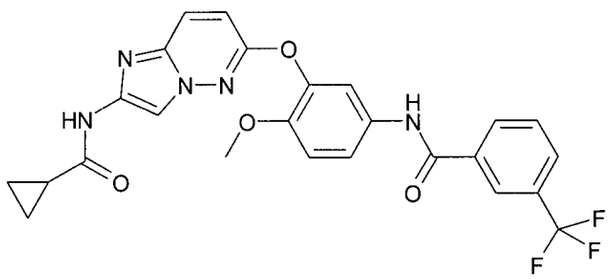
1136

forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,84 (4H, m), 1,74 (6H, s), 1,85 – 1,97 (1H, m), 3,72 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,0 Hz), 7,59 (1H, t, J = 7,8 Hz), 7,65 (1H, dd, J = 9,0, 2,4 Hz), 7,71 (1H, d, J = 2,4 Hz), 7,72 – 7,78 (1H, m), 7,89 (1H, s), 7,90 – 7,95 (1H, m), 7,97 – 8,07 (2H, m), 10,32 (1H, s), 11,05 (1H, s).

Ejemplo 344

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]–3–(trifluorometil)benzamida



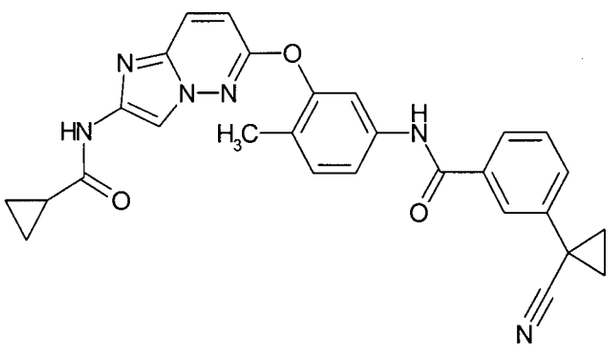
A una solución de N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,44 mmol) en N–metilpirrolidona (6,0 mL) se añadió cloruro de 3–(trifluorometil)benzoílo (92 mg, 0,44 mmol) bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se diluyó con ácido clorhídrico 1 N y se extrajo con acetato de etilo, y la capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano =

50/50→100/0), y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (180 mg, 80%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,83 (4H, m), 1,82 – 1,97 (1H, m), 3,73 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,23 (1H, d, J = 9,0 Hz), 7,66 (1H, dd, J = 9,0, 2,4 Hz), 7,73 (1H, d, J = 2,4 Hz), 7,78 (1H, t, J = 7,8 Hz), 7,89 (1H, s), 7,96 (1H, d, J = 7,8 Hz), 8,01 (1H, d, J = 10,2 Hz), 8,18 – 8,36 (2H, m), 10,48 (1H, s), 11,05 (1H, s).

Ejemplo 345

Producción de 3–(1–cianociclopropil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]benzamida



Usando N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol), ácido 3–(1–cianociclopropil)benzoico (91 mg, 0,49 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (94 mg, 0,49 mmol), 1–hidroxibenzotriazol (66 mg, 0,49 mmol) y N,N–dimetilformamida (7,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (178 mg, 75%) en

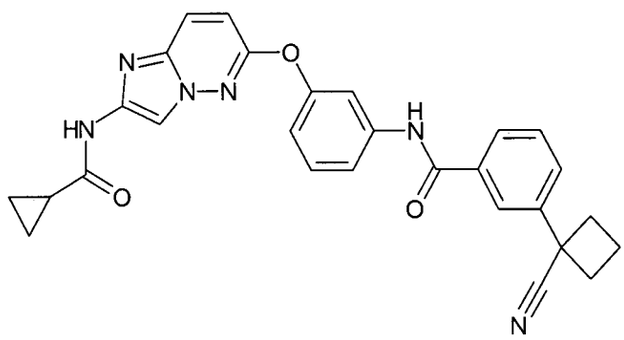
1138

forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,69 – 0,88 (4H, m), 1,55 – 1,65 (2H, m), 1,76 – 1,84 (2H, m), 1,85 – 2,00 (1H, m), 2,15 (3H, s), 7,08 (1H, d, J = 9,6 Hz), 7,34 (1H, d, J = 8,1 Hz), 7,48 – 7,69 (4H, m), 7,80 (1H, s), 7,82 – 7,89 (1H, m), 7,92 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,34 (1H, s), 11,06 (1H, s).

Ejemplo 346

Producción de 3–(1–cianociclobutil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida



Usando ácido 3–(1–cianociclobutil)benzoico (110 mg, 0,56 mmol), cloruro de oxalilo (60 μL, 0,70 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,47 mmol) y N–metilpirrolidona (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (140 mg, 60%) en forma de un polvo blanco.

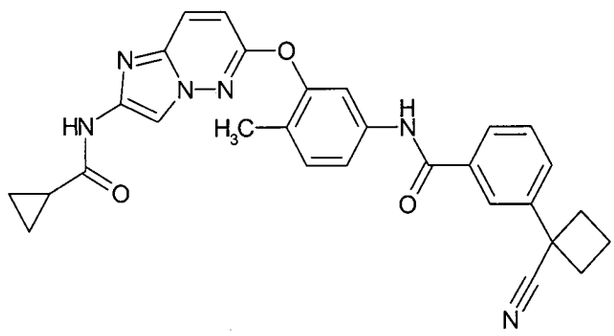
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,81 – 2,12 (2H, m), 2,20 – 2,41 (1H, m), 2,60 – 2,86 (4H, m), 6,97 – 7,05

1139

(1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,64 – 7,76 (3H, m), 7,89 – 8,01 (3H, m), 8,06 (1H, d, J = 9,6 Hz), 10,46 (1H, s), 11,09 (1H, s).

Ejemplo 347

Producción de 3–(1–cianociclobutil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]benzamida

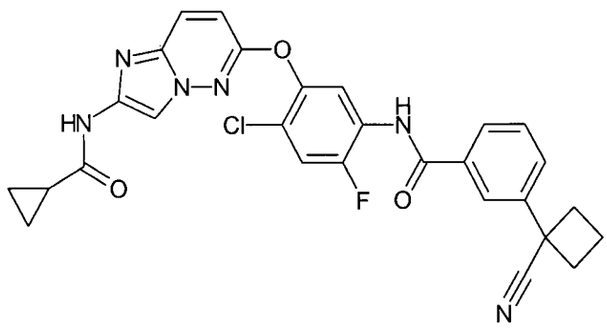


Usando ácido 3–(1–cianociclobutil)benzoico (110 mg, 0,56 mmol), cloruro de oxalilo (60 µL, 0,70 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,46 mmol) y N–metilpirrolidona (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (150 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,66 – 0,92 (4H, m), 1,72 – 2,11 (2H, m), 2,15 (3H, s), 2,20 – 2,42 (1H, m), 2,60 – 2,94 (4H, m), 7,08 (1H, d, J = 9,6 Hz), 7,34 (1H, d, J = 8,4 Hz), 7,53 – 7,75 (4H, m), 7,81 – 7,99 (3H, m), 8,05 (1H, d, J = 9,6 Hz), 10,38 (1H, s), 11,07 (1H, s).

Ejemplo 348

Producción de N–[4–cloro–5–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(1–cianociclobutil)benzamida



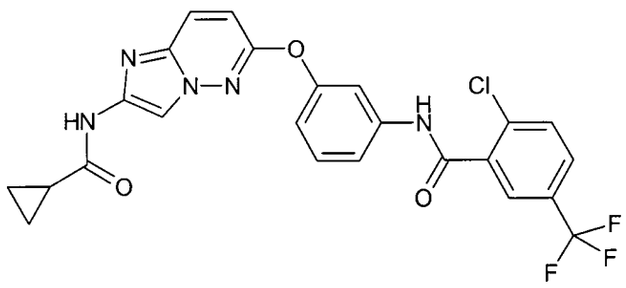
Usando ácido 3–(1–cianociclobutil)benzoico (110 mg, 0,56 mmol), cloruro de oxalilo (60 μL, 0,70 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–cloro–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (170 mg, 0,46 mmol) y N–metilpirrolidona (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (170 mg, 68%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,80 (4H, s), 1,85 – 1,96 (1H, m), 1,97 – 2,12 (1H, m), 2,20 – 2,41 (1H, m), 2,60 – 2,88 (4H, m), 7,18 (1H, d, J = 9,6 Hz), 7,61 (1H, t, J = 7,8 Hz), 7,67 – 7,75 (1H, m), 7,79 (1H, d, J = 2,7 Hz), 7,82 (1H, s), 7,88 – 7,97 (2H, m), 8,02 (1H, t, J = 1,5 Hz), 8,09 (1H, d, J = 9,6 Hz), 10,44 (1H, s), 11,08 (1H, s).

Ejemplo 349

Producción de 2–cloro–N–[3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–5–

(trifluorometil)benzamida

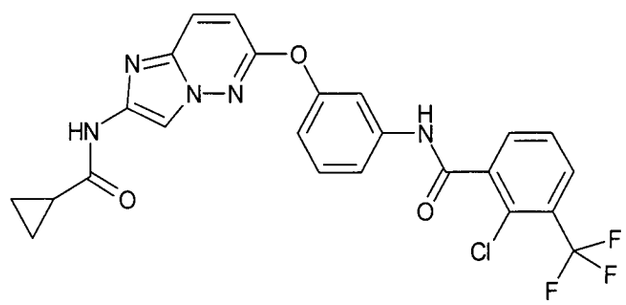


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol), 2cloruro de ácido –cloro–5–(trifluorometil)benzoílo (87 mg, 0,36 mmol) y N–metilpirrolidona (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 344, se obtuvo el compuesto del título (130 mg, 75%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,86 (4H, m), 1,86 – 1,98 (1H, m), 6,95 – 7,18 (2H, m), 7,45 (1H, t, J = 8,1 Hz), 7,50 – 7,58 (1H, m), 7,67 (1H, t, J = 2,1 Hz), 7,77 – 7,93 (2H, m), 7,97 (1H, s), 8,02 – 8,08 (2H, m), 10,80 (1H, s), 11,09 (1H, s).

Ejemplo 350

Producción de 2–cloro–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

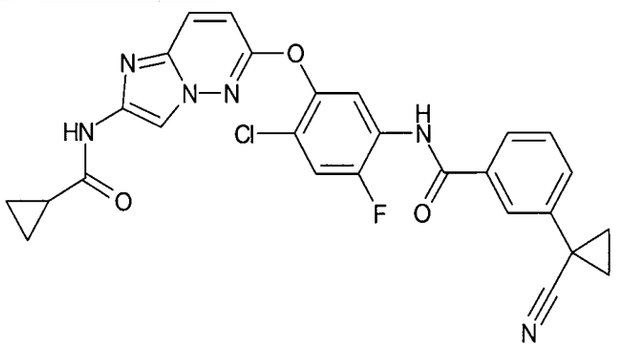


Usando ácido 2–cloro–3–(trifluorometil)benzoico (88 mg, 0,39 mmol), cloruro de oxalilo (42 μL, 0,49 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,32 mmol) y N–metilpirrolidona (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (110 mg, 68%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,86 – 1,97 (1H, m), 6,99 – 7,15 (2H, m), 7,45 (1H, t, J = 8,1 Hz), 7,49 – 7,58 (1H, m), 7,61 – 7,76 (2H, m), 7,88 – 7,95 (1H, m), 7,96 – 8,02 (2H, m), 8,05 (1H, d, J = 9,6 Hz), 10,83 (1H, s), 11,09 (1H, s).

Ejemplo 351

Producción de N–[4–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–(1–cianociclopropil)benzamida



Usando ácido 3–(1–cianociclopropil)benzoico (100 mg, 0,50 mmol), cloruro de oxalilo (55 μL, 0,62 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–cloro–4–fluorofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,42 mmol) y N–metilpirrolidona (3,0 mL) como materiales

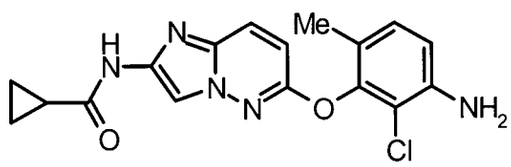
1143

de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (160 mg, 73%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,83 (4H, m), 1,55 – 1,66 (2H, m), 1,76 – 1,85 (2H, m), 1,86 – 1,97 (1H, m), 7,18 (1H, d, J = 9,6 Hz), 7,46 – 7,65 (2H, m), 7,79 (1H, d, J = 2,7 Hz), 7,82 (1H, s), 7,83 – 7,91 (2H, m), 7,92 (1H, s), 8,09 (1H, d, J = 9,6 Hz), 10,40 (1H, s), 11,08 (1H, s).

Ejemplo 352

Producción de N–[6–(3–amino–2–cloro–6–metilfenoxi)imidazo [1,2–b]piridazin–2–il]ciclopropancarboxamida



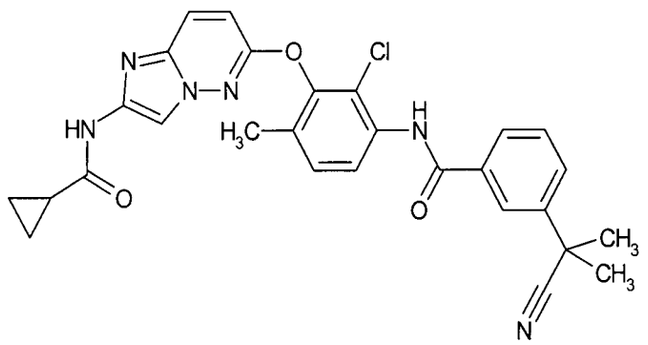
A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (2,0 g, 6,1 mmol) en N,N–dimetilformamida (20 mL) se añadieron 3–amino–2–cloro–6–metilfenol (1,9 g, 12 mmol) y carbonato de potasio (2,1 g, 15 mmol), y la mezcla se agitó a 140 °C durante 12 h. Tras enfriar la mezcla hasta temperatura ambiente, la mezcla se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de

etilo/hexano = 50/50→80/20) y se precipitó en metanol/éter diisopropílico para dar el compuesto del título (1,4 g, 64%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,83 (4H, m), 1,85 – 1,97 (1H, m), 2,00 (3H, s), 5,37 (2H, s), 6,69 (1H, d, J = 8,4 Hz), 6,99 (1H, d, J = 9,0 Hz), 7,07 (1H, d, J = 9,6 Hz), 7,87 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 11,04 (1H, s).

Ejemplo 353

Producción de N–[2–cloro–3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]–3–(1–ciano–1–metiletil)benzamida



Usando ácido 3–(1–cianociclopropil)benzoico (95 mg, 0,50 mmol), cloruro de oxalilo (55 μL, 0,63 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–amino–2–cloro–6–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,42 mmol) y N–metilpirrolidona (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (110 mg, 51%) en forma de un polvo blanco.

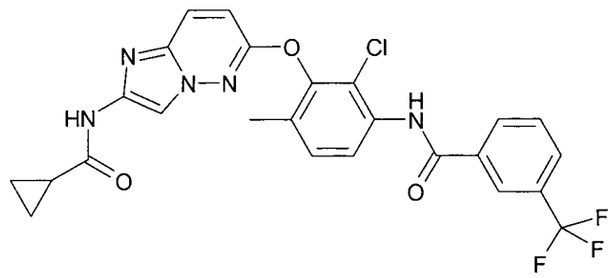
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,63 – 0,95 (4H, m), 1,74 (6H,

1145

s), 1,82 – 1,97 (1H, m), 2,22 (3H, s), 7,20 (1H, d, J = 9,6 Hz), 7,34 – 7,53 (2H, m), 7,59 (1H, t, J = 7,8 Hz), 7,76 (1H, dq, J = 7,8, 1,2 Hz), 7,85 (1H, s), 7,97 (1H, dt, J = 7,8, 1,2 Hz), 8,06 – 8,15 (2H, m), 10,25 (1H, s), 11,06 (1H, s).

Ejemplo 354

Producción de N–[2–cloro–3–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)–4–metilfenil]–3–(trifluorometil)benzamida



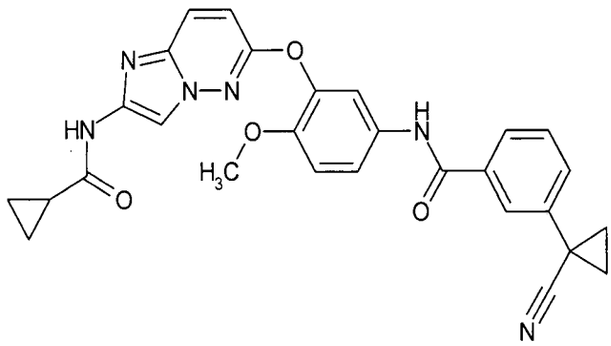
Usando N–[6–(3–amino–2–cloro–6–metilfenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,42 mmol), cloruro de 3–(trifluorometil)benzoílo (92 mg, 0,44 mmol) y N–metilpirrolidona (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 344, se obtuvo el compuesto del título (130 mg, 60%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,87 (4H, m), 1,81 – 1,98 (1H, m), 2,22 (3H, s), 7,20 (1H, d, J = 9,6 Hz), 7,33 – 7,58 (2H, m), 7,79 (1H, t, J = 7,8 Hz), 7,85 (1H, s), 7,98 (1H, d, J = 7,8 Hz), 8,09 (1H, d, J = 9,6 Hz), 8,29 (1H, d, J = 7,8 Hz), 8,34 (1H, s), 10,45 (1H, s), 11,06 (1H, s).

Ejemplo 355

L 146

Producción de 3-(1-cianociclopropil)-N-[3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)-4-metoxifenil]benzamida



Usando ácido 3-(1-cianociclopropil)benzoico (40 mg, 0,21 mmol), cloruro de oxalilo (23 μL, 0,27 mmol), N,N-dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N-[6-(5-amino-2-metoxifenoxi)imidazo[1,2-b]piridazin-2-il]ciclopropancarboxamida (60 mg, 0,18 mmol) y N-metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (67 mg, 74%) en forma de un polvo blanco.

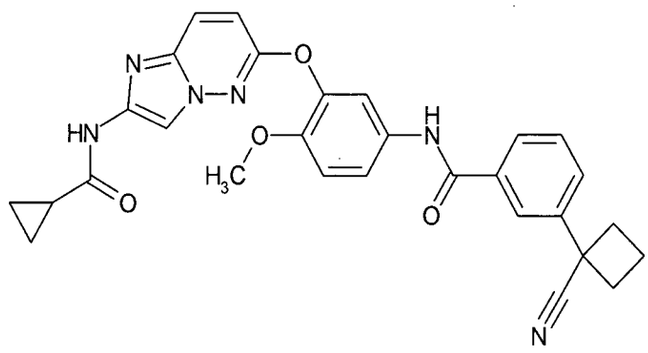
^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,70 – 0,83 (4H, m), 1,54 – 1,65 (2H, m), 1,75 – 1,86 (2H, m), 1,86 – 1,98 (1H, m), 3,72 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,0 Hz), 7,48 – 7,60 (2H, m), 7,64 (1H, dd, J = 9,0, 2,4 Hz), 7,71 (1H, d, J = 2,4 Hz), 7,82 (1H, s), 7,84 – 7,92 (2H, m), 8,01 (1H, d, J = 9,6 Hz), 10,31 (1H, s), 11,06 (1H, s).

Ejemplo 356

Producción de 3-(1-cianociclobutil)-N-[3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)-4-

P 147 P

metoxifenil]benzamida

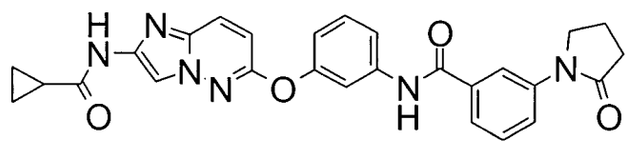


Usando ácido 3–(1–cianociclobutil)benzoico (43 mg, 0,21 mmol), cloruro de oxalilo (23 µL, 0,27 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (60 mg, 0,18 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (68 mg, 74%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,86 – 1,96 (1H, m), 2,21 – 2,38 (2H, m), 2,64 – 2,87 (4H, m), 3,72 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,0 Hz), 7,53 – 7,75 (4H, m), 7,89 (1H, s), 7,90 – 8,07 (3H, m), 10,35 (1H, s), 11,06 (1H, s).

Ejemplo 357

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(2–oxopirrolidin–1–il)benzamida



Usando ácido 3–(2–oxopirrolidin–1–il)benzoico (120 mg, 0,58

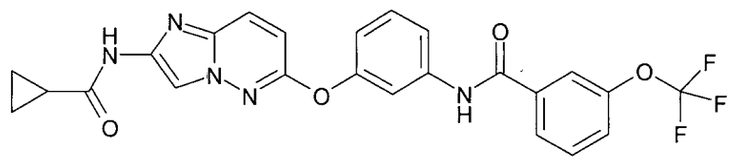
PR48

mmol), cloruro de oxalilo (60 μL, 0,68 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (170 mg, 70%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,85 – 1,97 (1H, m), 2,01 – 2,16 (2H, m), 2,52 – 2,56 (2H, m), 3,90 (2H, t, J = 6,6 Hz), 6,97 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,44 (1H, t, J = 8,1 Hz), 7,52 (1H, t, J = 8,1 Hz), 7,61 – 7,75 (3H, m), 7,89 – 7,95 (1H, m), 7,98 (1H, s), 8,02 – 8,11 (2H, m), 10,40 (1H, s), 11,09 (1H, s).

Ejemplo 358

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometoxi)benzamida



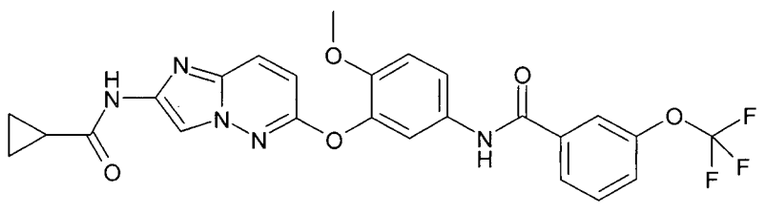
Usando ácido 3–(trifluorometoxi)benzoico (120 mg, 0,58 mmol), cloruro de oxalilo (60 μL, 0,68 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (130 mg, 54%) en forma de un polvo blanco.

P L49

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,83 – 1,98 (1H, m), 6,99 – 7,05 (1H, m), 7,08 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,58 – 7,70 (3H, m), 7,72 (1H, t, J = 2,1 Hz), 7,89 (1H, s), 7,95 – 8,03 (2H, m), 8,06 (1H, d, J = 9,6 Hz), 10,51 (1H, s) 11,09 (1H, s).

Ejemplo 359

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]–3–(trifluorometoxi)benzamida



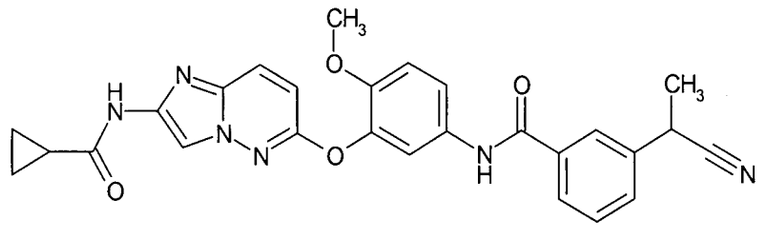
Usando ácido 3–(trifluorometoxi)benzoico (120 mg, 0,58 mmol), cloruro de oxalilo (60 μL, 0,68 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (130 mg, 54%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,72 – 0,86 (4H, m), 1,83 – 1,98 (1H, m), 3,72 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,1 Hz), 7,54 – 7,78 (4H, m), 7,84 – 7,93 (2H, m), 7,96 – 8,08 (2H, m), 10,40 (1H, s), 11,05 (1H, s).

Ejemplo 360

1150

Producción de 3–(1–cianoetil)–N–[3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]benzamida

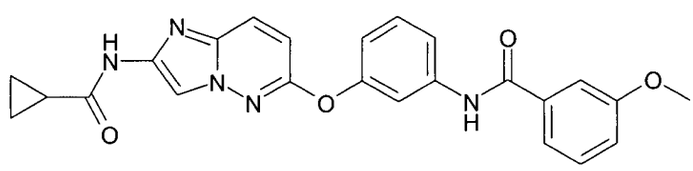


Usando ácido 3–(1–cianoetil)benzoico (62 mg, 0,35 mmol), cloruro de oxalilo (38 μL, 0,44 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,30 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (84 mg, 58%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,70 – 0,88 (4H, m), 1,60 (3H, d, J = 7,2 Hz), 1,81 – 1,99 (1H, m), 3,72 (3H, s), 4,42 (1H, q, J = 7,2 Hz), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,0 Hz), 7,47 – 7,70 (3H, m), 7,72 (1H, d, J = 2,4 Hz), 7,84 – 7,97 (3H, m), 8,01 (1H, d, J = 9,9 Hz), 10,32 (1H, s), 11,05 (1H, s).

Ejemplo 361

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–metoxibenzamida



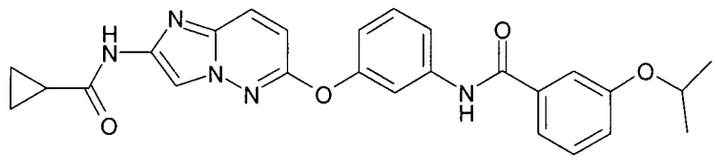
Usando ácido 3–metoxibenzoico (48 mg, 0,32 mmol), cloruro de

oxalilo (32 μL, 0,37 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,26 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (49 mg, 43%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,85 (4H, m), 1,85 – 1,99 (1H, m), 3,83 (3H, s), 6,95 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,12 – 7,21 (1H, m), 7,37 – 7,49 (3H, m), 7,48 – 7,56 (1H, m), 7,61 – 7,70 (1H, m), 7,73 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,34 (1H, s), 11,09 (1H, s).

Ejemplo 362

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–isopropoxibenzamida

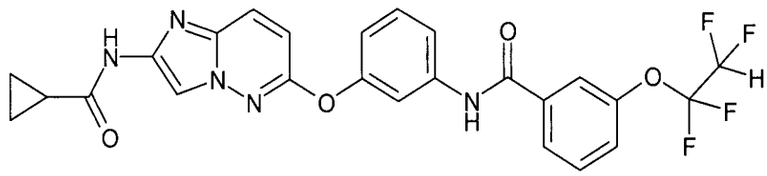


Usando ácido 3–(isopropoxi)benzoico (56 mg, 0,31 mmol), cloruro de oxalilo (33 μL, 0,39 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,26 mmol) y N,N–dimetilacetamida (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (82 mg, 67%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,85 (4H, m), 1,29 (6H, d, J = 6,0 Hz), 1,85 – 1,98 (1H, m), 4,60 – 4,78 (1H, m), 6,96 – 7,02 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,11 – 7,17 (1H, m), 7,33 – 7,55 (4H, m), 7,63 – 7,71 (1H, m), 7,74 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,31 (1H, s), 11,09 (1H, s).

Ejemplo 363

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(1,1,2,2–tetrafluoroetoxi)benzamida

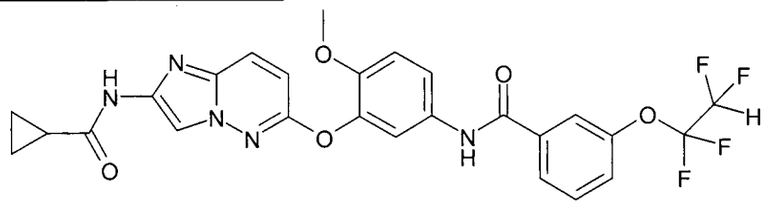


Usando ácido 3–(1,1,2,2–tetrafluoroetoxi)benzoico (74 mg, 0,31 mmol), cloruro de oxalilo (33 μL, 0,39 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (80 mg, 0,26 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (46 mg, 34%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,73 – 0,87 (4H, m), 1,85 – 1,99 (1H, m), 6,62 – 7,05 (2H, m), 7,07 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,1 Hz), 7,49 – 7,58 (1H, m), 7,61 – 7,69 (2H, m), 7,72 (1H, t, J = 2,1 Hz), 7,82 (1H, br. s.), 7,93 – 8,00 (2H, m), 8,06 (1H, d, J = 9,6 Hz), 10,50 (1H, s), 11,09 (1H, s).

Ejemplo 364

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]–3–(1,1,2,2–tetrafluoroetoxi)benzamida

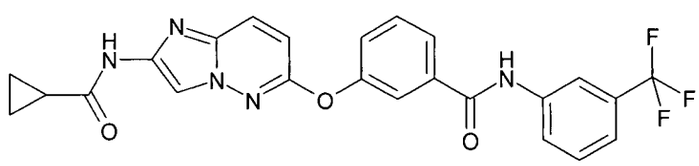


Usando ácido 3–(1,1,2,2–tetrafluoroetoxi)benzoico (85 mg, 0,35 mmol), cloruro de oxalilo (38 μL, 0,44 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3,0 mL), N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,30 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (110 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,86 (4H, m), 1,84 – 1,98 (1H, m), 3,83 (3H, s), 6,96 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,12 – 7,20 (1H, m), 7,36 – 7,49 (3H, m), 7,49 – 7,55 (1H, m), 7,62 – 7,70 (1H, m), 7,73 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,34 (1H, s), 11,09 (1H, s).

Ejemplo 365

Producción de 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–N–[3–(trifluorometil)fenil]benzamida



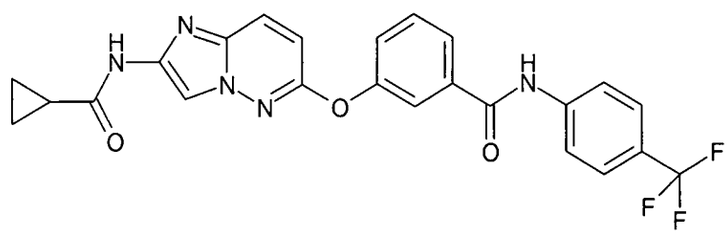
Usando ácido 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–

b]piridazin–6–il}oxi)benzoico (100 mg, 0,30 mmol), cloruro de oxalilo (100 μL, 1,2 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), 3–(trifluorometil)anilina (80 mg, 0,48 mmol) y N–metilpirrolidona (1,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (13 mg, 8,9%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,83 (4H, m), 1,86 – 1,97 (1H, m), 7,12 (1H, d, J = 9,6 Hz), 7,46 (1H, d, J = 7,8 Hz), 7,51 – 7,70 (3H, m), 7,83 – 7,99 (3H, m), 8,01 – 8,11 (2H, m), 8,23 (1H, s), 10,59 (1H, s), 11,08 (1H, s).

Ejemplo 366

Producción de 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–N–[4–(trifluorometil)fenil]benzamida

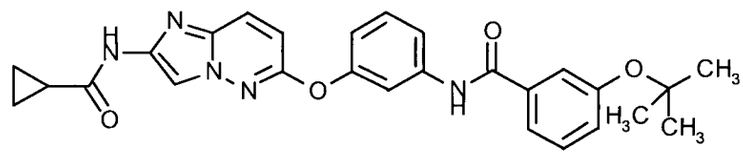


Usando ácido 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoico (30 mg, 0,089 mmol), 4–(trifluorometil)anilina (44 mg, 0,27 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (26 mg, 0,14 mmol), 4–(dimetilamino)piridina (17 mg, 0,14 mmol) y piridina (1,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (18 mg, 42%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,86 (4H, m), 1,84 – 1,98 (1H, m), 7,11 (1H, d, J = 9,6 Hz), 7,50 – 7,59 (1H, m), 7,65 (1H, t, J = 7,9 Hz), 7,73 (2H, d, J = 8,7 Hz), 7,81 – 7,93 (2H, m), 7,95 (1H, s), 8,00 (2H, d, J = 8,7 Hz), 8,07 (1H, d, J = 9,6 Hz), 10,63 (1H, s), 11,08 (1H, s).

Ejemplo 367

Producción de 3–ter–butoxi–N–[3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida



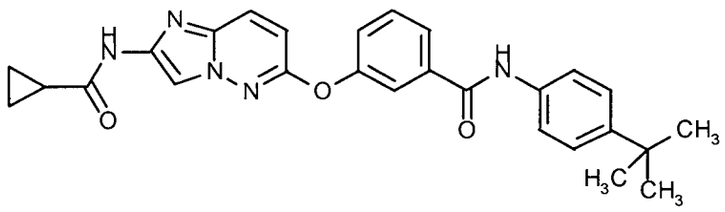
Usando ácido 3–ter–butoxibenzoico (110 mg, 0,58 mmol), cloruro de oxalilo (63 μL, 0,73 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (4,0 mL), N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,49 mmol) y N–metilpirrolidona (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (160 mg, 57%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,87 (4H, m), 1,33 (9H, s), 1,85 – 1,98 (1H, m), 6,90 – 7,03 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,16 – 7,27 (1H, m), 7,36 – 7,48 (2H, m), 7,48 – 7,53 (1H, m), 7,61 – 7,70 (2H, m), 7,73 (1H, t, J = 2,1 Hz), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,34 (1H, s), 11,09 (1H, s).

Ejemplo 368

Producción de N–(4–tert-butilfenil)–3–({2–[(ciclopropilcarbonil)

amino]imidazo[1,2–b]piridazin–6–il}oxi)benzamida

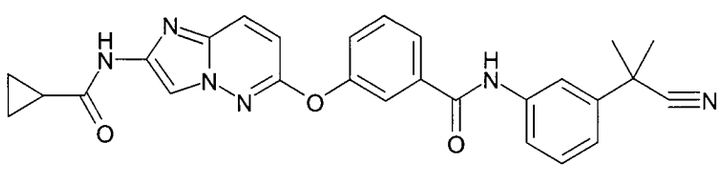


Usando ácido 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoico (100 mg, 0,30 mmol), 4–tert-butilanilina (57 mg, 0,36 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (68 mg, 0,36 mmol), 4–(dimetilamino)piridina (43 mg, 0,36 mmol) y piridina (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (70 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,68 – 0,88 (4H, m), 1,28 (9H, s), 1,85 – 1,98 (1H, m), 7,11 (1H, d, J = 9,6 Hz), 7,37 (2H, d, J = 8,7 Hz), 7,47 – 7,55 (1H, m), 7,56 – 7,72 (3H, m), 7,77 – 7,92 (2H, m), 7,96 (1H, s), 8,07 (1H, d, J = 9,6 Hz), 10,23 (1H, s), 11,08 (1H, s).

Ejemplo 369

Producción de N–[3–(1–ciano–1–metiletil)fenil]–3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzamida



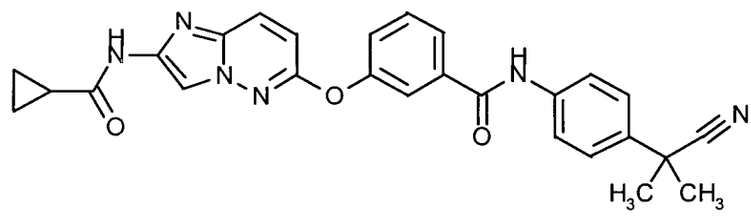
Usando ácido 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoico (100 mg, 0,30 mmol), 2–(3–aminofenil)–

2–metilpropanonitrilo (57 mg, 0,36 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (68 mg, 0,36 mmol), 4–(dimetilamino)piridina (43 mg, 0,36 mmol) y piridina (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318, se obtuvo el compuesto del título (64 mg, 45%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,68 – 0,89 (4H, m), 1,69 (6H, s), 1,85 –1,98 (1H, m), 7,11 (1H, d, J = 9,6 Hz), 7,20 – 7,30 (1H, m), 7,41 (1H, t, J = 8,0 Hz), 7,48 – 7,57 (1H, m), 7,64 (1H, t, J = 7,9 Hz), 7,74 – 8,00 (5H, m), 8,07 (1H, d, J = 9,6 Hz), 10,42 (1H, s), 11,08 (1H, s).

Ejemplo 370

Producción de N–[4–(1–ciano–1–metiletil)fenil]–3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzamida



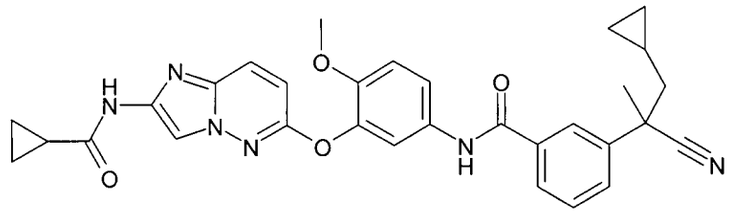
Usando ácido 3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)benzoico (100 mg, 0,30 mmol), 2–(4–aminofenil)–2–metilpropanonitrilo (57 mg, 0,36 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (63 mg, 0,33 mmol), 4–(dimetilamino)piridina (54 mg, 0,44 mmol) y piridina (3,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 318,

se obtuvo el compuesto del título (81 mg, 57%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,87 (4H, m), 1,68 (6H, s), 1,85 – 1,98 (1H, m), 7,11 (1H, d, J = 9,6 Hz), 7,45 – 7,56 (3H, m), 7,63 (1H, t, J = 7,9 Hz), 7,77 – 7,86 (3H, m), 7,86 – 7,92 (1H, m), 7,95 (1H, s), 8,07 (1H, d, J = 9,4 Hz), 10,38 (1H, s), 11,08 (1H, s).

Ejemplo 371

Producción de 3–(1–ciano–2–ciclopropil–1–metiletil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–4–metoxifenil]benzamida



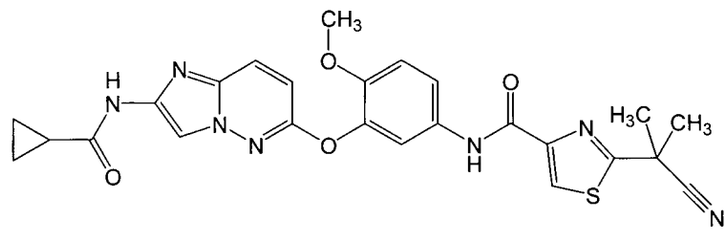
Usando ácido 3–(1–ciano–2–ciclopropil–1–metiletil)benzoico (70 mg, 0,31 mmol), cloruro de oxalilo (33 μL, 0,38 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (2,0 mL), N–[6–(5–amino–2–metoxifenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (86 mg, 0,25 mmol) y N–metilpirrolidona (2,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (67 mg, 48%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ –0,03 – 0,08 (1H, m), 0,16 – 0,27 (1H, m), 0,30 – 0,52 (2H, m), 0,55 – 0,69 (1H, m), 0,73 – 0,86 (4H, m, J = 4,5 Hz), 1,69 – 2,12 (6H, m), 3,72 (3H, s), 7,06 (1H, d, J

= 9,3 Hz), 7,22 (1H, d, J = 9,3 Hz), 7,59 (1H, t, J = 7,8 Hz), 7,65 (1H, dd, J = 8,7, 2,4 Hz), 7,69 – 7,80 (2H, m), 7,86 – 7,97 (2H, m), 7,96 – 8,07 (2H, m), 10,31 (1H, s), 11,05 (1H, s).

Ejemplo 372

Producción de 2-(1-ciano-1-metiletil)-N-[3-({2-[(ciclopropilcarbonil)amino]imidazo[1,2-b]piridazin-6-il}oxi)-4-metoxifenil]-1,3-tiazol-4-carboxamida



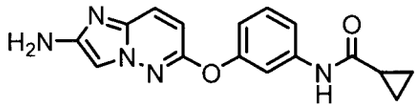
Usando ácido 2-(1-ciano-1-metiletil)-1,3-tiazol-4-carboxílico (104 mg, 0,53 mmol), cloruro de oxalilo (57 μL, 0,66 mmol), N,N-dimetilformamida (1 gota), tetrahidrofurano (5,0 mL), N-[6-(5-amino-2-metoxifenoxi)imidazo[1,2-b]piridazin-2-il]ciclopropancarboxamida (150 mg, 0,44 mmol) y N,N-dimetilacetamida (4,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (179 mg, 78%) en forma de un polvo blanco.

^{1}H-RMN (DMSO-d_6, 300 MHz) δ 0,70 – 0,89 (4H, m), 1,82 – 1,98 (7H, m), 3,73 (3H, s), 7,06 (1H, d, J = 9,6 Hz), 7,22 (1H, d, J = 9,4 Hz), 7,64 – 7,80 (2H, m), 7,89 (1H, s), 8,01 (1H, d, J = 10,2 Hz), 8,47 (1H, s), 10,13 (1H, s), 11,05 (1H, s).

Ejemplo 373

N-{3-[(2-aminoimidazo[1,2-b]piridazin-6-

il)oxi]fenil}ciclopropancarboxamida

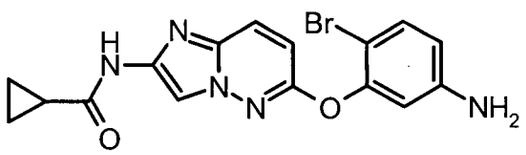


Una mezcla de N–{3–[(2–acetamidoimidazo[1,2–b]piridazin–6–il)oxi]fenil}ciclopropancarboxamida (465 mg, 1,32 mmol), solución de ácido clorhídrico 4 N–acetato de etilo (10 mL) y metanol (10 mL) se agitó a temperatura ambiente durante 14 h. La mezcla de reacción se neutralizó con la adición de solución acuosa 8 N de hidróxido de sodio, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo/éter diisopropílico para dar el compuesto del título (376 mg, 92%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,81 (4H, m), 1,69 – 1,79 (1H, m), 5,33 (2H, s), 6,76 (1H, d, J = 9,3 Hz), 6,80 – 6,86 (1H, m), 7,14 (1H, s), 7,28 – 7,39 (2H, m), 7,47 (1H, t, J = 1,9 Hz), 7,71 (1H, d, J = 9,3 Hz), 10,30 (1H, s).

Ejemplo 374

Producción de N–[6–(5–amino–2–bromofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



A una solución de N–(6–yodoimidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida (2,2 g, 6,7 mmol) en N,N–

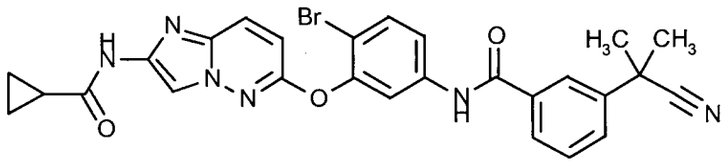
L161

dimetilformamida (60 mL) se le añadieron 5–amino–2–bromofenol (1,9 g, 10 mmol) y carbonato de potasio (1,8 g, 13 mmol), y la mezcla se agitó a 140 °C durante 12 h. Tras enfriar la mezcla hasta temperatura ambiente, la mezcla se diluyó con agua, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 50/50→100/0). El solvente se evaporó a presión reducida y el sólido obtenido se lavó con éter diisopropílico para dar el compuesto del título (0,79 g, 31%) en forma de un polvo amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,69 – 0,88 (4H, m), 1,84 – 1,97 (1H, m), 5,52 (2H, s), 6,45 (1H, dd, J = 8,7, 2,7 Hz), 6,50 (1H, d, J = 2,7 Hz), 7,03 (1H, d, J = 9,0 Hz), 7,29 (1H, d, J = 8,7 Hz), 7,94 (1H, s), 8,03 (1H, d, J = 9,0 Hz), 11,07 (1H, s).

Ejemplo 375

Producción de N–[4–bromo–3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(1–ciano–1–metiletil)benzamida



Usando ácido 3–(1–ciano–1–metiletil)benzoico (330 mg, 1,8 mmol), cloruro de oxalilo (170 μL, 2,0 mmol), N,N–dimetilformamida

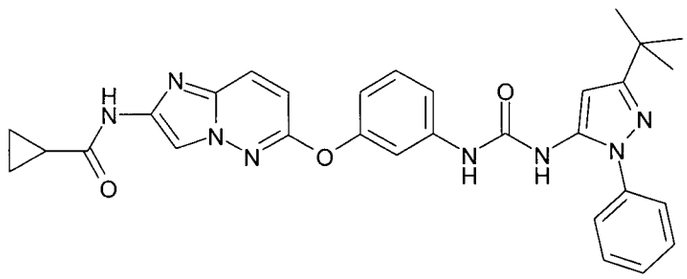
1162

(1 gota), tetrahidrofurano (15 mL), N–[6–(5–amino–2–bromofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (650 mg, 1,7 mmol) y N,N–dimetilacetamida (5,0 mL) como materiales de partida y de la misma manera que en el Ejemplo 335, se obtuvo el compuesto del título (800 mg, 85%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,71 – 0,88 (4H, m), 1,74 (6H, s), 1,85 – 1,96 (1H, m), 7,16 (1H, d, J = 9,6 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,64 – 7,71 (1H, m), 7,73 – 7,81 (2H, m), 7,83 – 7,97 (3H, m), 8,02 (1H, s), 8,10 (1H, d, J = 9,6 Hz), 10,56 (1H, s), 11,10 (1H, s).

Ejemplo 376

Producción de N–{6–[3–({[(3–tert-butil–1–fenil–1H–pirazol–5–il)amino]carbonil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



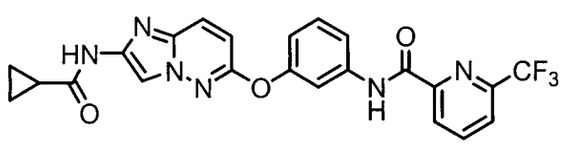
A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (160 mg, 0,52 mmol) y (3–tert-butil–1–fenil–1H–pirazol–5–il)carbamato de 2,2,2–tricloroetilo (200 mg, 0,52 mmol) en dimetilsulfóxido/agua (2,0 mL/1,5 mL) se añadió trietilamina (53 mg, 0,52 mmol), y la mezcla se agitó a 85 °C durante 8 h. La mezcla de reacción se diluyó con acetato de etilo, se

lavó con ácido clorhídrico 1 N, solución acuosa al 5% de hidrógeno–carbonato de sodio y salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 50/50→100/0) y se precipitó en acetato de etilo/éter diisopropílico/hexano para dar el compuesto del título (285 mg, 99%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,85 – 2,02 (1H, m), 3,32 (9H, s), 6,35 (1H, s), 6,84 (1H, dd, J = 7,8, 1,8 Hz), 7,03 (1H, d, J = 9,6 Hz), 7,16 (1H, dd, J = 8,1, 1,2 Hz), 7,28 – 7,46 (3H, m), 7,48 – 7,58 (4H, m), 7,96 (1H, s), 8,03 (1H, d, J = 9,6 Hz), 8,46 (1H, s), 9,22 (1H, s), 11,08 (1H, s).

Ejemplo 377

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–6–(trifluorometil)piridin–2–carboxamida



A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (95 mg, 0,307 mmol) en N,N–dimetilformamida (5 mL) se añadieron ácido 6–(trifluorometil)piridin–2–carboxílico (65 mg, 0,337 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,337 mmol) y 1–hidroxibenzotriazol (46 mg, 0,337 mmol), y la mezcla se

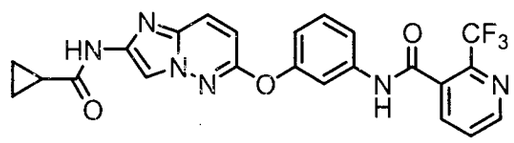
1164

agitó a temperatura ambiente durante 2 h. solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción. La mezcla se extrajo con acetato de etilo, y la capa orgánica se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo/éter diisopropílico para dar el compuesto del título (126 mg, 85%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,87 – 1,98 (1H, m), 7,03 – 7,11 (2H, m), 7,47 (1H, t, J = 8,2 Hz), 7,75 – 7,81 (1H, m), 7,83 (1H, t, J = 2,2 Hz), 7,98 (1H, s), 8,06 (1H, d, J = 9,2 Hz), 8,18 (1H, dd, J = 6,9, 2,0 Hz), 8,31 – 8,41 (2H, m), 10,56 (1H, s), 11,09 (1H, s).

Ejemplo 378

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–(trifluorometil)nicotinamida



A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (95 mg, 0,307 mmol) en N,N–dimetilformamida (5 mL) se añadieron ácido 2–(trifluorometil)nicotínico (65 mg, 0,337 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,337 mmol) y 1–hidroxibenzotriazol (46 mg, 0,337 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h, se calentó hasta 50°C y se agitó

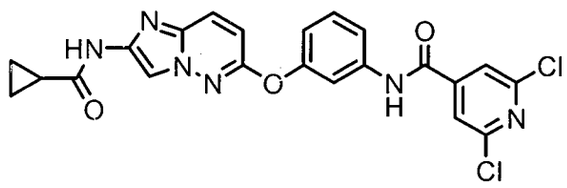
1165

durante 2 h. 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 solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→100/0), y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (79,6 mg, 54%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,87 – 1,98 (1H, m), 7,01 – 7,11 (2H, m), 7,41 – 7,53 (2H, m), 7,62 (1H, t, J = 2,0 Hz), 7,82 – 7,89 (1H, m), 7,94 – 7,99 (1H, m), 8,05 (1H, d, J = 9,6 Hz), 8,25 (1H, d, J = 7,5 Hz), 8,86 (1H, d, J = 4,7 Hz), 10,85 (1H, s), 11,09 (1H, s).

Ejemplo 379

Producción de 2,6–dicloro–N–[3–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}oxi)fenil]isonicotinamida



Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (95 mg, 0,307 mmol), ácido 2,6–dicloropiridin–4–carboxílico (65 mg, 0,337 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,337 mmol), 1–hidroxibenzotriazol (46 mg, 0,337 mmol) y N,N–dimetilformamida (5

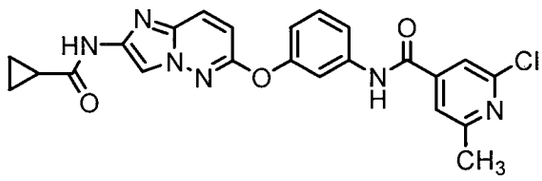
1166

mL) como materiales de partida y de la misma manera que en el Ejemplo 377, se obtuvo el compuesto del título (124 mg, 84%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,84 (4H, m), 1,87 – 1,98 (1H, m), 7,04 – 7,11 (2H, m), 7,47 (1H, t, J = 8,2 Hz), 7,60 – 7,65 (1H, m), 7,68 (1H, t, J = 2,1 Hz), 7,96 – 8,02 (3H, m), 8,06 (1H, d, J = 9,2 Hz), 10,73 (1H, s), 11,09 (1H, s).

Ejemplo 380

Producción de 2–cloro–N–[3–({2–[(ciclopropilcarbonil) amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–6–metilisonicotinamida



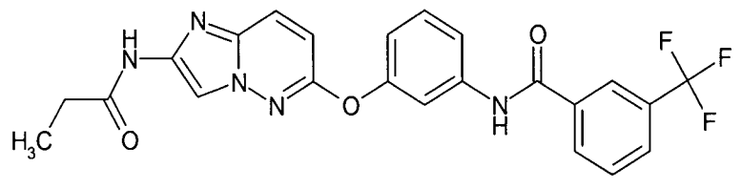
A una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (95 mg, 0,307 mmol) en N,N–dimetilformamida (5 mL) se añadieron ácido 2–cloro–6–metilpiridin–4–carboxílico (58 mg, 0,337 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (65 mg, 0,337 mmol) y 1–hidroxibenzotriazol (46 mg, 0,337 mmol), y la mezcla se agitó a temperatura ambiente durante 2 h. 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 solvente se evaporó a presión reducida, y el residuo se purificó por

cromatografía en columna de gel de sílice (acetato de etilo/hexano = 3/97→100/0) y se precipitó en acetato de etilo/hexano para dar el compuesto del título (115 mg, 82%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,83 (4H, m), 1,86 – 1,98 (1H, m), 2,55 (3H, s), 7,01 – 7,11 (2H, m), 7,46 (1H, t, J = 8,2 Hz), 7,60 – 7,79 (4H, m), 7,98 (1H, s), 8,06 (1H, d, J = 9,6 Hz), 10,64 (1H, s), 11,09 (1H, s).

Ejemplo 381

Producción de N–(3–{[2–(propionilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(trifluorometil)benzamida

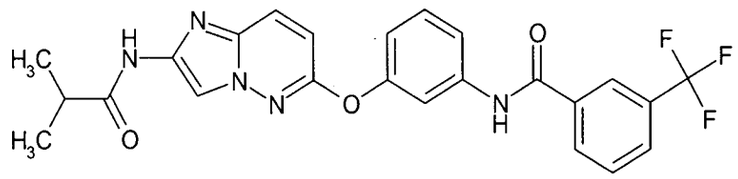


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,363 mmol), ácido propiónico (40 μL, 0,544 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (104 mg, 0,544 mmol), 1–hidroxibenzotriazol (73 mg, 0,544 mmol), trietilamina (76 μL, 0,544 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 380, se obtuvo el compuesto del título (116 mg, 68%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,07 (3H, t, J = 7,5 Hz), 2,37 (2H, q, J = 7,5 Hz), 7,01 – 7,11 (2H, m), 7,46 (1H, t, J = 8,2 Hz), 7,65 – 7,83 (3H, m), 7,94 – 8,00 (1H, m), 8,02 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 8,22 – 8,30 (2H, m), 10,59 (1H, s), 10,75 (1H, s).

Ejemplo 382

Producción de N–(3–{[2–(isobutirilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(trifluorometil)benzamida

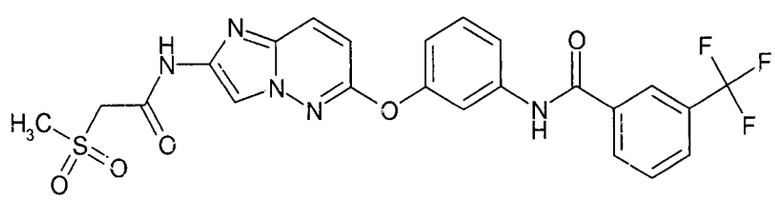


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,363 mmol), ácido 2–metilpropanoico (50 µL, 0,544 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (104 mg, 0,544 mmol), 1–hidroxibenzotriazol (73 mg, 0,544 mmol), trietilamina (76 µL, 0,544 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 380, se obtuvo el compuesto del título (74 mg, 42%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,08 (6H, d, J = 7,0 Hz), 2,65 – 2,77 (1H, m), 7,00 – 7,11 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,63 – 7,83 (3H, m), 7,94 – 8,09 (3H, m), 8,22 – 8,30 (2H, m), 10,59 (1H, s), 10,75 (1H, s).

Ejemplo 383

Producción de N–{3–[(2–{[(metilsulfonil)acetil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida

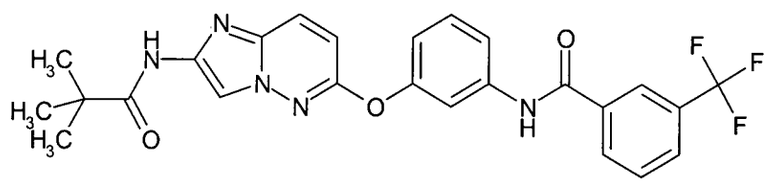


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,363 mmol), ácido (metilsulfonil)acético (75 mg, 0,544 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (104 mg, 0,544 mmol), 1–hidroxibenzotriazol (73 mg, 0,544 mmol), trietilamina (76 μL, 0,544 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 377, se obtuvo el compuesto del título (171 mg, 88%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,16 (3H, s), 4,37 (2H, m), 7,05 (1H, dd, J = 8,1, 2,0 Hz), 7,14 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,1 Hz), 7,65 – 7,83 (3H, m), 7,94 – 8,01 (1H, m), 8,06 (1H, s), 8,12 (1H, d, J = 9,6 Hz), 8,22 – 8,30 (2H, m), 10,60 (1H, s), 11,29 (1H, s).

Ejemplo 384

Producción de N–[3–({2–[(2,2–dimetilpropanoil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



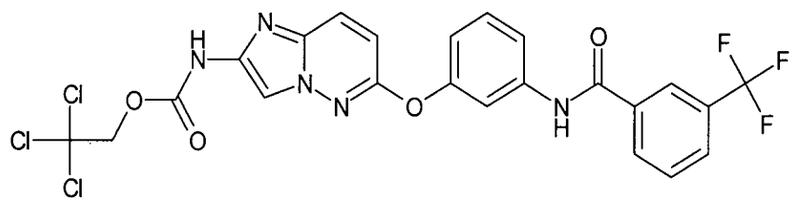
A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,363 mmol) en piridina (5 mL) se añadió gota a gota cloruro de 2,2–dimetilpropanoílo (49 μL, 0,399 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió solución acuosa

saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 0/100→50/50), y se precipitó en acetato de etilo/hexano para dar el compuesto del título (90 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,22 (9 H, s), 6,99 – 7,12 (2 H, m), 7,46 (1 H, t, J = 8,2 Hz), 7,63 – 7,84 (3 H, m), 7,98 (1 H, d, J = 7,9 Hz), 8,05 (2 H, m), 8,22 – 8,30 (2 H, m), 10,36 (1 H, s), 10,60 (1 H, s)

Ejemplo 385

Producción de [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi) imidazo[1,2–b]piridazin–2–il]carbamato de 2,2,2–tricloroetilo



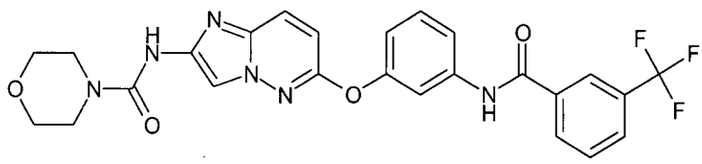
A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (400 mg, 0,967 mmol) en tetrahidrofurano (10 mL) se añadieron gota a gota clorocarbonato de 2,2,2–tricloroetilo (159 μL, 1,16 mmol) y trietilamina (202 μL, 1,45 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. El solvente se evaporó a presión reducida, y el residuo se lavó con éter diisopropílico y agua para dar el compuesto del título (436 mg, 76%)

en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,97 (2H, s), 7,01 – 7,14 (2H, m), 7,46 (1H, t, J = 8,0 Hz), 7,64 – 7,88 (4H, m), 7,98 (1H, d, J = 8,0 Hz), 8,08 (1H, d, J = 9,6 Hz), 8,22 – 8,30 (2H, m), 10,59 (1H, s), 10,97 (1H, s).

Ejemplo 386

Producción de N–[6–(3–{[3–(trifluorometil)benzoil]amino} fenoxi)imidazo[1,2–b]piridazin–2–il]morfoline–4–carboxamida



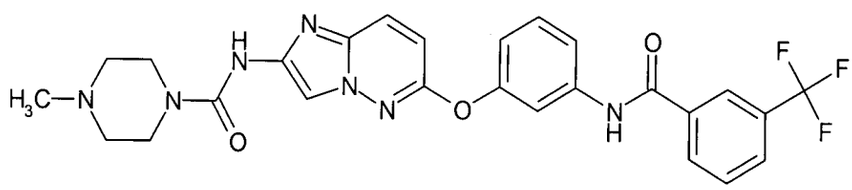
Una mezcla de [6–(3–{[3–(trifluorometil)benzoil]amino} fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de 2,2,2–tricloroetilo (140 mg, 0,237 mmol), morfolina (31 μL, 0,356 mmol), N,N–diisopropilpropan–2–amina (123 μL, 0,713 mmol) y dimetilsulfóxido (10 mL) se calentó hasta 80°C y la mezcla se agitó durante 24 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con agua y salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 50/50→100/0) y se precipitó en éter diisopropílico para dar el

compuesto del título (92 mg, 73%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,41 – 3,49 (4H, m), 3,58 (4H, m), 6,98 – 7,06 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,64 – 7,83 (3H, m), 7,89 (1H, s), 7,93 – 8,03 (2H, m), 8,20 – 8,32 (2H, m), 9,56 (1H, s), 10,59 (1H, s).

Ejemplo 387

Producción de 4–metil–N–[6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]piperazin–1–carboxamida



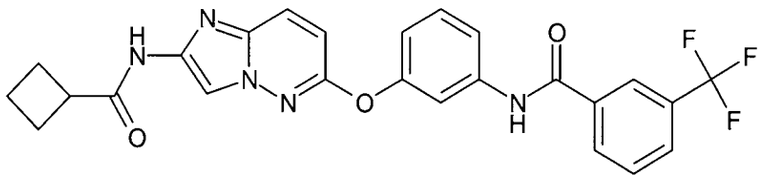
Usando [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de 2,2,2–tricloroetilo (140 mg, 0,237 mmol), 1–metilpiperazina (40 μL, 0,356 mmol), N,N–diisopropilpropan–2–amina (123 μL, 0,713 mmol) y dimetilsulfóxido (10 mL) como materiales de partida y de la misma manera que en el Ejemplo 386, se obtuvo el compuesto del título (65 mg, 50%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,18 (3H, s), 2,25 – 2,32 (4H, m), 3,41 – 3,49 (4H, m), 6,98 – 7,06 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,63 – 7,83 (3H, m), 7,88 (1H, s), 7,94 – 8,03 (2H, m), 8,22 – 8,30 (2H, m), 9,51 (1H, s), 10,59 (1H, s).

1173

Ejemplo 388

Producción de N–[3–({2–[(ciclobutilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol) en tetrahidrofurano (5 mL) se añadieron gota a gota trietilamina (75 μL, 0,544 mmol) y cloruro de ciclobutancarbonilo (50 μL, 0,435 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 50/50→100/0) para dar el compuesto del título (98 mg, 54%) en forma de un polvo blanco.

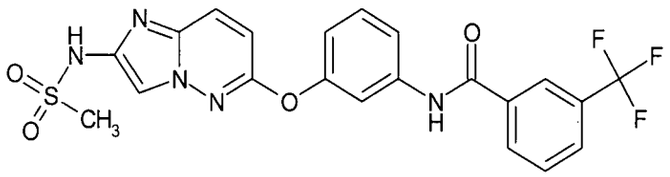
^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,83 – 2,11 (2H, m), 2,15 – 2,46 (4H, m), 3,14 – 3,28 (1H, m), 6,88 (1H, d, J = 9,4 Hz), 7,00 – 7,06 (1H, m), 7,42 – 7,48 (2H, m), 7,60 – 7,68 (1H, m), 7,69 – 7,85 (4H, m), 7,91 – 7,98 (1H, m), 8,04 – 8,09 (1H, m), 8,13 (1H, s), 8,19 (1H, s).

Ejemplo 389

Producción de N–[3–({2–[(metilsulfonil)amino]imidazo[1,2–

1174

b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

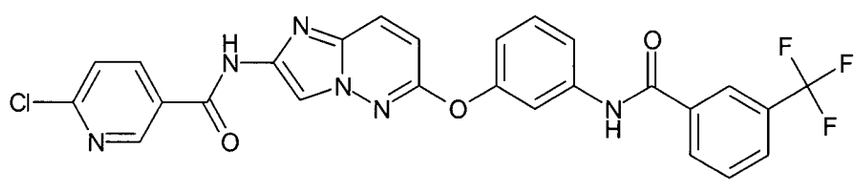


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol), trietilamina (76 μL, 0,544 mmol), cloruro de metansulfonilo (34 μL, 0,435 mmol) y tetrahidrofurano (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 388, se obtuvo el compuesto del título (108 mg, 61%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,13 (3H, s), 7,05 (1H, dd, J = 8,0, 1,6 Hz), 7,14 (1H, d, J = 9,6 Hz), 7,46 (1H, t, J = 8,0 Hz), 7,63 – 7,84 (4H, m), 7,98 (1H, d, J = 8,0 Hz), 8,10 (1H, d, J = 9,6 Hz), 8,22 – 8,30 (2H, m), 10,29 (1H, s), 10,60 (1H, s).

Ejemplo 390

Producción de 6–cloro–N–[6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]nicotinamida



Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol), trietilamina (76 μL, 0,544 mmol), cloruro de 6–cloronicotinoílo (76 mg, 0,435 mmol) y tetrahidrofurano (5 mL) como materiales de partida y de la misma

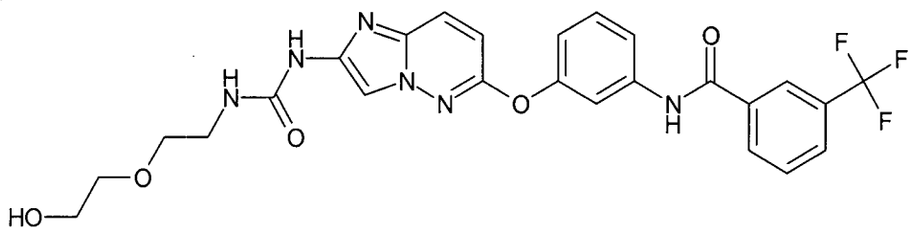
1175

manera que en el Ejemplo 388, se obtuvo el compuesto del título (155 mg, 77%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,07 (1H, dd, J = 8,2, 1,8 Hz), 7,15 (1H, d, J = 9,7 Hz), 7,48 (1H, t, J = 8,2 Hz), 7,69 (2H, d, J = 8,5 Hz), 7,74 – 7,84 (2H, m), 7,98 (1H, d, J = 7,7 Hz), 8,14 (1H, d, J = 9,7 Hz), 8,20 – 8,33 (3H, m), 8,43 (1H, dd, J = 8,5, 2,4 Hz), 9,03 (1H, d, J = 2,4 Hz), 10,61 (1H, s), 11,66 (1H, s).

Ejemplo 391

Producción de N–(3–{[2–({[2–(2–hidroxietoxi)etil]carbamoil}amino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(trifluorometil)benzamida



Usando [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de 2,2,2–tricloroetilo (140 mg, 0,237 mmol), 2–(2–aminoetoxi)etanol (43 μL, 0,435 mmol), N,N–diisopropilpropan–2–amina (76 μL, 0,435 mmol) y dimetilsulfóxido (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 386, se obtuvo el compuesto del título (86 mg, 62%) en forma de un polvo de color amarillo pálido.

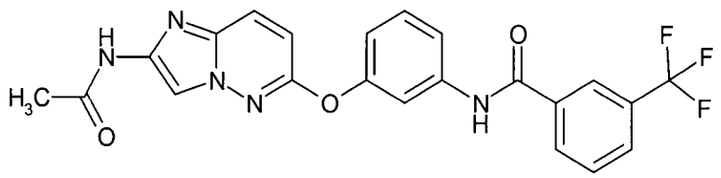
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,40 – 3,67 (8H, m), 4,58 (1H, t, J = 5,4 Hz), 6,67 (1H, brs), 7,01 (2H, d, J = 9,4 Hz), 7,45 (1H, t, J

1176

= 8,0 Hz), 7,63 – 7,83 (4H, m), 7,93 – 8,02 (2H, m), 8,21 – 8,30 (2H, m), 9,11 (1H, s), 10,58 (1H, s).

Ejemplo 392

Producción de N–{3–[(2–acetamidoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida

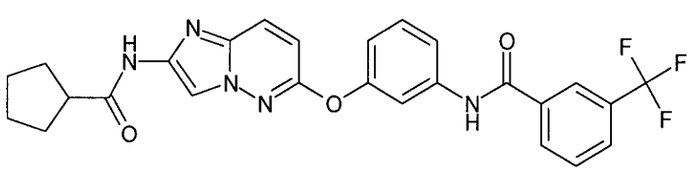


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol), cloruro de acetilo (31 μL, 0,435 mmol) y piridina (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 384, se obtuvo el compuesto del título (99 mg, 60%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,07 (3H, s), 7,01 – 7,11 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,63 – 7,83 (3H, m), 7,95 – 8,01 (2H, m), 8,06 (1H, d, J = 9,6 Hz), 8,22 – 8,30 (2H, m), 10,59 (1H, s), 10,80 (1H, s).

Ejemplo 393

Producción de N–[3–({2–[(ciclopentilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



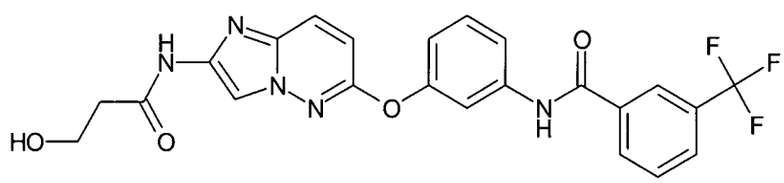
Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–

3–(trifluorometil)benzamida (150 mg, 0,362 mmol), cloruro de ciclopentancarbonilo (53 μL, 0,435 mmol), trietilamina (75 μL, 0,544 mmol) y tetrahidrofurano (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 388, se obtuvo el compuesto del título (105 mg, 57%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,47 – 1,90 (8H, m), 2,81 – 2,95 (1H, m), 7,00 – 7,10 (2H, m), 7,46 (1H, t, J = 8,2 Hz), 7,63 – 7,83 (3H, m), 7,94 – 8,09 (3H, m), 8,21 – 8,30 (2H, m), 10,59 (1H, s), 10,77 (1H, s).

Ejemplo 394

Producción de N–[3–({2–[(3–hidroxipropanoil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



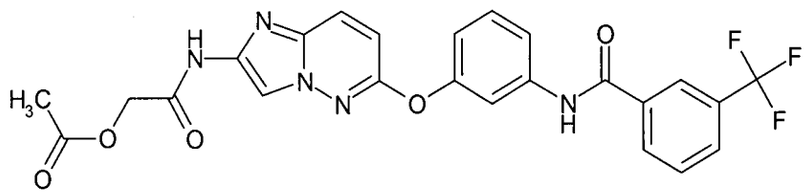
A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol) y ácido 3–hidroxipropanoico (131 mg, 0,435 mmol) en N,N–dimetilformamida (5 mL) se le añadió cloruro de 4–(4,6–dimetoxi–1,3,5–triazin–2–il)–4–metilmorfolin–4–io (160 mg, 0,544 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El

solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 30/70→100/0) y se precipitó en etanol para dar el compuesto del título (30 mg, 17%) en forma de un polvo de color verde pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,63 – 2,70 (2H, m), 3,73 (1H, brs), 3,96 – 4,03 (2H, m), 6,89 (1H, d, J = 9,4 Hz), 7,01 – 7,07 (1H, m), 7,42 – 7,48 (2H, m), 7,59 – 7,86 (4H, m), 7,95 (1H, s), 8,07 (1H, d, J = 7,9 Hz), 8,11 – 8,17 (2H, m), 8,54 (1H, s).

Ejemplo 395

Producción de 2–oxo–2–{[6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]amino}acetato de etilo



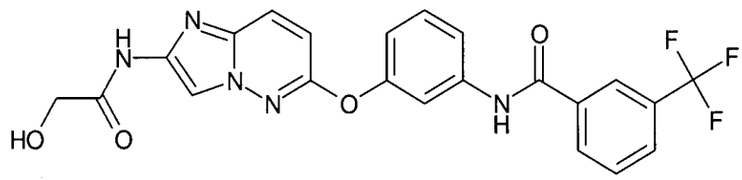
Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (300 mg, 0,725 mmol), trietilamina (152 μL, 1,08 mmol), 2–cloro–2–oxoacetato de etilo (94 μL, 0,870 mmol) y tetrahidrofurano (7 mL) como materiales de partida y de la misma manera que en el Ejemplo 388, se obtuvo el compuesto del título (299 mg, 80%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 2,11 (3H, s), 4,70 (2H, s), 7,04 (1H, dd, J = 8,6, 2,0 Hz), 7,11 (1H, d, J = 9,8 Hz), 7,46 (1H, t, J = 8,0 Hz), 7,64 – 7,83 (3H, m), 7,94 – 8,02 (2H, m), 8,09 (1H, d, J = 9,8 Hz), 8,22 – 8,30 (2H, m), 10,59 (1H, s), 11,03 (1H, s).

1179

Ejemplo 396

Producción de N–(3–{[2–(glicoloilamino)imidazo[1,2–b]piridazin–6–il]oxi}fenil)–3–(trifluorometil)benzamida



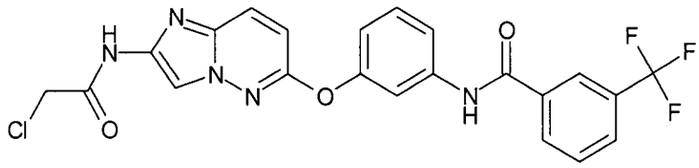
Una mezcla de 2–oxo–2–{[6–(3–{[3–(trifluorometil)benzoil] amino}fenoxi)imidazo[1,2–b]piridazin–2–il]amino}acetato de etilo (250 mg, 0,486 mmol), solución acuosa 1 N de hidróxido de sodio (3 mL) y metanol (5 mL) se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se neutralizó con la adición de ácido clorhídrico 1 N, y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con etanol para dar el compuesto del título (185 mg, 81%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,02 – 4,08 (2H, m), 5,46 – 5,55 (1H, m), 7,05 (1H, dd, J = 7,6, 2,2 Hz), 7,11 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,0 Hz), 7,64 – 7,83 (3H, m), 7,98 (1H, d, J = 8,0 Hz), 8,03 – 8,12 (2H, m), 8,22 – 8,30 (2H, m), 10,23 (1H, s), 10,60 (1H, s).

Ejemplo 397

Producción de N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

1180

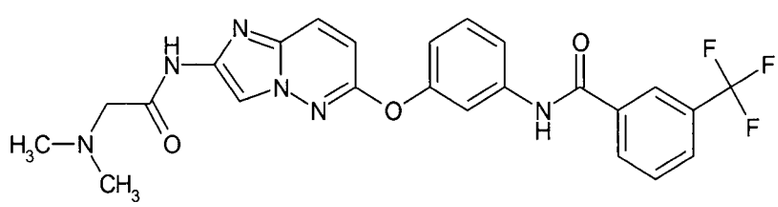


A una solución de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (500 mg, 1,20 mmol) en tetrahidrofurano (10 mL) se añadieron cloruro de cloroacetilo (168 μL, 1,45 mmol) y trietilamina (253 μL, 1,81 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. solución acuosa saturada de cloruro de amonio se añadió a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con etanol para dar el compuesto del título (418 mg, 71%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 4,31 (2H, s), 7,05 (1H, dd, J = 8,2, 2,4 Hz), 7,12 (1H, d, J = 9,4 Hz), 7,47 (1 H, t, J = 8,2 Hz), 7,64 – 7,84 (3H, m), 7,93 – 8,13 (3H, m), 8,21 – 8,30 (2H, m), 10,59 (1H, s), 11,20 (1H, s).

Ejemplo 398

Producción de N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



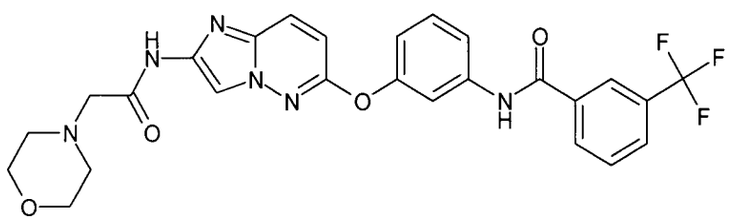
1181

Una mezcla de N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (120 mg, 0,244 mmol), solución acuosa de dimetilamina (3 mL) y acetonitrilo (3 mL) se calentó hasta 80 °C y se agitó durante 3 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con etanol para dar el compuesto del título (85 mg, 70%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,37 (6H, s), 3,11 (2H, s), 6,88 (1H, d, J = 9,6 Hz), 6,99 – 7,06 (1H, m), 7,39 – 7,50 (2H, m), 7,63 (1H, t, J = 7,9 Hz), 7,69 – 7,72 (1H, m), 7,75 (1H, d, J = 9,6 Hz), 7,81 (1H, d, J = 7,9 Hz), 8,00 (1H, s), 8,06 (1H, d, J = 7,5 Hz), 8,13 (1H, s), 8,21 (1H, s), 9,65 (1H, brs).

Ejemplo 399

Producción de N–[3–({2–[(morfolin–4–ilacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



Usando N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (120 mg, 0,244 mmol),

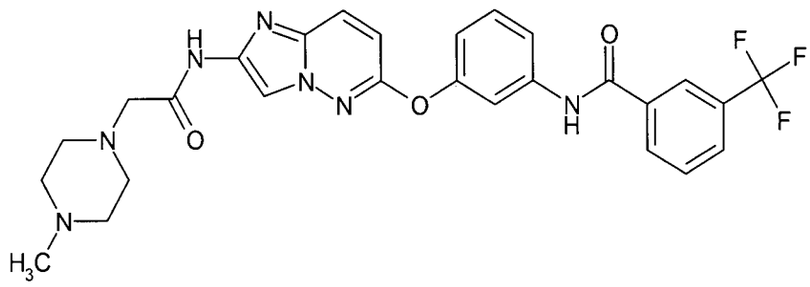
1182

morfolina (1 mL) y acetonitrilo (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 398, se obtuvo el compuesto del título (116 mg, 87%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,59 – 2,65 (4H, m), 3,18 (2H, s), 3,75 – 3,82 (4H, m), 6,90 (1H, d, J = 9,6 Hz), 7,01 – 7,07 (1H, m), 7,42 – 7,46 (2H, m), 7,59 – 7,68 (1H, m), 7,71 – 7,85 (3H, m), 7,92 – 7,98 (1H, m), 8,06 (1H, d, J = 7,9 Hz), 8,13 (1H, s), 8,21 (1H, s), 9,50 (1H, s).

Ejemplo 400

Producción de N–{3–[(2–{[(4–metilpiperazin–1–il)acetil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida



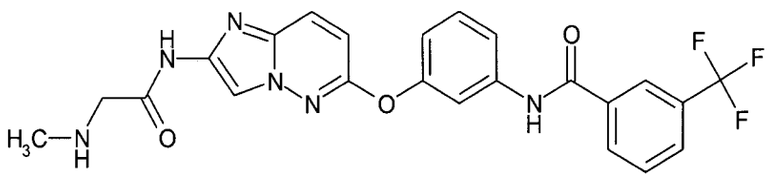
Usando N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (120 mg, 0,244 mmol), 1–metilpiperazina (1 mL) y acetonitrilo (2 mL) como materiales de partida y de la misma manera que en el Ejemplo 398, se obtuvo el compuesto del título (67 mg, 50%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,32 (3H, s), 2,43 – 2,74 (8H, m), 3,18 (2H, s), 6,89 (1H, d, J = 9,6 Hz), 7,00 – 7,07 (1H, m), 7,41 – 7,48 (2H, m), 7,64 (1H, t, J = 7,8 Hz), 7,71 – 7,85 (3H, m), 7,96 –

8,01 (1H, m), 8,06 (1H, d, J = 7,8 Hz), 8,13 (1H, s), 8,21 (1H, s), 9,55 (1H, s).

Ejemplo 401

Producción de N–[3–({2–[(N–metilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida

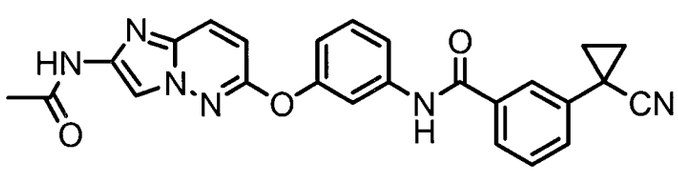


Usando N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida (92 mg, 0,187 mmol), solución de metilamina/metanol (2 mL) y acetonitrilo (1 mL) como materiales de partida y de la misma manera que en el Ejemplo 398, se obtuvo el compuesto del título (22 mg, 25%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 2,50 (3H, s), 3,39 (2H, s), 6,88 (1H, d, J = 9,4 Hz), 7,03 (1H, dd, J = 6,7, 2,0 Hz), 7,39 – 7,51 (2H, m), 7,59 – 7,85 (4H, m), 7,93 – 8,10 (2H, m), 8,13 (1H, s), 8,20 – 8,25 (1H, m), 9,72 (1H, s).

Ejemplo 402

Producción de N–{3–[(2–acetamidoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida



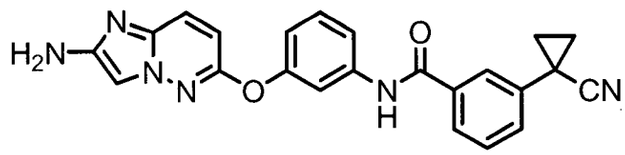
1184

A una solución de ácido 3–(1–cianociclopropil)benzoico (1,50 g, 8,01 mmol) en tetrahidrofurano (30 mL) se añadieron N,N–dimetilformamida (2 gotas) y cloruro de oxalilo (1,16 mL, 13,3 mmol), y la mezcla se agitó a temperatura ambiente durante 1,5 h. El solvente se evaporó a presión reducida, y el residuo y N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]acetamida (1,89 g, 6,67 mmol) se disolvieron en N–metilpirrolidona (30 mL), y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro y se filtró, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 0/100→100/0) para dar el compuesto del título (2,25 g, 75%) en forma de un polvo de color color café pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,77 – 1,84 (2H, m), 2,07 (3H, s), 6,99 – 7,11 (2H, m), 7,45 (1H, t, J = 8,2 Hz), 7,51 – 7,60 (2H, m), 7,62 – 7,68 (1H, m), 7,72 (1H, t, J = 2,1 Hz), 7,82 (1H, s), 7,84 – 7,90 (1H, m), 8,00 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,42 (1H, s), 10,80 (1H, s).

Ejemplo 403

Producción de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida

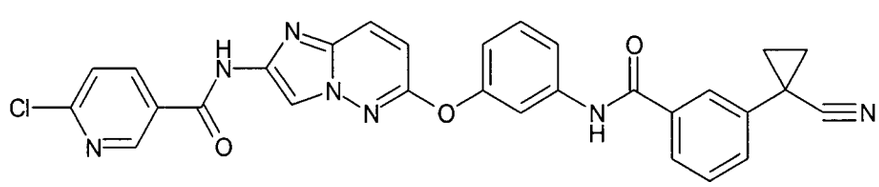


Una mezcla de N–{3–[(2–acetamidoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (2,20 g, 4,86 mmol), solución de ácido clorhídrico 4 N–acetato de etilo (35 mL) y metanol (35 mL) se agitó a temperatura ambiente durante 14 h. La mezcla de reacción se neutralizó con la adición de solución acuosa 8 N de hidróxido de sodio y se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con éter diisopropílico para dar el compuesto del título (1,63 g, 82%) en forma de un polvo amarillo.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,64 (2H, m), 1,77 – 1,84 (2H, m), 5,34 (2H, brs), 6,80 (1H, d, J = 9,3 Hz), 6,91 – 6,97 (1H, m), 7,15 (1H, s), 7,41 (1H, t, J = 8,3 Hz), 7,51 – 7,67 (4H, m), 7,73 (1H, d, J = 9,3 Hz), 7,81 (1H, s), 7,84 – 7,89 (1H, m), 10,38 (1H, s).

Ejemplo 404

Producción de 6–cloro–N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]nicotinamida



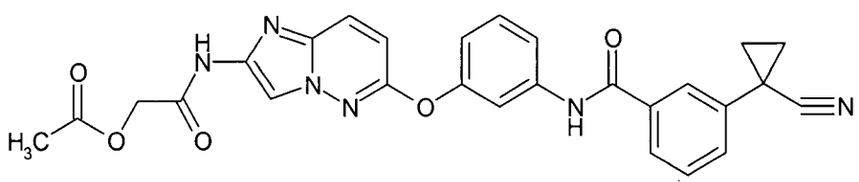
1186

Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (120 mg, 0,292 mmol), cloruro de 6–cloronicotinoílo (61 mg, 0,350 mmol), trietilamina (62 μL, 0,438 mmol) y tetrahidrofurano (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 385, se obtuvo el compuesto del título (121 mg, 75%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,78 – 1,84 (2H, m), 7,05 (1H, dd, J = 8,2, 1,8 Hz), 7,14 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,52 – 7,60 (2H, m), 7,64 – 7,72 (2H, m), 7,73 – 7,77 (1H, m), 7,82 (1H, s), 7,85 – 7,91 (1H, m), 8,13 (1H, d, J = 9,6 Hz), 8,22 (1H, s), 8,43 (1H, dd, J = 8,2, 2,4 Hz), 9,02 (1H, d, J = 2,4 Hz), 10,44 (1H, s), 11,65 (1H, s).

Ejemplo 405

Producción de 2–{[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]amino}–2–oxoacetato de etilo



Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (200 mg, 0,487 mmol), trietilamina (101 μL, 0,730 mmol), 2–cloro–2–oxoacetato de etilo (63 μL, 0,584 mmol) y tetrahidrofurano (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 385, se obtuvo el compuesto del título (183 mg, 74%) en forma de un polvo gris.

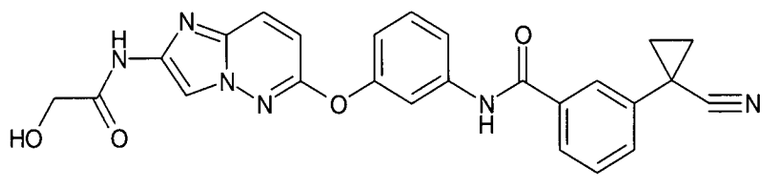
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,77 –

1184

1,85 (2H, m), 2,11 (3H, s), 4,70 (2H, s), 7,02 (1H, dd, J = 7,9, 2,0 Hz), 7,10 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 7,9 Hz), 7,51 – 7,61 (2H, m), 7,66 (1H, d, J = 7,9 Hz), 7,72 (1H, t, J = 2,0 Hz), 7,82 (1H, s), 7,84 – 7,90 (1H, m), 8,00 (1H, s), 8,08 (1H, d, J = 9,6 Hz), 10,42 (1H, s), 11,03 (1H, s).

Ejemplo 406

Producción de 3–(1–cianociclopropil)–N–(3–{[2–(glicoloilamino) imidazo[1,2–b]piridazin–6–il]oxi}fenil)benzamida



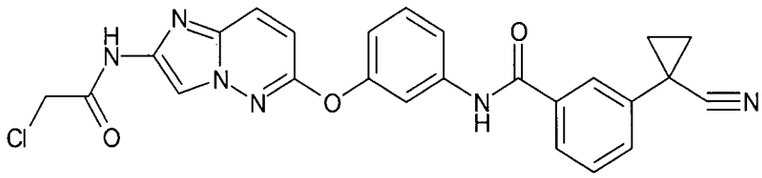
Usando 2–{[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi) imidazo[1,2–b]piridazin–2–il]amino}–2–oxoacetato de etilo (130 mg, 0,254 mmol), solución acuosa 1 N de hidróxido de sodio (1,5 mL) y metanol (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 396, se obtuvo el compuesto del título (59 mg, 50%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,64 (2H, m), 1,78 – 1,84 (2H, m), 4,02 – 4,08 (2H, m), 5,47 – 5,54 (1H, m), 7,03 (1H, dd, J = 8,0, 2,0Hz), 7,10 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,0Hz), 7,53 – 7,59 (2H, m), 7,63 – 7,69 (1H, m), 7,73 (1H, t, J = 2,0), 7,81 (1H, d, J = 2,0), 7,84 – 7,90 (1H, m), 8,03 – 8,11 (2H, m), 10,22 (1H, s), 10,42 (1H, s).

Ejemplo 407

Producción de N–[3–({2–[(cloroacetil)amino]imidazo[1,2–

b]piridazin–6–il}oxi)fenil]–3–(1–cianociclopropil)benzamida

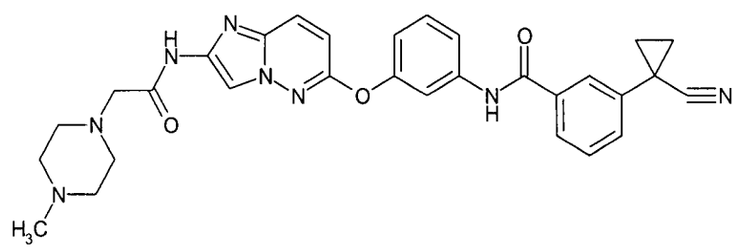


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (600 mg, 1,46 mmol), trietilamina (305 μL, 2,19 mmol), cloruro de cloroacetilo (202 μL, 1,75 mmol) y tetrahidrofurano (10 mL) como materiales de partida y de la misma manera que en el Ejemplo 385, se obtuvo el compuesto del título (636 mg, 89%) en forma de un polvo gris.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,57 – 1,65 (2H, m), 1,77 – 1,85 (2H, m), 4,31 (2H, s), 7,03 (1H, dd, J = 8,0, 2,2 Hz), 7,12 (1H, d, J = 9,6 Hz), 7,45 (1H, t, J = 8,0 Hz), 7,52 – 7,60 (2H, m), 7,66 (1H, d, J = 8,0 Hz), 7,73 (1H, t, J = 2,2 Hz), 7,82 (1H, s), 7,85 – 7,91 (1H, m), 8,04 (1H, s), 8,09 (1H, d, J = 9,6 Hz), 10,43 (1H, s), 11,20 (1H, s).

Ejemplo 408

Producción de 3–(1–cianociclopropil)–N–{3–[(2–{[(4–metilpiperazin–1–il)acetil]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}benzamida

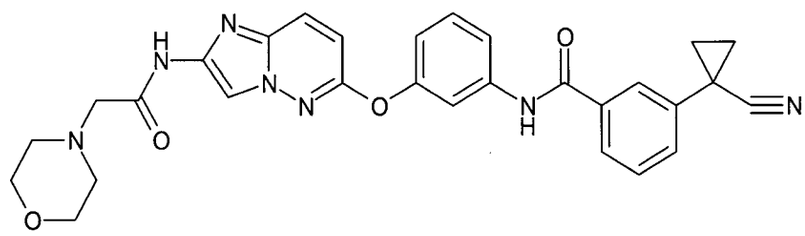


Una mezcla de N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(1–cianociclopropil)benzamida (140 mg, 0,287 mmol), 1–metilpiperazina (1 mL) y acetonitrilo (2 mL) se agitó con calentamiento a 80 °C durante 4 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (acetato de etilo/hexano = 0/100→100/0) para dar el compuesto del título (65 mg, 41%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,43 – 1,53 (2H, m), 1,75 – 1,83 (2H, m), 2,32 (3H, s), 2,40 – 2,72 (8H, m), 3,18 (2H, s), 6,89 (1H, d, J = 9,6 Hz), 6,98 – 7,05 (1H, m), 7,38 – 7,59 (4H, m), 7,69 – 7,80 (4H, m), 8,01 (1H, s), 8,21 (1H, s), 9,55 (1H, s).

Ejemplo 409

Producción de 3–(1–cianociclopropil)–N–[3–({2–[(morfolin–4–ilacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida



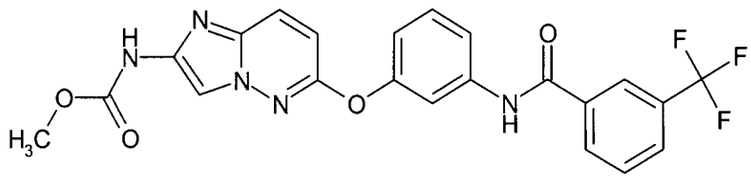
Usando N–[3–({2–[(cloroacetil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(1–cianociclopropil)benzamida (140 mg, 0,287

mmol), morfolina (1 mL) y acetonitrilo (2 mL) como materiales de partida y de la misma manera que en el Ejemplo 408, se obtuvo el compuesto del título (123 mg, 79%) en forma de un polvo blanco.

^{1}H–RMN ($CDCl_3$, 300 MHz) δ 1,45 – 1,52 (2H, m), 1,75 – 1,82 (2H, m), 2,59 – 2,66 (4H, m), 3,18 (2H, s), 3,75 – 3,82 (4H, m), 6,90 (1H, d, J = 9,4 Hz), 6,98 – 7,05 (1H, m), 7,37 – 7,59 (4H, m), 7,70 – 7,79 (4H, m), 8,02 (1H, s), 8,20 (1H, s), 9,50 (1H, s).

Ejemplo 410

Producción de [6–(3–{[3–(trifluorometil)benzoil]amino} fenoxi)imidazo[1,2–b]piridazin–2–il]carbamato de metilo



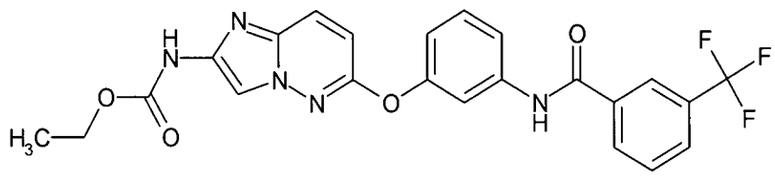
Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol), clorocarbonato de metilo (33 μL, 0,435 mmol), trietilamina (75 μL, 0,544 mmol) y tetrahidrofurano (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 388, se obtuvo el compuesto del título (104 mg, 61%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,68 (3H, s), 7,01 – 7,09 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,64 – 7,84 (4H, m), 7,94 – 8,06 (2H, m), 8,22 – 8,30 (2H, m), 10,40 (1H, brs), 10,58 (1H, s).

Ejemplo 411

Producción de [6–(3–{[3–(trifluorometil)benzoil]amino}fenoxi)

imidazo[1,2–b]piridazin–2–il]carbamato de etilo

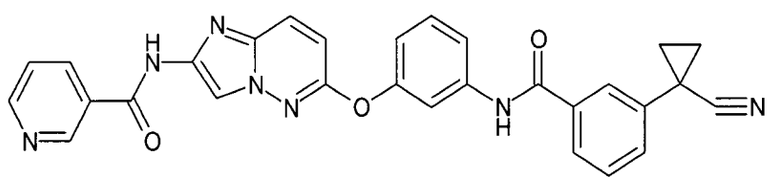


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (150 mg, 0,362 mmol), clorocarbonato de etilo (41 µL, 0,435 mmol), trietilamina (75 µL, 0,544 mmol) y tetrahidrofurano (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 388, se obtuvo el compuesto del título (109 mg, 62%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,23 (3H, t, J = 7,1 Hz), 4,14 (2H, q, J = 7,1 Hz), 7,00 – 7,09 (2H, m), 7,46 (1H, t, J = 8,1 Hz), 7,63 – 7,84 (4H, m), 7,94 – 8,06 (2H, m), 8,22 – 8,30 (2H, m), 10,33 (1H, brs), 10,58 (1H, s).

Ejemplo 412

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]nicotinamida



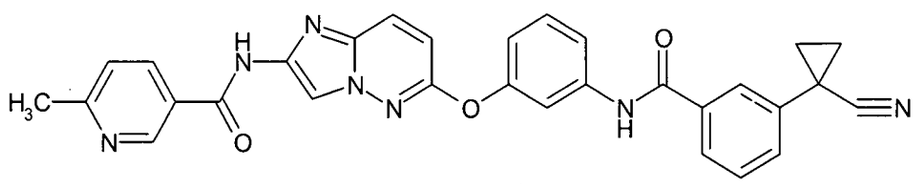
A una solución de ácido nicotínico (54 mg, 0,438 mmol) en tetrahidrofurano (3 mL) se le añadieron N,N–dimetilformamida (1 gota) y cloruro de oxalilo (64 µL, 0,734 mmol), y la mezcla se agitó a

temperatura ambiente durante 1 h. El solvente se evaporó a presión reducida, y el residuo y N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol) se disolvieron en N–metilpirrolidona (3 mL), y la mezcla se agitó a temperatura ambiente durante 14 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 20/80→100/0) para dar el compuesto del título (100 mg, 53%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,57 – 1,65 (2H, m), 1,76 – 1,85 (2H, m), 7,05 (1H, d, J = 8,5 Hz), 7,14 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,1 Hz), 7,51 – 7,61 (3H, m), 7,63 – 7,93 (4H, m), 8,13 (1H, d, J = 9,6 Hz), 8,24 (1H, s), 8,39 (1H, d, J = 7,7 Hz), 8,75 (1H, d, J = 4,9 Hz), 9,18 (1H, d, J = 1,1 Hz), 10,44 (1H, s), 11,57 (1H, s).

Ejemplo 413

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]–6–metilnicotinamida



Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–

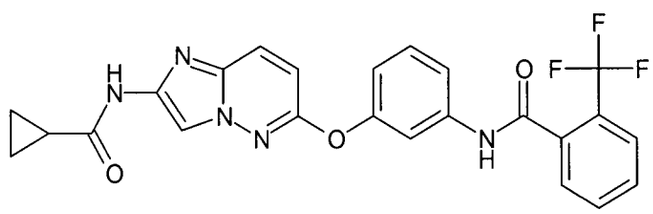
L193

3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol), cloruro de 6–metilnicotinoílo (75 mg, 0,548 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (105 mg, 0,548 mmol), 1–hidroxibenzotriazol (74 mg, 0,548 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 380, se obtuvo el compuesto del título (44 mg, 23%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,59 – 1,65 (2H, m), 1,78 – 1,84 (2H, m), 2,55 (3H, s), 7,03 – 7,07 (1H, m), 7,14 (1H, d, J = 9,6 Hz), 7,40 (1H, d, J = 8,2 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,54 – 7,60 (2H, m), 7,65 – 7,69 (1H, m), 7,75 (1H, t, J = 2,2 Hz), 7,81 – 7,83 (1H, m), 7,86 – 7,90 (1H, m), 8,12 (1H, dd, J = 9,6, 0,5 Hz), 8,22 (1H, s), 8,29 (1H, dd, J = 8,2, 2,2 Hz), 9,08 (1H, d, J = 2,2 Hz), 10,45 (1H, s), 11,50 (1H, s).

Ejemplo 414

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2–(trifluorometil)benzamida



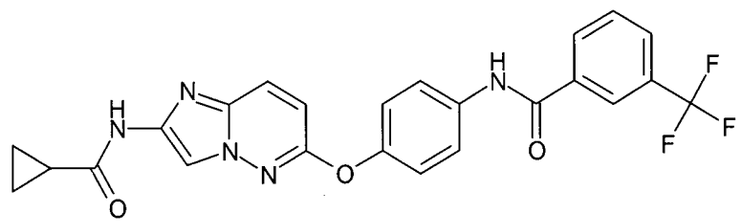
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol), 2–(trifluorometil)benzoico (110 mg, 0,581 mmol), cloruro de oxalilo (84 μL, 0,969 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (5

mL) y N–metilpirrolidona (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (175 mg, 75%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,84 (4H, m), 1,86 – 1,98 (1H, m), 6,98 – 7,04 (1H, m), 7,07 (1H, d, J = 9,6 Hz), 7,43 (1H, t, J = 8,1 Hz), 7,51 – 7,57 (1H, m), 7,64 (1H, t, J = 2,1 Hz), 7,67 – 7,76 (2H, m), 7,76 – 7,88 (2H, m), 7,98 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 10,71 (1H, s), 11,07 (1H, s).

Ejemplo 415

Producción de N–[4–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida



Usando N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol), ácido 3–(trifluorometil)benzoico (110 mg, 0,581 mmol), cloruro de oxalilo (84 μL, 0,969 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (5 mL) y N–metilpirrolidona (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (57 mg, 24%) en forma de un polvo blanco.

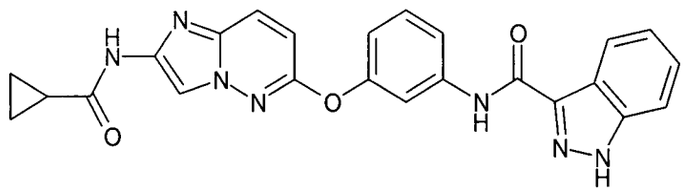
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,86 – 1,97 (1H, m), 7,05 (1H, d, J = 9,6 Hz), 7,29 (2H, d, J = 8,9 Hz), 7,77 – 7,88 (3H, m), 7,94 (1H, s), 7,96 – 8,06 (2H, m), 8,25 – 8,32 (2H,

L195

m), 10,57 (1H, s), 11,06 (1H, s).

Ejemplo 416

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–indazol–3–carboxamida

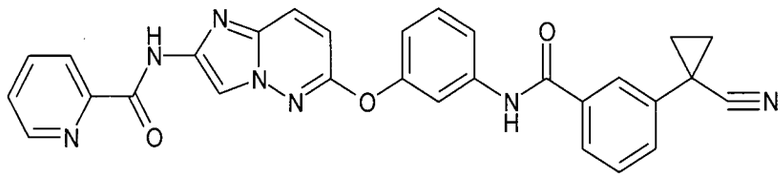


Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol), ácido 1H–indazol–3–carboxílico (94 mg, 0,581 mmol), cloruro de oxalilo (84 μL, 0,969 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (5 mL) y N–metilpirrolidona (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (149 mg, 68%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,84 – 1,98 (1H, m), 6,98 (1H, dd, J = 7,6, 2,0 Hz), 7,07 (1H, d, J = 9,6 Hz), 7,28 (1H, t, J = 7,6 Hz), 7,38 – 7,49 (2H, m), 7,66 (1H, d, J = 8,3 Hz), 7,78 – 7,83 (1H, m), 7,88 (1H, t, J = 2,0 Hz), 7,99 (1H, s), 8,05 (1H, d, J = 9,6 Hz), 8,20 (1H, d, J = 8,3 Hz), 10,51 (1H, s), 11,08 (1H, s), 13,79 (1H, brs).

Ejemplo 417

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]piridin–2–carboxamida

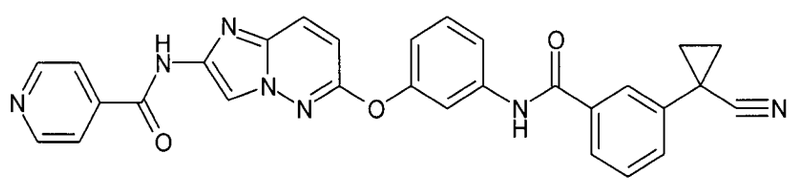


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol), ácido piridin–2–carboxílico (54 mg, 0,438 mmol), cloruro de oxalilo (63 μL), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N–metilpirrolidona (5 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (125 mg, 67%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,78 – 1,85 (2H, m), 7,05 (1H, dd, J = 8,0, 1,8 Hz), 7,16 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,0 Hz), 7,52 – 7,61 (2H, m), 7,65 – 7,77 (3H, m), 7,83 (1H, s), 7,85 – 7,91 (1H, m), 8,05 – 8,20 (3H, m), 8,24 (1H, s), 8,73 – 8,78 (1H, m), 10,44 (1H, s), 10,69 (1H, s).

Ejemplo 418

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]isonicotinamida



Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol), ácido piridin–4–carboxílico (54 mg, 0,438 mmol), cloruro de oxalilo (63 μL,

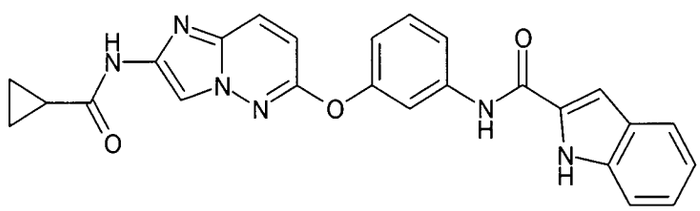
1197

0,734 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N–metilpirrolidona (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (111 mg, 59%) en forma de un polvo de color verde pálido.

1H–RMN (DMSO–d_6, 300 MHz) δ 1,57 – 1,65 (2H, m), 1,77 – 1,85 (2H, m), 7,01 – 7,09 (1H, m), 7,15 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,51 – 7,61 (2H, m), 7,64 – 7,70 (1H, m), 7,75 (1H, t, J = 2,1 Hz), 7,79 – 7,84 (1H, m), 7,85 – 7,91 (1H, m), 7,93 – 7,98 (2H, m), 8,13 (1H, d, J = 9,6 Hz), 8,24 (1H, s), 8,73 – 8,81 (2H, m), 10,44 (1H, s), 11,67 (1H, s).

Ejemplo 419

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1H–indol–2–carboxamida



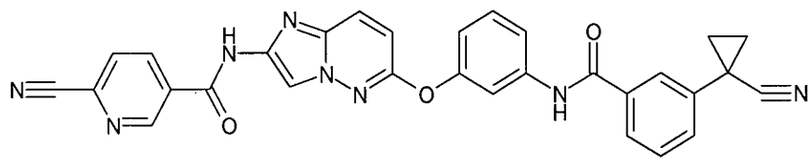
Usando N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol), 1H–indol–2–carboxílico (93 mg, 0,581 mmol), cloruro de oxalilo (84 μL, 0,969 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (5 mL) y N–metilpirrolidona (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (153 mg, 70%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,83 –

2,01 (1H, m), 6,96 – 7,12 (3H, m), 7,18 – 7,26 (1H, m), 7,39 – 7,49 (3H, m), 7,69 (2H, t, J = 8,1 Hz), 7,76 (1H, t, J = 2,1 Hz), 8,00 (1H, s), 8,06 (1H, d, J = 9,4 Hz), 10,33 (1H, s), 11,09 (1H, s), 11,75 (1H, s).

Ejemplo 420

Producción de 6–ciano–N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]nicotinamida



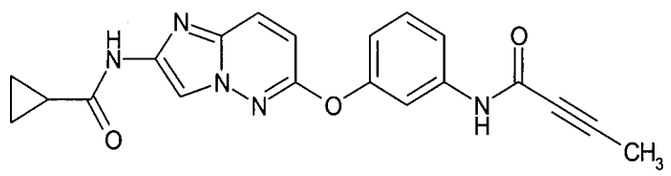
Una mezcla de 6–cloro–N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]nicotinamida (120 mg, 0,201 mmol), tetrakis(trifenilfosfina)paladio (0) (58 mg, 50,4 μmol), cianuro de cinc (26 mg, 0,225 mmol) y N,N–dimetilformamida (2,5 mL) se agitó con calentamiento bajo una atmósfera de argón a 100 °C durante 6,5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 50/50→100/0) para dar el compuesto del título (51 mg, 47%) en forma de un polvo amarillo.

LL99

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,78 – 1,85 (2H, m), 7,05 (1H, dd, J = 8,2, 1,4 Hz), 7,16 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,51 – 7,60 (2H, m), 7,67 (1H, d, J = 8,5 Hz), 7,74 – 7,91 (3H, m), 8,14 (1H, d, J = 9,6 Hz), 8,19 – 8,27 (2H, m), 8,60 (1H, dd, J = 8,0, 2,0 Hz), 9,29 (1H, s), 10,45 (1H, s), 11,84 (1H, s).

Ejemplo 421

Producción de N–{6–[3–(but–2–inoilamino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



A una solución de ácido but–2–inoico (61 mg, 0,581 mmol) en tetrahidrofurano (3 mL) se le añadieron clorocarbonato de isobutilo (76 μL, 0,581 mmol) y 4–metilmorfolina (80 μL, 0,727 mmol), una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol) en piridina (1,5 mL)/N,N–dimetilformamida (2 mL) también se agregó bajo enfriamiento con hielo, y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo/tetrahidrofurano. El extracto se lavó con salmuera saturada, se secó sobre sulfato de sodio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se lavó con acetato de etilo para dar el compuesto del título (132 mg, 73%)

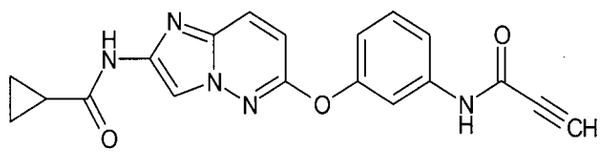
1200

en forma de un polvo de color anaranjado pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,85 (4H, m), 1,86 – 1,97 (1H, m), 2,04 (3H, s), 6,92 – 6,99 (1H, m), 7,04 (1H, d, J = 9,6 Hz), 7,32 – 7,47 (2H, m), 7,54 (1H, t, J = 1,9 Hz), 7,93 – 7,99 (1H, m), 8,04 (1H, d, J = 9,6 Hz), 10,75 (1H, s), 11,08 (1H, s).

Ejemplo 422

Producción de N–{6–[3–(propioloilamino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



A una solución de ácido propiólico (27 mg, 0,387 mmol) en tetrahidrofurano (2 mL) y N,N–dimetilformamida (2 mL) se añadió N,N'–diciclohexilcarbodiimida (100 mg, 0,484 mmol) bajo enfriamiento con hielo, y la mezcla se agitó durante 30 min. A la mezcla de reacción se añadió N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (100 mg, 0,323 mmol), y la mezcla se agitó bajo enfriamiento con hielo durante 4 h. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 0/100→100/0) para dar el compuesto del título (24 mg, 21%) en forma de un polvo de color anaranjado pálido.

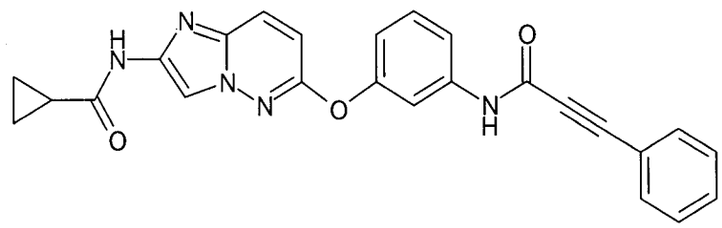
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,85 (4H, m), 1,87 – 1,98 (1H, m), 4,45 (1H, s), 6,97 – 7,08 (2H, m), 7,35 – 7,48 (2H, m), 7,51 – 7,57 (1H, m), 7,96 (1H, s), 8,04 (1H, d, J = 9,8 Hz), 10,95 (1H,

1201

s), 11,08 (1H, s).

Ejemplo 423

Producción de N–(6–{3–[(3–fenilprop–2–inoil)amino]fenoxi} imidazo[1,2–b]piridazin–2–il)ciclopropancarboxamida

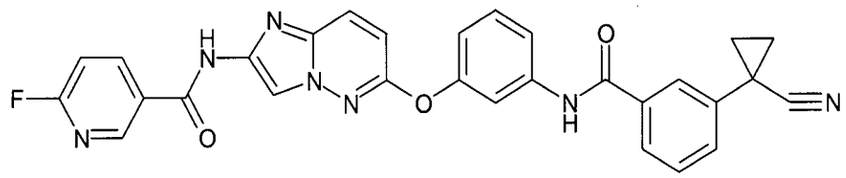


A una solución de ácido 3–fenilprop–2–inoico (85 mg, 0,581 mmol) en tetrahidrofurano (3 mL) se añadieron clorocarbonato de isobutilo (76 μL, 0,581 mmol) y 4–metilmorfolina (80 μL, 0,727 mmol) bajo enfriamiento con hielo, una solución de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (150 mg, 0,484 mmol) en N,N–dimetilformamida (3 mL) también se agregó tereto, y la mezcla se agitó a temperatura ambiente durante 16 h. Se añadió agua a la mezcla de reacción, y el sólido precipitado se filtró y se lavó con agua para dar el compuesto del título (188 mg, 89%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,84 (4H, m), 1,88 – 1,98 (1H, m), 6,98 – 7,04 (1H, m), 7,06 (1H, d, J = 9,5 Hz), 7,38 – 7,56 (5H, m), 7,59 (1H, t, J = 2,0 Hz), 7,62 – 7,68 (2H, m), 7,98 (1H, s), 8,05 (1H, d, J = 9,5 Hz), 11,01 (1H, s), 11,08 (1H, s).

Ejemplo 424

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino} fenoxi)imidazo[1,2–b]piridazin–2–il]–6–fluoronicotinamida

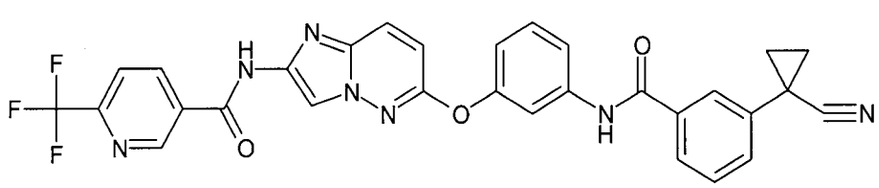


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol), ácido 6–fluoronicotínico (61 mg, 0,438 mmol), cloruro de oxalilo (64 μL, 0,730 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N,N–dimetilacetamida (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (38 mg, 20%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,57 – 1,65 (2H, m), 1,78 – 1,85 (2H, m), 7,05 (1H, dd, J = 8,2, 2,2 Hz), 7,15 (1H, d, J = 9,5 Hz), 7,35 (1H, dd, J = 8,2, 2,8 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,52 – 7,60 (2H, m), 7,64 – 7,69 (1H, m), 7,75 (1H, t, J = 2,2 Hz), 7,80 – 7,84 (1H, m), 7,85 – 7,91 (1H, m), 8,13 (1H, d, J = 9,5 Hz), 8,22 (1H, s), 8,55 – 8,63 (1H, m), 8,90 (1H, d, J = 2,2 Hz), 10,45 (1H, s), 11,61 (1H, s).

Ejemplo 425

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]–6–(trifluorometil)nicotinamida

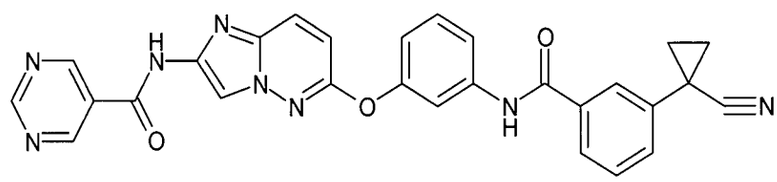


Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (150 mg, 0,365 mmol), ácido 6–(trifluorometil)nicotínico (83 mg, 0,438 mmol), cloruro de oxalilo (64 μL, 0,730 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N,N–dimetilacetamida (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (57 mg, 27%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,58 – 1,65 (2H, m), 1,78 – 1,85 (2H, m), 7,03 – 7,09 (1H, m), 7,16 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,1 Hz), 7,52 – 7,61 (2H, m), 7,64 – 7,70 (1H, m), 7,74 – 7,85 (2H, m), 7,86 – 7,91 (1H, m), 8,06 – 8,18 (2H, m), 8,25 (1H, s), 8,62 – 8,69 (1H, m), 9,31 – 9,35 (1H, m), 10,45 (1H, s), 11,83 (1H, s).

Ejemplo 426

Producción de N–[6–(3–{[3–(1–cianociclopropil)benzoil]amino}fenoxi)imidazo[1,2–b]piridazin–2–il]pirimidin–5–carboxamida



Usando N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(1–cianociclopropil)benzamida (140 mg, 0,313 mmol), ácido pirimidin–5–carboxílico (58 mg, 0,471 mmol), clorhidrato de N–[3–(dimetilamino)propil]–N'–etilcarbodiimida (90 mg, 0,471 mmol), 1–hidroxibenzotriazol (63 mg, 0,471 mmol), trietilamina (60 μL, 0,471 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida y

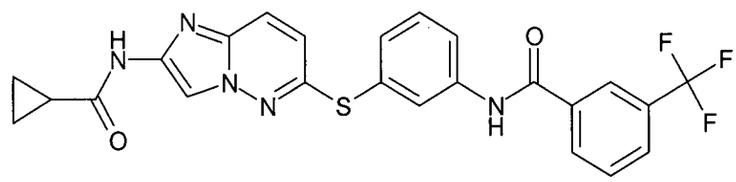
1204

de la misma manera que en el Ejemplo 380, se obtuvo el compuesto del título (42 mg, 26%) en forma de un polvo de color amarillo pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 1,59 – 1,65 (2H, m), 1,79 – 1,85 (2H, m), 7,03 – 7,08 (1H, m), 7,16 (1H, d, J = 9,6 Hz), 7,47 (1H, t, J = 8,2 Hz), 7,54 – 7,60 (2H, m), 7,65 – 7,70 (1H, m), 7,76 (1H, t, J = 2,1 Hz), 7,81 – 7,84 (1H, m), 7,86 – 7,91 (1H, m), 8,15 (1H, dd, J = 9,6, 0,7 Hz), 8,23 (1H, s), 9,32 – 9,37 (3H, m), 10,46 (1H, s), 11,79 (1H, s).

Ejemplo 427

Producción de N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–3–(trifluorometil)benzamida



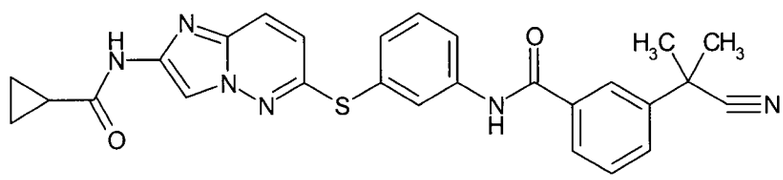
Usando N–{6–[(3–aminofenil)sulfanil]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (140 mg, 0,430 mmol), ácido 3–(trifluorometil)benzoico (98 mg, 0,516 mmol), cloruro de oxalilo (75 μL, 0,860 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N,N–dimetilacetamida (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (148 mg, 75%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 – 0,86 (4H, m), 1,89 – 2,00 (1H, m), 6,96 (1H, d, J = 9,4 Hz), 7,34 – 7,39 (1H, m), 7,50 (1H, t, J = 8,0 Hz), 7,79 (1H, t, J = 8,0 Hz), 7,88 – 7,94 (2H, m), 7,98 (1H, d, J = 8,0 Hz), 8,03 (1H, t, J = 1,8 Hz), 8,15 (1H, s), 8,25 (1H, d, J =

8,0 Hz), 8,28 (1H, s), 10,60 (1H, s), 11,18 (1H, s).

Ejemplo 428

Producción de 3–(1–ciano–1–metiletil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]benzamida



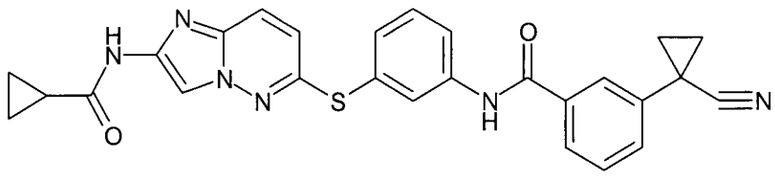
Usando N–{6–[(3–aminofenil)sulfanil]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (140 mg, 0,430 mmol), ácido 3–(1–ciano–1–metiletil)benzoico (97 mg, 0,516 mmol), cloruro de oxalilo (75 μL, 0,860 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N,N–dimetilacetamida (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (108 mg, 51%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,87 (4H, m), 1,74 (6H, s), 1,89 – 1,99 (1H, m), 6,95 (1H, d, J = 9,4 Hz), 7,32 – 7,38 (1H, m), 7,49 (1H, t, J = 8,0 Hz), 7,60 (1H, t, J = 7,8 Hz), 7,72 – 7,79 (1H, m), 7,86 – 7,96 (3H, m), 8,00 – 8,05 (2H, m), 8,15 (1H, s), 10,45 (1H, s), 11,18 (1H, s).

Ejemplo 429

Producción de 3–(1–cianociclopropil)–N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]benzamida

1206.

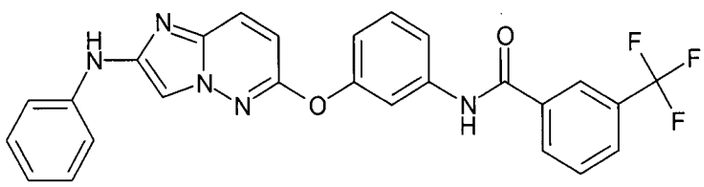


Usando N–{6–[(3–aminofenil)sulfanil]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida (130 mg, 0,399 mmol), ácido 3–(1–cianociclopropil)benzoico (89 mg, 0,479 mmol), cloruro de oxalilo (70 μL, 0,799 mmol), N,N–dimetilformamida (1 gota), tetrahidrofurano (3 mL) y N,N–dimetilacetamida (3 mL) como materiales de partida y de la misma manera que en el Ejemplo 412, se obtuvo el compuesto del título (158 mg, 80%) en forma de un polvo de color color café pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,88 (4H, m), 1,58 – 1,65 (2H, m), 1,77 – 1,85 (2H, m), 1,89 – 2,00 (1H, m), 6,95 (1H, d, J = 9,4 Hz), 7,32 – 7,38 (1H, m), 7,45 – 7,53 (1H, m), 7,54 – 7,61 (2H, m), 7,82 (1H, s), 7,84 – 7,94 (3H, m), 8,02 (1H, t, J = 1,7 Hz), 8,15 (1H, s), 10,44 (1H, s), 11,18 (1H, s).

Ejemplo 430

Producción de N–{3–[(2–anilinoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida



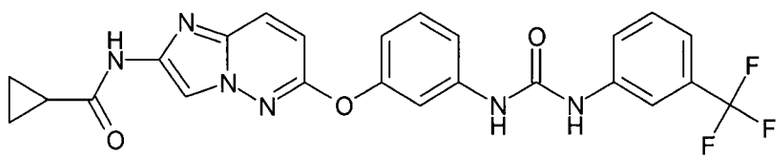
Una mezcla de N–{3–[(2–aminoimidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida (100 mg, 0,242 mmol), yodobenceno (32 μl, 0,290 mmol), tris(dibencilidenacetona)dipaladio (0) (11 mg, 24,2 μmol), diciclohexil(2',4',6'–triisopropilbifenil–2–il)

fosfina (23 mg, 48,4 μmol), tert-butóxido de sodio (34 mg, 0,362 mmol) y tolueno (2 mL) se agitó bajo una atmósfera de argón con calentamiento a 80 °C durante 5 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se le añadió solución acuosa saturada de hidrógeno–carbonato de sodio a la mezcla, y la mezcla se extrajo con acetato de etilo. El extracto se lavó con salmuera saturada, se secó sobre sulfato de magnesio anhidro, y se filtró. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/hexano = 0/100→50/50) para dar el compuesto del título (19 mg, 16%) en forma de un polvo de color verde pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,78 (1H, t, J = 7,3 Hz), 6,96 – 7,07 (2H, m), 7,18 – 7,25 (2H, m), 7,36 – 7,50 (3H, m), 7,65 – 7,72 (3H, m), 7,79 (1H, t, J = 7,6 Hz), 7,98 (2H, d, J = 9,2 Hz), 8,18 – 8,32 (2H, m), 8,91 (1H, s), 10,58 (1H, s).

Ejemplo 431

Producción de N–{6–[3–({[3–(trifluorometil)fenil]carbamoil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



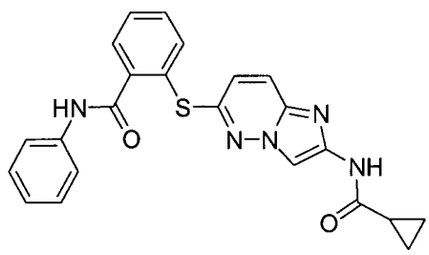
Una mezcla de N–[6–(3–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (300 mg, 0,969 mmol), 3–

(trifluorometil)isocianato de fenilo (667 µL, 4,84 mmol), tolueno (4 mL) y tetrahidrofurano (1 mL) se agitó con calentamiento a reflujo durante 3 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, el precipitado se recogió por filtración y se lavó con acetato de etilo/éter diisopropílico para dar el compuesto del título (268 mg, 56%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,84 (4H, m), 1,87 – 1,98 (1H, m), 6,83 – 6,89 (1H, m), 7,04 (1H, d, J = 9,5 Hz), 7,23 – 7,40 (3H, m), 7,46 – 7,53 (2H, m), 7,56 – 7,64 (1H, m), 7,95 – 8,00 (2H, m), 8,03 (1H, d, J = 9,5 Hz), 9,12 – 9,35 (2H, m), 11,08 (1H, s).

Ejemplo 432

Producción de 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)–N–fenilbenzamida

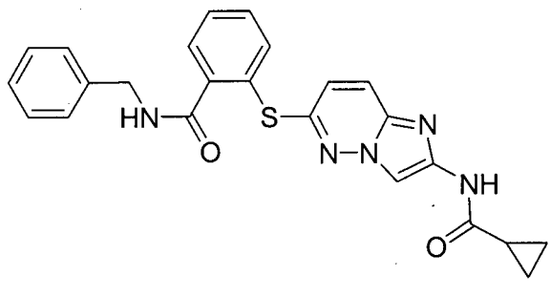


De la misma manera que en el Ejemplo 278 y usando ácido 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (250 mg, 0,71 mmol), anilina (184 mg, 2,0 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (380 mg, 1,0 mmol), N,N–diisopropiletilamina (270 mg, 2,0 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (280 mg, 93%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,76 – 0,88 (4H, m), 1,88 – 1,97 (1H, m), 6,98 (1H, d, J = 9,5 Hz), 7,08 (1H, t, J = 7,4 Hz), 7,31 (2H, t, J = 8,0 Hz), 7,49 – 7,60 (3H, m), 7,61 – 7,76 (3H, m), 7,88 (1H, d, J = 9,1 Hz), 8,14 (1H, s), 10,51 (1H, s), 11,16 (1H, s).

Ejemplo 433

Producción de N–bencil–2–({2–[(ciclopropilcarbonil)amino] imidazo[1,2–b]piridazin–6–il}tio)benzamida

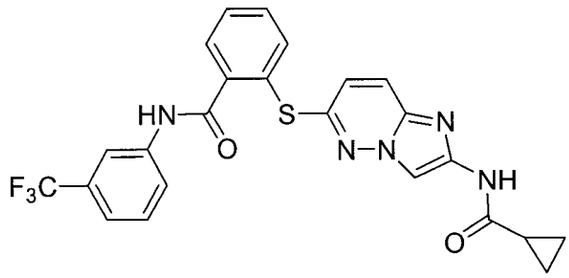


De la misma manera que en el Ejemplo 278 y usando ácido 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (250 mg, 0,71 mmol), bencilamine (212 mg, 2,0 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (380 mg, 1,0 mmol), N,N–diisopropiletilamina (270 mg, 2,0 mmol) y N,N–dimetilformamida (7 mL) como materiales de partida, se obtuvo el compuesto del título (280 mg, 89%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,90 (4H, m), 1,90 – 2,01 (1H, m), 4,42 (2H, d, J = 6,1 Hz), 6,96 (1H, d, J = 9,5 Hz), 7,17 – 7,35 (4H, m), 7,43 – 7,52 (4H, m), 7,61 (1H, dd, J = 7,0, 2,5 Hz), 7,88 (1H, d, J = 9,5 Hz), 8,16 (1H, s), 9,04 (1H, t, J = 5,9 Hz), 11,17 (1H, s).

Ejemplo 434

Producción de 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)–N–[3–(trifluorometil)fenil]benzamida

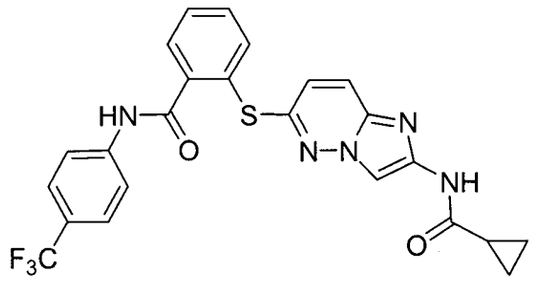


De la misma manera que en el Ejemplo 278 y usando ácido 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (150 mg, 0,42 mmol), 3–(trifluorometil)anilina (191 mg, 1,2 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (230 mg, 0,6 mmol), N,N–diisopropiletilamina (160 mg, 1,3 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (208 mg, 99%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,88 (4H, m), 1,87 – 1,97 (1H, m), 6,99 (1H, d, J = 9,4 Hz), 7,40 – 7,46 (1H, m), 7,49 – 7,63 (4H, m), 7,72 – 7,78 (1H, m), 7,83 – 7,90 (2H, m), 8,09 – 8,16 (2H, m), 10,85 (1H, s), 11,14 (1H, s).

Ejemplo 435

Producción de 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)–N–[4–(trifluorometil)fenil]benzamida

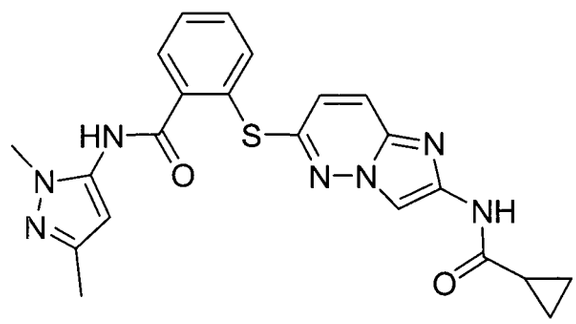


De la misma manera que en el Ejemplo 278 y usando ácido 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (150 mg, 0,42 mmol), 4–(trifluorometil)anilina (191 mg, 1,2 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (230 mg, 0,6 mmol), N,N–diisopropiletilamina (160 mg, 1,3 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (155 mg, 74%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,74 – 0,89 (4H, m), 1,86 – 1,98 (1H, m), 6,99 (1H, d, J = 9,3 Hz), 7,49 – 7,62 (3H, m), 7,67 (2H, d, J = 8,7 Hz), 7,72 – 7,77 (1H, m), 7,83 – 7,90 (3H, m), 8,13 (1H, s), 10,87 (1H, s), 11,14 (1H, s).

Ejemplo 436

Producción de 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)–N–(1,3–dimetil–1H–pirazol–5–il)benzamida



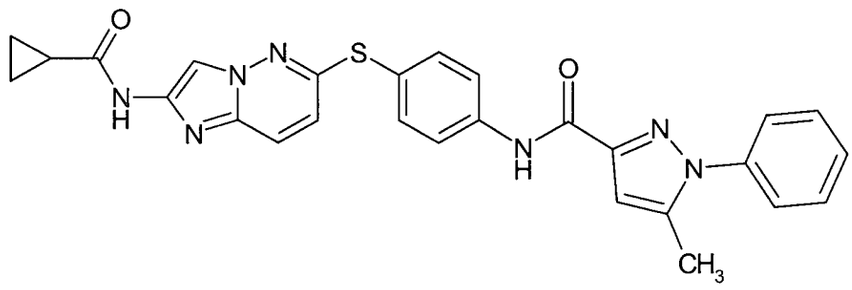
1212

De la misma manera que en el Ejemplo 278 y usando ácido 2–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)benzoico (150 mg, 0,42 mmol), 1,3–dimetil–1H–pirazol–5–amina (130 mg, 1,2 mmol), hexafluorofosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio (230 mg, 0,6 mmol), N,N–diisopropiletilamina (160 mg, 1,3 mmol) y N,N–dimetilformamida (5 mL) como materiales de partida, se obtuvo el compuesto del título (130 mg, 70%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,75 – 0,86 (4H, m), 1,89 – 1,99 (1H, m), 2,08 (3H, s), 3,59 (3H, s), 5,97 (1H, s), 7,00 (1H, d, J = 9,8 Hz), 7,46 – 7,63 (3H, m), 7,71 – 7,79 (1H, m), 7,90 (1H, d, J = 9,8 Hz), 8,15 (1H, s), 10,49 (1H, s), 11,17 (1H, s).

Ejemplo 437

Producción de N–[4–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–5–metil–1–fenil–1H–pirazol–3–carboxamida



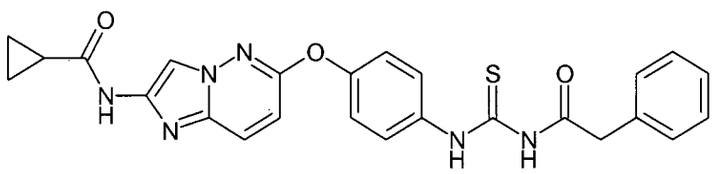
Usando ácido 5–metil–1–fenil–1H–pirazol–3–carboxílico (186 mg, 0,92 mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (80 μL, 0,92 mmol), N–{6–[(4–aminofenil)tio]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida

(200 mg, 0,62 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 249, se obtuvo el compuesto del título (201 mg, 64%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,79 –0,85 (4H, m), 1,89 – 1,97 (1H, m), 2,31 (3H, s), 6,81 (1H, d, J = 9,3 Hz), 6,89 (1H, s), 7,35 – 7,49 (5H, m), 7,57 – 7,61 (2H, m), 7,76 – 7,86 (3H, m), 8,09 (1H, s), 10,74 (1H, s), 11,14 (1H, s).

Ejemplo 438

Producción de N–{6–[4–({[(fenilacetil)amino]tiocarbonil}amino) fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida



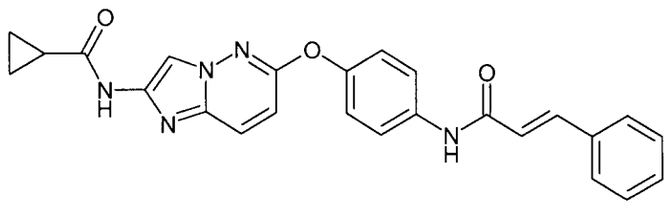
A una solución de cloruro de fenilacetilo (342 μL, 2,59 mmol) en acetonitrilo (8,0 mL) se añadió tiocianato de potasio (0,31 g, 3,23 mmol), y la mezcla se agitó a 50 °C durante 1 h. Tras enfriar la mezcla hasta temperatura ambiente, el solvente se evaporó a presión reducida. Se añadió salmuera saturada al residuo, y la mezcla se extrajo con acetato de etilo, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida. Toluene/etanol (2,0 mL/2,0 mL) se añadió al residuo, N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,65 mmol) se añadió a la mezcla, y la mezcla se agitó a temperatura ambiente durante 1 h. Se añadió salmuera saturada a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo, se

lavó con salmuera saturada, y se secó sobre sulfato de magnesio anhidro. El solvente se evaporó a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (hexano/acetato de etilo = 1/3) para dar el compuesto del título (164 mg, 51%) en forma de cristales blancos.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,78 – 0,82 (4H, m), 1,87 – 1,95 (1H, m), 3,82 (2H, s), 7,05 (1H, d, J = 9,6 Hz), 7,24 – 7,36 (7H, m), 7,66 (2H, d, J = 9,0 Hz), 7,93 (1H, s), 8,02 (1H, d, J = 9,6 Hz), 11,06 (1H, s), 11,71 (1H, s), 12,36 (1H, s).

Ejemplo 439

Producción de N–[6–(4–{[(2E)–3–fenilprop–2–enoil]amino}fenoxi) imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida



Usando ácido (2E)–3–fenilacrílico (135 mg, 0,91 mmol), tetrahidrofurano (3,0 mL), N,N–dimetilformamida (20 μL, 0,26 mmol), cloruro de oxalilo (80 μL, 0,91 mmol), N–[6–(4–aminofenoxi)imidazo[1,2–b]piridazin–2–il]ciclopropancarboxamida (200 mg, 0,65 mmol) y N,N–dimetilacetamida (4,0 mL), y de la misma manera que en el Ejemplo 255, se obtuvo el compuesto del título (133 mg, 47%) en forma de un polvo blanco.

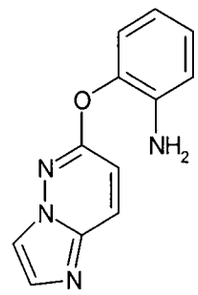
^{1}H–RMN (DMSO–d_6, 300 MHz) δ 0,77 – 0,82 (4H, m), 1,86 – 1,96 (1H, m), 6,84 (1H, d, J =15,9 Hz), 7,04 (1H, d, J = 9,8 Hz), 7,25

P215

(2H, d, J = 9,0 Hz), 7,38 – 7,50 (3H, m), 7,58 – 7,66 (3H, m), 7,77 (2H, d, J = 9,0 Hz), 7,93 (1H, s), 8,02 (1H, d, J = 9,8 Hz), 10,33 (1H, s), 11,07 (1H, s).

Ejemplo 440

Producción de 2–(imidazo[1,2–b]piridazin–6–iloxi)anilina



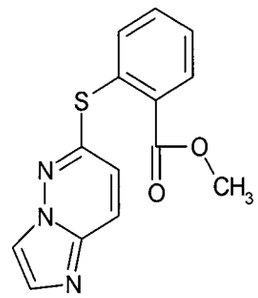
Una mezcla de 6–cloroimidazo[1,2–b]piridazina (1536 mg, 10,0 mmol), 2–aminofenol (1419 mg, 13,0 mmol), carbonato de potasio (4146 mg, 30,0 mmol) y N–metilpirrolidona (10 mL) se agitó a 120 °C durante 3 días. La mezcla de reacción se diluyó con solución acuosa 1 N de hidróxido de sodio y se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice NH (hexano/acetato de etilo = 70/30→0/100). La fracción objeto se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→75/25), y se precipitó en éter diisopropílico para dar el compuesto del título (307 mg, 1,4 mmol, rendimiento 14%) en forma de un sólido de color color café pálido.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 5,08 (2H, s), 6,57 (1H, td, J = 7,6, 1,6Hz), 6,81 (1H, dd, J = 7,9, 1,7Hz), 6,95–7,04 (2H, m), 7,04

(1H, d, J = 9,9Hz), 7,61 (1H, d, J = 0,9Hz), 8,02 (1H, s), 8,11 (1H, d, J = 9,9Hz).

Ejemplo 441

Producción de 2–(imidazo[1,2–b]piridazin–6–iltio)benzoato de metilo



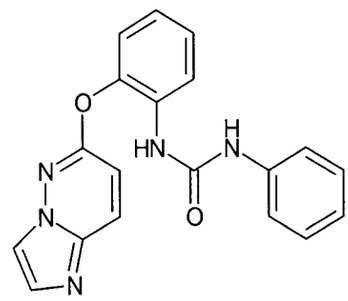
Una mezcla de 6–cloroimidazo[1,2–b]piridazina (1536 mg, 10,0 mmol), 2–mercaptobenzoato de metilo (1,788 mL, 13,0 mmol), carbonato de potasio (4146 mg, 30,0 mmol) y N,N–dimetilformamida (20 mL) se agitó a 70 °C durante 18 h. A la mezcla de reacción se añadió 2–mercaptobenzoato de metilo (0,963 mL, 7,0 mmol), y la mezcla se agitó a 70 °C durante 6 h. La mezcla de reacción se concentró a presión reducida, el residuo se diluyó con agua, y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice NH (hexano/acetato de etilo = 90/10→20/80) y se precipitó en éter diisopropílico para dar el compuesto del título (663 mg, 2,3 mmol, rendimiento 23%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,83 (3H, s), 7,14 (1H, d, J = 9,5Hz), 7,37 (1H, dd, J = 7,7, 1,0Hz), 7,47 (1H, td, J = 7,4, 1,4Hz), 7,55 (1H, td, J = 7,7, 1,5Hz), 7,80 (1H, d, J = 1,2Hz), 7,95 (1H, dd, J

= 7,7, 1,4Hz), 8,10 (1H, dd, J = 9,5, 0,6Hz), 8,29 (1H, t, J = 0,9Hz).

Ejemplo 442

Producción de N–[2–(imidazo[1,2–b]piridazin–6–iloxi)fenil]–N'–fenilurea

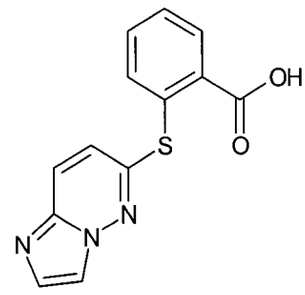


A una solución de 2–(imidazo[1,2–b]piridazin–6–iloxi)anilina (90 mg, 0,40 mmol) y trietilamina (0,011 mL, 0,08 mmol) en tetrahidrofurano (20 mL) se añadió isocianato de fenilo (0,061 mL, 0,56 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró a presión reducida, y el residuo se recristalizó en metanol para dar el compuesto del título (99 mg, 0,29 mmol, rendimiento 72%) en forma de un polvo blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,92–7,00 (1H, m), 7,02–7,09 (1H, m), 7,17–7,30 (5H, m), 7,38–7,44 (2H, m), 7,66 (1H, d, J = 6,9Hz), 8,09 (1H, s), 8,20–8,28 (2H, m), 8,33 (1H, s), 9,04 (1H, s).

Ejemplo 443

Producción de ácido 2–(imidazo[1,2–b]piridazin–6–iltio)benzoico

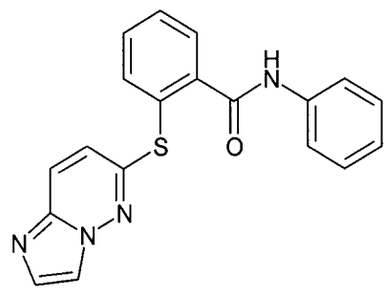


A una solución de 2–(imidazo[1,2–b]piridazin–6–iltio)benzoato de metilo (619 mg, 2,17 mmol) en metanol (20 mL) se le añadió solución acuosa 8 N de hidróxido de sodio (1,00 mL), y la mezcla se agitó a 70 °C durante 18 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, ácido clorhídrico 6 N (1,33 mL) se añadió a la mezcla de reacción, y El precipitado se recogió por filtración, y se lavó con agua. El precipitado se suspendió en metanol (10 mL), y la suspensión se agitó con calentamiento a reflujo durante 10 min. Después de dejar enfriar la suspensión hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con metanol, y se secó a presión reducida para dar el compuesto del título (496 mg, 1,83 mmol, rendimiento 84%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,15 (1H, d, J = 9,5Hz), 7,29 (1H, dd, J = 7,9, 1,1Hz), 7,42 (1H, td, J = 7,5, 1,2Hz), 7,50 (1H, td, J = 7,6, 1,6Hz), 7,80 (1H, d, J = 1,2Hz), 7,95 (1H, dd, J = 7,5, 1,5Hz), 8,10 (1H, d, J = 9,5Hz), 8,30 (1H, t, J = 0,9Hz), 13,39 (1H, br s).

Ejemplo 444

Producción de 2–(imidazo[1,2–b]piridazin–6–iltio)–N–fenilbenzamida



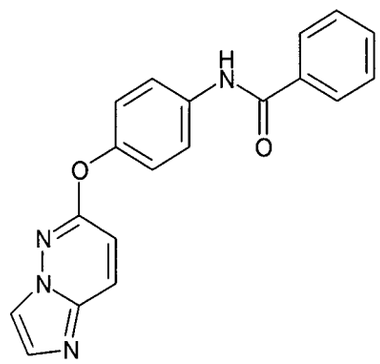
1219

A una mezcla de ácido 2–(imidazo[1,2–b]piridazin–6–iltio)benzoico (109 mg, 0,40 mmol), anilina (75 mg, 0,81 mmol), hidrato de 1–hidroxibenzotriazol (61 mg, 0,40 mmol) y N,N–dimetilformamida (5 mL) se le añadieron clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (153 mg, 0,80 mmol) y trietilamina (0,167 mL, 1,20 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. Una solución acuosa 1 N de hidróxido de sodio se añadió a la mezcla y la mezcla se extrajo con acetato de etilo. La capa orgánica se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→80/20) y se precipitó en acetato de etilo/éter diisopropílico para dar el compuesto del título (110 mg, 0,32 mmol, rendimiento 79%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 6,97 (1H, d, J = 9,5Hz), 7,08 (1H, t, J = 7,4Hz), 7,31 (2H, t, J = 7,8Hz), 7,51 – 7,76 (7H, m), 8,02 (1H, dd, J = 9,5, 0,5Hz), 8,18 (1H, s), 10,51 (1H, s).

Ejemplo 445

Producción de N–[4–(imidazo[1,2–b]piridazin–6–iloxi)fenil]benzamida



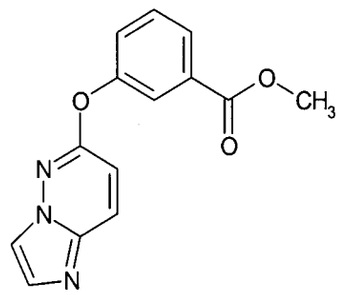
Usando 4–(imidazo[1,2–b]piridazin–6–iloxi)anilina (113 mg,

0,50 mmol), N–metilpirrolidona (1 mL) y cloruro de benzoílo (0,116 mL, 1,00 mmol), y de la misma manera que en el Ejemplo 145, se obtuvo el compuesto del título (144 mg, 0,44 mmol, rendimiento 87%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,12 (1H, d, J = 9,6Hz), 7,29 (2H, d, J = 8,9Hz), 7,51 – 7,66 (3H, m), 7,65 (1H, d, J = 1,2Hz), 7,85 (2H, d, J = 8,9Hz), 7,94 – 8,01 (2H, m), 8,06 (1H, s), 8,17 (1H, dd, J = 9,6, 0,3Hz), 10,35 (1H, s).

Ejemplo 446

Producción de 3–(imidazo[1,2–b]piridazin–6–iloxi)benzoato de metilo



Una mezcla de 6–cloroimidazo[1,2–b]piridazina (1536 mg, 10,0 mmol), 3–hidroxibenzoato de metilo (1978 mg, 13,0 mmol), carbonato de potasio (4146 mg, 30,0 mmol) y N–metilpirrolidona (10 mL) se agitó a 120 °C durante 18 h. La mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice NH (hexano/acetato de etilo = 90/10→20/80). La fracción objeto se concentró a presión reducida, y el residuo se purificó por cromatografía en columna de

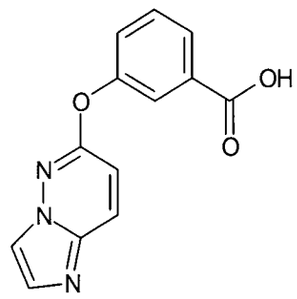
1121

gel de sílice (hexano/acetato de etilo = 60/40→0/100) y se precipitó en éter diisopropílico para dar el compuesto del título (1722mg, 6,4 mmol, rendimiento 64%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 3,87 (3H, s), 7,16 (1H, d, J = 9,5Hz), 7,60 – 7,68 (3H, m), 7,79 – 7,83 (1H, m), 7,84 – 7,93 (1H, m), 8,05 (1H, s), 8,19 (1H, d, J = 9,5Hz).

Ejemplo 447

Producción de ácido 3–(imidazo[1,2–b]piridazin–6–iloxi)benzoico



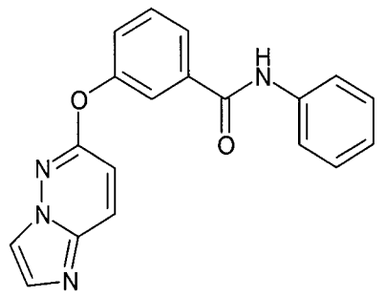
A una solución de 3–(imidazo[1,2–b]piridazin–6–iloxi)benzoato de metilo (1665 mg, 6,18 mmol) en metanol (30 mL) se añadió solución acuosa 8 N de hidróxido de sodio (3,00 mL), y la mezcla se agitó a temperatura ambiente durante 18 h y a 80 °C durante 8 h. Después de dejar enfriar la mezcla de reacción hasta temperatura ambiente, se añadió ácido clorhídrico 6 N (4,00 mL) a la mezcla, y la mezcla se concentró a presión reducida. Se agregó agua (30 mL) al residuo, y el precipitado se recogió por filtración y se lavó con agua. El precipitado se suspendió en metanol (10 mL) y la suspensión se agitó con calentamiento a reflujo durante 10 min. Después de dejar enfriar la suspensión hasta temperatura ambiente, el precipitado se recogió por filtración, se lavó con metanol y se secó a presión

reducida para dar el compuesto del título (1045 mg, 4,09 mmol, rendimiento 66%) en forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,15 (1H, d, J = 9,9Hz), 7,54 – 7,68 (3H, m), 7,74 – 7,80 (1H, m), 7,82 – 7,91 (1H, m), 8,06 (1H, s), 8,19 (1H, d, J = 9,9Hz), 13,17 (1H, br s).

Ejemplo 448

Producción de 3–(imidazo[1,2–b]piridazin–6–iloxi)–N–fenilbenzamida



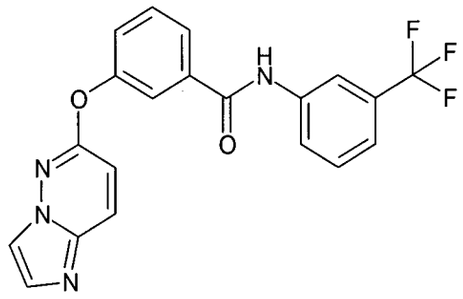
A una mezcla de ácido 3–(imidazo[1,2–b]piridazin–6–iloxi)benzoico (128 mg, 0,50 mmol), anilina (56 mg, 0,60 mmol), hidrato de 1–hidroxibenzotriazol (92 mg, 0,60 mmol) y N,N–dimetilformamida (5 mL) se añadieron clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (192 mg, 1,00 mmol) y trietilamina (0,209 mL, 1,50 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. Se añadió solución acuosa 1 N de hidróxido de sodio a la mezcla de reacción, y la mezcla se extrajo con acetato de etilo. La capa orgánica se lavó con agua y salmuera saturada y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice (acetato de etilo/metanol = 100/0→75/25) y se precipitó en acetato de etilo para dar el compuesto del título (122 mg, 0,37 mmol, rendimiento 74%) en

forma de un sólido blanco.

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,11 (1H, t, J = 7,4Hz), 7,18 (1H, d, J = 9,6Hz), 7,35 (2H, t, J = 7,9Hz), 7,52 – 7,58 (1H, m), 7,63 (1H, d, J = 8,1Hz), 7,66 (1H, d, J = 0,9Hz), 7,73 – 7,80 (2H, m), 7,86 – 7,93 (2H, m), 8,07 (1H, s), 8,21 (1H, d, J = 9,6Hz), 10,28 (1H, s).

Ejemplo 449

Producción de 3–(imidazo[1,2–b]piridazin–6–iloxi)–N–[3–(trifluorometil)fenil]benzamida



Usando ácido 3–(imidazo[1,2–b]piridazin–6–iloxi)benzoico (128 mg, 0,50 mmol), 3–(trifluorometil)anilina (97 mg, 0,60 mmol), hidrato de 1–hidroxibenzotriazol (92 mg, 0,60 mmol), N,N–dimetilformamida (5 mL), clorhidrato de 1–[3–(dimetilamino)propil]–3–etilcarbodiimida (192 mg, 1,00 mmol) y trietilamina (0,209 mL, 1,50 mmol), y de la misma manera que en el Ejemplo 448, se obtuvo el compuesto del título (114 mg, 0,29 mmol, rendimiento 57%).

^{1}H–RMN (DMSO–d_6, 300 MHz) δ 7,18 (1H, d, J = 9,9Hz), 7,47 (1H, d, J = 7,8Hz), 7,55 – 7,71 (4H, m), 7,89 – 7,95 (2H, m), 8,02 – 8,08 (2H, m), 8,19 – 8,25 (2H, m), 10,59 (1H, s).

Ejemplo de formulación 1

Un agente farmacéutico que contiene el compuesto de la

presente invención como un ingrediente activo se puede producir, por ejemplo, de acuerdo con la siguiente formulación.

1. Cápsula

(1) compuesto obtenido en el Ejemplo 1	40 mg
(2) lactosa	70 mg
(3) celulosa microcristalina	9 mg
(4) estearato de magnesio	1 mg
1 cápsula	120 mg

(1), (2), (3) y 1/2 de (4) se mezclan, granulan y el resto de (4) se le añade. Toda la mezcla se sella en una cápsula de gelatina.

2. Comprimido

(1) compuesto obtenido en el Ejemplo 1	40 mg
(2) lactosa	58 mg
(3) almidón de maíz	18 mg
(4) celulosa microcristalina	3,5mg
(5) estearato de magnesio	0,5mg
1 comprimido	120 mg

(1), (2), (3), 2/3 de (4), y 1/2 de (5) se mezclan y se granulan. El resto de (4) y (5) se le añade a los gránulos. La mezcla se forma por compresión en un comprimido.

Ejemplo de formulación 2

El compuesto (50 mg) obtenido en el Ejemplo 1 se disuelve en agua destilada para inyectables de la Pharmacopoeia japonesa (50 mL), y el agua destilada para inyectables de la farmacopea japonesa se añade a 100 mL. Esta solución se filtra en condiciones de

1125

esterilidad. Se toma la solución (1 mL), se envasa en un vial para inyección en condiciones de esterilidad, se liofiliza y e sella.

Ejemplo experimental 1

Clonación del gen humano del receptor del factor de crecimiento endotelial vascular 2 (VEGFR2) y preparación de baculovirus recombinantes

Se clonó un gen humano del receptor del factor de crecimiento endotelial vascular 2 (de ahora en adelante, denominado VEGFR2) por PCR usando placenta humana de una biblioteca de ADNc (Clontech) como plantilla. El cebador utilizado para PCR se preparó a partir de información de secuencias de bases (Genbank Accession AF035121) del gen de VEGFR2 por adición de una secuencia de base que codifica un péptido bandera y una secuencia de reconocimiento a una secuencia base (2671–4374 de número de acceso Genbank AF035121) que codifica la región del dominio intracelular de VEGFR2, de modo que la proteína contiene una etiqueta de rótulo en el terminal N. La secuencia base del cebador se indica a continuación.

VEGFR2–U:

5'–AATTAAGTCGACATGGACTACAAGGATGACGATGACAAG AAGCGGGCCAATGGAGGGGAACTGAAGACA–3' (SEQ ID NO: 1)

y

VEGFR2–L:

5'–AATTAAGCATGCTTAAACAGGAGGAGAGCTCAGTGTGGTC CC–3' (SEQ ID NO: 2)

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La secuencia base del cebador VEGFR2–U se indica en SEQ ID NO: 1 del listado de secuencias, y la secuencia base del cebador VEGFR2–L se indica en SEQ ID NO: 2 del listado de secuencias.

La reacción PCR se realizó usando un estuche KOD–plus (TOYOBO). El producto PCR obtenido se sometió a electroforesis en gel de agarosa (1%), el fragmento de ADN amplificado por PCR se recuperó del gel, y luego se digirió con enzimas de restricción Sal I y Sph I. El ADN tratado con enzimas de restricción se sometió a electroforesis en gel de agarosa (1%), y el fragmento de ADN obtenido se recuperó y se ligó al plásmido pFASTBAC1 (Invitrogen) direrido con enzimas de restricción Sal I y Sph I para dar el plásmido de expresión pFB–VEGFR2. Se confirmó la secuencia base del fragmento insertado y se halló que era idéntica a la secuencia base (2671–4374 de número de acceso a Genbank AF035121) del dominio intracelular de VEGFR2. Adicionalmente, usando el sistema de expresión de baculovirus BAC–TO–BAC (Invitrogen), se preparó una reserva de virus BAC–VEGFR2 de baculovirus recombinante.

Ejemplo experimental 2

Preparación de la proteína del dominio intracelular del receptor del factor de crecimiento endotelial vascular 2 (VEGFR2)

Se sembraron células SF–21 en cantidad de 1×10^6 células/mL en medio Sf–900II SFM (1 L, Invitrogen) con contenido de suero fetal bovino al 10% (traza), 50 mg/L de gentamicina (Invitrogen) y 0,1% de Pluronic F–68 (Invitrogen), y la agitación del cultivo se llevó a cabo usando un matraz Erlenmeyer de 2 litros en volumen a 27 °C, 100

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rpm. Después de cultivar durante 24 hs, se le añadió baculovirus recombinante BAC–VEGFR2 (13,4 mL) a la mezcla, y la mezcla se siguió cultivando durante 3 días. El medio de cultivo se centrifugó a 2,000 rpm durante 5 min para dar células infectadas por el virus. Las células infectadas se lavaron con un salina amortiguada con fosfato (Invitrogen), se centrifugaron en las mismas condiciones, y las células se conservaron a –80 °C. Las células criopreservadas se descongelaron en hielo, se suspendieron en amortiguador A (50 mM de amortiguador Tris (30 mL, pH 7,4) que contenía 20% de glicerol, NaCl 0,15 M) complementado con inhibidor completo de proteasa (Boehringer), y se dividieron tres veces con un homogeneizador Polytron (Kinematica) a 20.000 rpm durante 30 seg. El medio dividido se clarificó por centrifugación a 40.000 rpm durante 30 min y se filtró con un filtro de 0,45 µm. El filtrado se hizo pasar a través de una columna empaquetada con gel de afinidad Anti–FLAG M2 (4 mL, Sigma) a una velocidad de flujo de aprox. 0,5 mL/min. La columna se lavó con amortiguador A, y se eluyó con amortiguador A que contenía 100 µg/mL de péptido rótulo. El eluido se concentró con Vivaspin 20 (Vivascience) con un corte de peso molecular de 30K. El amortiguador de este concentrado se cambió usando una columna NAP™ 25 (Amersham Bioscience) equilibrada con amortiguador A. Se recogieron las fracciones que contenían la proteína del dominio intracelular de VEGFR2, se le agregó glicerol hasta la concentración final de 50% y se criopreservó a –80 °C.

Ejemplo experimental 3

Clonación de gen BRAF humano (B–Raf) y preparación de baculovirus recombinante

El gen BRAF humano fue clonado mediante PCR usando como plantilla la biblioteca de ADNc de testículo humano (Clontech). El cebador usado para la PCR se preparó a partir de información de la secuencia de base (Nº de acceso a Genbank NM_004333) del gen BRAF añadiendo una secuencia de base que codifica un péptido rótulo y una secuencia de reconocimiento de la enzima de restricción al área codificadora de la región del dominio de BRAF quinasa, de manera tal que la proteína contiene un rótulo en el terminal N. La primera secuencia de base se muestra continuación.

BRAF–U:

5'– AAAGAATTCACCATGGACTACAAGGACGACGATGACAAGA CCCCCCCTGCCTCATTACCTGGCT –3' (SEQ ID NO: 3)

y

BRAF–L:

5'– AAAAGTCGACTCAGTGGACAGGAAACGCACCATAT–3' (SEQ ID NO: 4)

La reacción por PCR se realizó usando Pirobest (Takara Shuzo Co., Ltd). El producto obtenido por PCR se sometió a electroforesis en gel de agarosa (1%), el fragmento de ADN amplificado por PCR se recuperó del gel, y luego se digirió con enzimas de restricción EcoRI y SalI. El ADN tratado con enzimas de restricción se sometió a electroforesis en gel de agarosa (1%), y el fragmento de ADN obtenido se recuperó y se ligó al plásmido pFASTBAC1 (Invitrogen) y

se digirió con enzimas de restricción EcoRI y SalI para obtener el plásmido de expresión pFB–BRAF, y se confirmó la secuencia de base del fragmento insertado. Además, se introdujo una mutación en V600E usando un estuche para cambio rápido de mutagénesis dirigida al sitio (Stratagene). Las secuencias de nucléotidos de los cebadores usados se muestran a continuación.

V600E–U:

5'– GGTCTAGCTACAGAGAAATCTCGATGGAG –3' (SEQ ID NO: 5)

y

V600E–L:

5'– CTCCATCGAGATTTCTCTGTAGCTAGACC – 3' (SEQ ID NO: 6)

Se determinó la secuencia del plásmido obtenido para confirmar la introducción de la mutación en V600E. El plásmido se digirió con enzimas de restricción EcoRI y SalI, se sometió el ADN a electroforesis en gel de agarosa (1%), y el fragmento de ADN obtenido se recuperó y se ligó al plásmido pFASTBAC1 (Invitrogen) que se digirió con enzimas de restricción EcoRI y SalI para obtener el plásmido de expresión pFB–V600E.

Usando el sistema de expresión de Baculovirus BAC–TO–BAC (Invitrogen), se preparó una reserva de virus BAC–V600E a partir del baculovirus recombinante.

Ejemplo experimental 4

Preparación de proteína BRAF (V600E)

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Se sembraron células SF–21 en cantidad de 1×10^6 células/mL en medio Sf–900II SFM (1 L, Invitrogen) que contenía suero fetal bovino al 10% (Trace), 50 mg/L de gentamicina (Invitrogen) y 0,1% de Pluronic F–68 (Invitrogen), y se realizó agitación del cultivo en un matraz Erlenmeyer con volumen de 2 litros a 27 °C, con 100 rpm. Después de cultivar durante 24 h, se le añadió a la mezcla baculovirus recombinante BAC–V600E (13,4 mL) y la mezcla se siguió cultivando durante 3 días. El medio de cultivo se centrifugó a 2,000 rpm durante 5 min para dar células infectadas por el virus. Las células infectadas se lavaron con salina amortiguada con fosfato (Invitrogen), se centrifugaron en las mismas condiciones, y las células se preservaron a –80°C. Las células criopreservadas se descongelaron en hielo, se suspendieron en amortiguador A (50 mM de amortiguador Tris (30 mL, pH 7,4) que contenía 20% de glicerol, NaCl 0,15 M) complementado con inhibidor completo de proteasa (Boehringer), y se dividieron tres veces con un homogeneizador Polytron (Kinematica) a 20.000 rpm durante 30 s. El medio separado se clarificó por centrifugación a 40.000 rpm durante 30 min y se filtró con un filtro de 0,45 µm. El filtrado se pasó a través de una columna empaquetada con gel de afinidad Anti–FLAG M2 (4 mL, Sigma) a una velocidad de flujo de aprox. 0,5 mL/min. La columna se lavó con amortiguador A y se eluyó con amortiguador A que contenía 100 µg/mL de péptido de rótulo. El amortiguador de este concentrado se cambió usando columna NAP25 (Amersham Bioscience) equilibrada con amortiguador A y las fracciones se crioconservaron a –80°C.

Ejemplo de prueba 1

Determinación de la actividad inhibidora de quinasa del receptor del factor de crecimiento endotelial vascular 2 (VEGFR2)

Un compuesto de prueba disuelto en dimetilsulfóxido (DMSO) se diluyó con amortiguador (50 mM Tris–HCl (pH 7,5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, ditiotreitol 2 mM, Tween–20al 0,01%). A esta solución compuesta (5 μL) se añadió amortiguador (10 μL) que contenía 50 ng/mL de proteína de dominio intracelular VEGFR2 y 250 ng/mL de polipéptido biotinil–poli–Glu:Tir (4:1) con rótulo de biotina (CIS bio International). A la mezcla obtenida se añadió amortiguador (10 μL) que contenía ATP (25 μM), la mezcla se dejó reaccionar a 25 °C durante 5 min y la reacción se extinguió con 25 μL de una solución de detención (100 mM EDTA disódico, 62,5 mM amortiguador HEPES (pH 7,4), 250 mM NaCl, 0,1% de albúmina sérica bovina, 10 μg/mL de perlas donantes de estreptavidina de ensayo AlfaScreen (Streptavidin Donor beads: PerkinElmer), 10 μg/mL de perlas aceptoras de fijación de anticuerpo de reconocimiento antifosfotirosina en análisis AlfaScreen PY–100 (perlas aceptoras antifosfotirosina (P–Tir–100): PerkinElmer)). La solución de reacción se dejó reposar a 25 °C durante 16 h, y se contaron las cavidades usando un lector de placas Fusion™ (PerkinElmer). La tasa de inhibición de quinasa (%) del compuesto de prueba se calculó mediante la siguiente fórmula:

Tasa de inhibición (%)=(1–(conteo del compuesto de prueba – blanco)÷(control – blanco))×100

El conteo de la solución que reaccionó sin adición del compuesto se usó como "control", y el conteo de la solución sin el compuesto y ATP se usó como "blanco". La tasa de inhibición de los compuestos de los Ejemplos 95, 97, 103, 108, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 y 317 en 1 μM no fue inferior al 90%.

Ejemplo de prueba 2

Prueba de inhibición del crecimiento de células endoteliales vasculares

Se cultivaron células endoteliales vasculares obtenidas de vena umbilical humana (HUVEC adquiridas de KURABO INDUSTRIES LTD.) en una incubadora a 37 °C, con 5% de dióxido de carbono en un medio para células endoteliales vasculares (Invitrogen) que contenía 5% de suero fetal bovino y 2,5 ng/mL de factor de crecimiento de fibroblastos básico. Para ser específico, se suspendió HUVEC en un medio para células endoteliales vasculares que contenía el antes mencionado 5% de suero fetal bovino y se colocó en placa en una placa de fondo plano de 96 cavidades con 50 μL (3000 células) en cada cavidad. Después de cultivar durante la noche, se disolvieron diversas concentraciones de la sustancia de prueba y 120 ng/mL de factor de crecimiento endotelial vascular (VEGF) en un medio para células endoteliales vasculares que contenía 5% de suero fetal bovino y se añadió a cada cavidad 50 μL. Después de 5 días de cultivo, se le añadió un reactivo XTT

(Wako Pure Chemical Industries, Ltd.) a cada cavidad en 10 µL, y la mezcla se hizo reaccionar en un incubador a 37 °C, con 5% de dióxido de carbono durante 2–3 h. La absorbancia a 450 nm se midió mediante un lector de placa de microtitulación y se determinó la actividad inhibitoria de crecimiento celular. Usando la absorbancia con adición de una sustancia de prueba en cada concentración y sobre la base del análisis no lineal de mínimos cuadrados con una curva log del procedimiento NLIN del sistema SAS, se calculó la concentración de la sustancia de prueba (valor IC_{50}) necesaria para demostrar el 50% del valor obtenido sin adición de la sustancia de prueba.

Como consecuencia, el valor IC_{50} de los compuestos de los Ejemplos 95, 97, 103, 108, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 y 317 no fue superior a 500 nM.

Ejemplo de prueba 3

Prueba antitumor

Se cultivaron células cancerosas en una incubadora a 37 °C, con 5% de dióxido de carbono en un medio de cultivo que contenía 10% de suero fetal bovino. Las células se aislaron mediante un tratamiento con tripsina, se lavaron con HBSS (solución salina equilibrada de HANK) y se ajustaron a una densidad celular de $5x10^7$ células/mL con HBSS. La suspensión celular (0,1 mL, $5x10^6$ células) se trasplantó por inyección subcutánea en el abdomen de ratones desnudos hembras de 6 semanas (BALB/c nu/nu, CLEA Japan, Inc.).

Cuando el volumen del tumor alcanzó 100–200 mm^3, se agruparon los ratones y se les administraron oralmente diversas dosis de sustancia de prueba durante 14 días consecutivos a partir del día siguiente. La longitud del eje mayor y la longitud del eje menor del tumor se midieron respecto del tiempo y se calculó el volumen del tumor a partir de la fórmula volumen de tumor = longitud del eje mayor × longitud del eje menor × longitud del eje menor × 0,5.

Ejemplo de prueba 4

Determinación de la actividad inhibidora de quinasa del receptor α del factor de crecimiento derivado de plaquetas (PDGFRα)

Se diluyó un compuesto de prueba disuelto en dimetilsulfóxido (DMSO) con un amortiguador (50 mM Tris–HCl (pH 7,5), 5 mM $MgCl_2$, $MnCl_2$ 5 mM, ditiotreitol 2 mM, Tween–20 al 0,01%). A este compuesto en solución (5 μL) se añadió un amortiguador (10 μL) que contenía 125 ng/ml de proteína de dominio intracelular PDGFRα (UPSTATE) y 250 ng/mL de polipéptido con rótulo de biotina biotinil–poli–Glu:Tir (4:1) (CIS bio International). A los 5 min de mezclar la enzima quinasa y el compuesto y el polipéptido con rótulo de biotina, se le añadió a la mezcla obtenida amortiguador (10 μL) que contenía ATP (25 μM), la mezcla dejó reaccionar a 25 °C durante 30 min y la reacción se extinguió con 25 μL de solución de detención (EDTA disódico 100 mM, amortiguador HEPES 62,5 mM (pH 7,4), NaCl 250 mM, albúmina sérica bovina al 0,1% , 10 μg/mL de perlas donantes de estreptavidina de ensayo AlfaScreen (perlas donantes de estreptavidina: PerkinElmer), 10 μg/mL de perlas aceptoras de

fijación de anticuerpo de reconocimiento antifosfotirosina en análisis AlfaScreen PT–66 (perlas aceptoras de antifosfotirosina (P–Tir–66): PerkinElmer)). La solución de reacción se dejó reposar a 25 °C durante 16 h, y las cavidades se contaron con un lector de placas Fusion™ (PerkinElmer). La tasa de inhibición de quinasa (%) del compuesto de prueba se calculó mediante la siguiente fórmula:

Tasa de inhibición (%)=(1–(conteo del compuesto de prueba – blanco)÷(control – blanco))×100

El conteo de la solución que reaccionó sin adición del compuesto se usó como "control", y el conteo de la solución sin el compuesto y ATP se usó como "blanco".

El valor de IC_{50} de los compuestos de los Ejemplos 95, 97, 111, 148, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 267, 287, 289, 298, 302, 314 y 317 no fue superior a 500 nM.

Ejemplo de prueba 5

Determinación de la actividad inhibidora de quinasa del receptor β del factor de crecimiento derivado de plaquetas (PDGFRβ)

Se diluyó un compuesto de prueba disuelto en dimetilsulfóxido (DMSO) con un amortiguador (50 mM Tris–HCl (pH 7,5), 5 mM $MgCl_2$, 5 mM $MnCl_2$, ditiotreitol 2 mM, Tween–20 al 0,01%). A esta solución de compuesto (5 μL) se añadió amortiguador (10 μL) que conteníae 125 ng/ml de proteína de dominio intracelular PDGFRβ (UPSTATE) y 250 ng/mL de polipéptido con rótulo de biotina biotinil–poli–Glu:Tir (4:1) (CIS bio International). 5 min después de mezclar la enzima quinasa y el compuesto y el polipéptido con rótulo de

biotina, a la mezcla obtenida se le añadió amortiguador (10 μL) que contenía ATP (25 μM), la mezcla se dejó reaccionar a 25 °C durante 30 min y la reacción se extinguió con 25 μL de una solución de detención (EDTA disódico 100 mM, amortiguador HEPES 62,5 mM (pH 7,4), NaCl 250 mM, 0,1% de albúmina sérica bovina, 10 μg/mL de perlas donantes de estreptavidina de ensayo AlfaScreen (perlas donantes de estreptavidina: PerkinElmer), 10 μg/mL de perlas aceptoras de fijación de anticuerpo de reconocimiento antifosfotirosina en análisis AlfaScreen PT–66 (perlas aceptoras de antifosfotirosina (P–Tir–66) perlas aceptoras: PerkinElmer)). La solución de reacción se dejó reposar a 25 °C durante 16 h, y las cavidades se contaron con un lector de placas Fusion™ (PerkinElmer). La tasa de inhibición de quinasa (%) del compuesto de prueba se calculó mediante la siguiente fórmula:

Tasa de inhibición (%)=(1–(conteo de compuesto de prueba – blanco)÷(control – blanco))×100

El conteo de la solución que reaccionó sin adición del compuesto se usó como "control", y el conteo de la solución sin el compuesto y ATP se usó como "blanco".

El valor de IC_{50} de los compuestos de los Ejemplos 97, 103, 111, 114, 117, 127, 148, 149, 150, 161, 165, 173, 174, 180, 187, 208, 241, 243, 247, 254, 267, 287, 289, 298, 302, 314 y 317 no fue superior a 500 nM.

Ejemplo de prueba 6

Determinación de la actividad inhibidora de quinasa BRAF

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(V600E)

Se le añadió un compuesto de prueba (2,5 µl) disuelto en dimetilsulfóxido (DMSO) a 37,5 µl de una solución de reacción (HEPES 25 mM (pH 7,5), acetato de magnesio 10 mM, ditiotreitol 1 mM) que contenía enzima BRAF (V600E) (30 ng) y proteína de tipo recombinante GST–MEK1 (K96R) 250 ng, y la mezcla se incubó a temperatura ambiente durante 10 min. Se le añadió solución de ATP (10 µl) (2,5 µM ATP, 0,1 µCi [γ–^{32}P]ATP) a la mezcla obtenida, y la mezcla se hizo reaccionar a temperatura ambiente durante 20 min. La reacción se extinguió mediante adición de 50 µL de ácido tricloroacético al 20% enfriado con hielo (Wako Pure Chemical Industries, Ltd.). La solución de reacción se dejó reposar a 4 °C durante 30 min, y la fracción precipitable con ácido se transfirió a una placa de filtro GF/C (Millipore Corporation) con un cosechador de células (PerkinElmer). La placa se secó a 45 °C durante 60 min, y se le añadieron 40 µL de MicroScinti 0 (PerkinElmer). Se midió la radiactividad con TopCount (PerkinElmer). La tasa de inhibición de quinasa (%) del compuesto de prueba se calculó mediante la siguiente fórmula:

Tasa de inhibición (%)=(1–(conteo del compuesto de prueba–blanco)÷(control – blanco))×100

El conteo de la solución que reaccionó sin adición del compuesto se usó como "control", y el conteo de la solución sin el compuesto y la enzima se usó como "blanco". La tasa de inhibición de los compuestos de los Ejemplos 70, 319, 330, 398, 427 y 431 en

1208

1 μM no fue inferior a 90%.

LISTADO DE SECUENCIAS texto libre

[SEQ ID NO: 1]

Cebador de oligonucleótido diseñado para amplificar el ADN que codifica VEGFR2 humano

[SEQ ID NO: 2]

Cebador de oligonucleótido diseñado para amplificar el ADN que codifica VEGFR2 humano

[SEQ ID NO: 3]

Cebador de oligonucleótido diseñado para amplificar el ADN que codifica BRAF humano

[SEQ ID NO: 4]

Cebador de oligonucleótido diseñado para amplificar el ADN que codifica BRAF humano

[SEQ ID NO: 5]

Cebador de oligonucleótido diseñado para introducir la mutación de V600E

[SEQ ID NO: 6]

Cebador de oligonucleótido diseñado para introducir la mutación de V600E

Aplicabilidad Industrial

Los compuestos (I) – (IV), una sal de ellos y un profármaco de ellos de la presente invención muestran actividad inhibidora superior con respecto a quinasas tales como el receptor del factor de crecimiento endotelial vascular y similares. En consecuencia, se

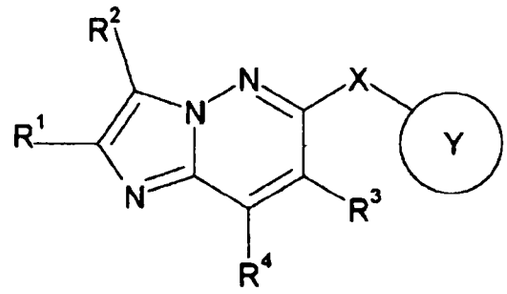
puede proveer un agente clínicamente útil para la prevención o el tratamiento de enfermedades relacionadas con la acción del factor de crecimiento endotelial vascular en el cuerpo vivo (por ejemplo, cáncer etc.). Además, dado que los compuestos (I) – (IV), una sal de ellos y un profármaco de ellos de la presente invención también son superiores en eficacia de expresión, farmacocinética, solubilidad, interacción con otros productos farmacéuticos, seguridad y estabilidad, son útiles como agentes farmacéuticos.

La presente solicitud se basa en las solicitudes de patente N.º 2006–213981, 2006–331230 y 2007–144072 presentadas en Japón, cuyos contenidos se incorporan en su totalidad en la presente mediante referencia.

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REIVINDICACIONES

1. Un compuesto representado por la fórmula (I):



(I)

en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

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6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4,2,0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

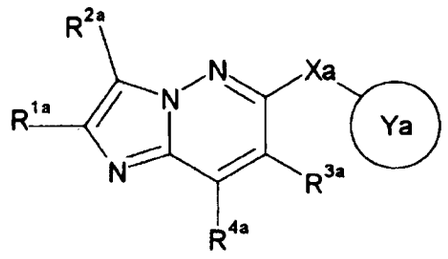
3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales.

2. El compuesto de acuerdo con la reivindicación 1,

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caracterizado además porque es un compuesto representado por la fórmula (II):



(II)

en donde

el anillo Ya es un grupo cíclico sustituido opcionalmente;

Xa es –O–, –S–, –S(O)–, $-S(O)_2-$ o $-NR^a-$ (en donde R^a es un átomo de hidrógeno o un sustituyente);

R^{1a} es un amino sustituido opcionalmente;

R^{2a} es un átomo de hidrógeno o un sustituyente;

R^{3a} es un átomo de hidrógeno o un sustituyente;

R^{4a} es un átomo de hidrógeno o un sustituyente;

con la condición de que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo y

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

o una de sus sales.

3. El compuesto de acuerdo con la reivindicación 2, caracterizado además porque R^{1a} es

(1) amino,

(2) alquilcarbonilamino sustituido opcionalmente,

(3) alquenilcarbonilamino sustituido opcionalmente,

(4) alquinilcarbonilamino sustituido opcionalmente,

(5) cicloalquilcarbonilamino sustituido opcionalmente,

(6) cicloalquil–alquilcarbonilamino sustituido opcionalmente,

(7) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente,

(8) aminocarbonilamino sustituido opcionalmente,

(9) alcoxicarbonilamino sustituido opcionalmente,

(10) alquilsulfonilamino sustituido opcionalmente,

(11) cicloalquilsulfonilamino sustituido opcionalmente,

(12) arilamino sustituido opcionalmente, o

(13) heterociclilamino sustituido opcionalmente.

4. El compuesto de acuerdo con la reivindicación 2, caracterizado porque R^{1a} es

(1) amino,

(2) alquil C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) hidroxi,

(c) alcoxi C_{1-4},

(d) alquil C_{1-4}–carboniloxi,

(e) alquil C_{1-4}–amino,

(f) di–alquil C_{1-4}–amino,

(g) alquil C_{1-4}–sulfonilo, y

(h) un grupo heterocíclico de 6 miembros que opcionalmente tiene 1 a 3 alquilo C_{1-4},

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(3) alquenil C_{2-4}–carbonilamino que opcionalmente tiene alcoxi C_{1-4},

(4) alquinil C_{2-4}–carbonilamino,

(5) cicloalquil C_{3-6}–carbonilamino sustituido opcionalmente con 1 a 4 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) hidroxi,

(c) alquilo C_{1-4} que opcionalmente tiene hidroxi,

(d) alcoxi C_{1-4},

(e) alcoxi C_{1-4}–carbonilo, y

(f) alquil C_{1-4}–carboniloxi,

(6) cicloalquil C_{3-6}–alquil C_{1-4}–carbonilamino,

(7) heterociclil–carbonilamino de 6 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) ciano, y

(c) alquilo C_{1-4} que opcionalmente tiene 1 a 3 átomos de halógeno,

(8) aminocarbonilamino sustituido opcionalmente con 1 ó 2 sustituyentes seleccionados de

(a) alquilo C_{1-4} que opcionalmente tiene 1 a 3 alcoxi C_{1-4} que opcionalmente tiene 1 a 3 hidroxi, y

(b) alcoxi C_{1-4},

(9) alcoxi C_{1-4}–carbonilamino sustituido opcionalmente con 1 a 3 átomos de halógeno,

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(10) alquil C_{1-4}–sulfonilamino,

(11) cicloalquil C_{3-6}–sulfonilamino,

(12) aril C_{6-10}–amino, o

(13) heterociclilamino sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) alquil C_{1-4}–amino.

5. El compuesto de acuerdo con la reivindicación 2, caracterizado además porque R^{2a} es un átomo de hidrógeno.

6. El compuesto de acuerdo con la reivindicación 2, caracterizado además porque R^{3a} es un átomo de hidrógeno.

7. El compuesto de acuerdo con la reivindicación 2, caracterizado porque R^{4a} es un átomo de hidrógeno.

8. El compuesto de acuerdo con la reivindicación 2, caracterizado porque Xa es –O–, –S– o –NH–.

9. El compuesto de acuerdo con la reivindicación 2, caracterizado porque el anillo Ya es un grupo hidrocarburo aromático sustituido opcionalmente o un grupo heterocíclico aromático sustituido opcionalmente.

10. El compuesto de acuerdo con la reivindicación 2, caracterizado porque el anillo Ya es

(1) arilo C_{6-10} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno,

(b) alquilo C_{1-4},

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(c) alcoxi C_{1-4},

(d) amino sustituido opcionalmente con los sustituyentes seleccionados de

(i) alquilo C_{1-4} sustituido opcionalmente con un grupo heterocíclico aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(ii) alquil C_{1-4}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') hidroxi,

(ii') alquil C_{1-4}–sulfonilo, y

(iii') un grupo heterocíclico aromático de 6 miembros,

(iii) alquenil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(iv) alquinil C_{2-4}–carbonilo sustituido opcionalmente con arilo C_{6-10},

(v) cicloalquil C_{3-6}–carbonilo,

(vi) cicloalquenil C_{3-6}–carbonilo,

(vii) aril C_{6-10}–carbonilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') un átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, ciano, hidroxi y cicloalquilo C_{3-6},

(iii') cicloalquilo C_{3-6} sustituido opcionalmente con ciano,

(iv') alcoxi C_{1-4} sustituido opcionalmente con 1 a 5 átomos de

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halógeno,

(v') alcoxi C_{1-4}–carbonilo, y

(vi') un grupo heterocíclico de 5 ó 6 miembros sustituido opcionalmente con ciano u oxo,

(viii) heterociclil–carbonilo de 5 ó 6 miembros que contiene, como átomo constitutivo del anillo, 1 a 3 heteroátomos seleccionados de átomo de oxígeno, átomo de azufre y átomo de nitrógeno además de átomos de carbono, que está sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(i') un átomo de halógeno,

(ii') alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno, ciano, hidroxi y alcoxi C_{1-4},

(iii') arilo C_{6-10},

(iv') aril C_{6-10}–alquilo C_{1-4},

(v') alcoxi C_{1-4} sustituido opcionalmente con alcoxi C_{1-4},

(vi') alquil C_{1-4}–sulfonilo,

(vii') alquil C_{1-4}–carbonilo, y

(viii') oxo,

(ix) heterociclil–carbonilo fusionado aromático,

(x) alquil C_{1-4}–aminocarbonilo,

(xi) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno,

(xii) alcoxi C_{1-4}–aminocarbonilo,

(xiii) heterociclil–aminocarbonilo de 5 miembros sustituido

opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(xiv) aminotiocarbonilo sustituido opcionalmente con aril C_{6-10}–alquil C_{1-4}–carbonilo, y

(xv) heterociclil–sulfonilo aromático de 5 miembros sustituido opcionalmente con 1 a 3 alquilo C_{1-4},

(e) alquil C_{1-4}–aminocarbonilo que opcionalmente tiene arilo C_{6-10},

(f) heterociclil–aminocarbonilo de 5 miembros sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo C_{1-4} y arilo C_{6-10},

(g) aril C_{6-10}–aminocarbonilo sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de un átomo de halógeno y ciano,

(h) carboxi, y

(i) nitro,

(2) heterociclo aromático monocíclico sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) un átomo de halógeno, y

(b) aril C_{6-10}–carbonilamino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno, o

(3) heterociclo aromático fusionado sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de

(a) alquilo C_{1-4}, y

(b) aril C_{6-10}–amino sustituido opcionalmente con alquilo C_{1-4} sustituido opcionalmente con 1 a 3 átomos de halógeno.

11. Un compuesto seleccionado del grupo que consiste en:

N–{3–[(2–{[2–(metilamino)pirimidin–4–il]amino}imidazo[1,2–b]piridazin–6–il)oxi]fenil}–3–(trifluorometil)benzamida;

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,4–dimetil–1,3–tiazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–2,5–dimetil–1,3–oxazol–4–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}sulfanil)fenil]–1,3–dimetil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–3–metil–1H–pirazol–4–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]benzamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1,3–dimetil–1H–pirazol–4–carboxamida;

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N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–etil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–metoxi–1–metil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–3–etil–1–metil–1H–pirazol–5–carboxamida;

N–[2–cloro–5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–1–etil–3–metil–1H–pirazol–4–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–1–metil–1H–pirazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2,4–dimetil–1,3–oxazol–5–carboxamida;

N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–fluorofenil]–2–etil–4–metil–1,3–oxazol–5–carboxamida;

N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida;

3–(1–ciano–1–metiletil)–N–[5–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}oxi)–2–metilfenil]benzamida;

N–[3–({2–[(N,N–dimetilglicil)amino]imidazo[1,2–b]piridazin–6–il}oxi)fenil]–3–(trifluorometil)benzamida;

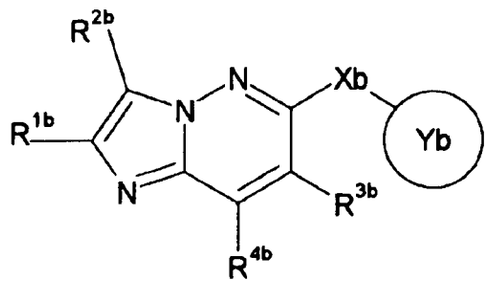
N–[3–({2–[(ciclopropilcarbonil)amino]imidazo[1,2–b]piridazin–6–il}tio)fenil]–3–(trifluorometil)benzamida; y

N–{6–[3–({[3–(trifluorometil)fenil]carbamoil}amino)fenoxi]imidazo[1,2–b]piridazin–2–il}ciclopropancarboxamida,

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o una de sus sales.

12. El compuesto de acuerdo con la reivindicación 1, caracterizado además porque es un compuesto de la fórmula (III):



(III)

en donde

el anillo Yb es un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente;

Xb es –O–, –S–, –S(O)–, $–S(O)_2–$ o $–NR^b–$ (en donde R^b es un átomo de hidrógeno o un sustituyente);

R^{1b} es un átomo de hidrógeno o un sustituyente (con la condición de que se excluya un amino sustituido opcionalmente);

R^{2b} es un átomo de hidrógeno o un sustituyente;

R^{3b} es un átomo de hidrógeno o un sustituyente;

R^{4b} es un átomo de hidrógeno o un sustituyente;

con la condición de que se excluyan

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–

1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4,2,0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales.

13. Un profármaco del compuesto de acuerdo con la reivindicación 1.

14. Un agente farmacéutico que contiene el compuesto de acuerdo con la reivindicación 1 o uno de sus profármacos.

15. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un inhibidor de quinasa.

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16. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un inhibidor del receptor del factor de crecimiento endotelial vascular (VEGFR).

17. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado porque es un inhibidor de receptor del factor de crecimiento endotelial vascular (VEGFR) 2.

18. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un inhibidor del receptor del factor de crecimiento derivado de plaquetas (PDGFR).

19. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado porque es un inhibidor de Raf.

20. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un inhibidor de la angiogénesis.

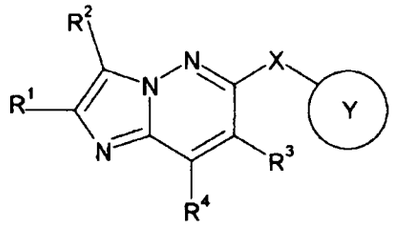
21. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un agente para la prevención o el tratamiento del cáncer.

22. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un inhibidor del crecimiento del cáncer.

23. El agente farmacéutico de acuerdo con la reivindicación 14, caracterizado además porque es un supresor de metástasis de cáncer.

24. Un método para la prevención o el tratamiento del cáncer, caracterizado además porque comprende la administración de una cantidad efectiva de un compuesto de la fórmula (I):

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(I)

en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–

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1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4,2,0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

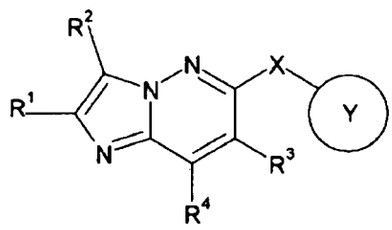
3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

o una de sus sales o uno de sus profármacos al mamífero.

25. Uso de un compuesto de la fórmula (I) para la producción de un agente para la prevención o el tratamiento del cáncer:



(I)

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en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, $-S(O)_2-$ o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–

tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,

(6R,7R)–3–(imidazo[1,2–b]piridazin–6–iltio)–8–oxo–7–[(fenilacetil)amino]–5–tia–1–azabiciclo[4,2,0]oct–2–en–2–carboxilato de 4–metoxibencilo,

4–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)tio]–N,N–dimetilanilina,

3–metoxi–6–(3–nitrofenoxi)–2–fenilimidazo[1,2–b]piridazina,

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]anilina, y

3–[(3–metoxi–2–fenilimidazo[1,2–b]piridazin–6–il)oxi]–N,N–dimetilanilina,

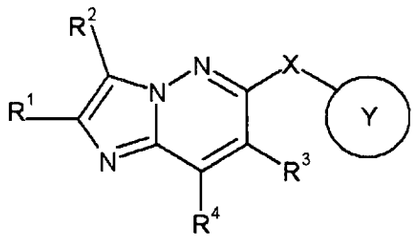
o una de sus sales o uno de sus profármacos.

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RESUMEN

La presente invención provee un derivado heterocíclico fusionado que tiene una potente actividad inhibidora de quinasa y su uso.

Un compuesto representado por la fórmula (I):



en donde cada símbolo es como se define en la memoria descriptiva, excepto un compuesto particular, o una de sus sales, y un agente farmacéutico que contiene el compuesto o uno de sus profármacos, que es un inhibidor de quinasa (VEGFR, VEGFR2, PDGFR, Raf), un inhibidor de angiogénesis, un agente para la prevención o el tratamiento del cáncer, un inhibidor del crecimiento del cáncer o un supresor de la metástasis del cáncer.

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LISTA DE SECUENCIAS

<110> Takeda Pharmaceutical Company Limited

<120> Derivado heterocíclico fusionado y su uso

<130> 091073

<150> JP 2006-213981
<151> 2006-08-04

<150> JP 2006-331230
<151> 2006-12-07

<150> JP 2007-144072
<151> 2007-05-30

<160> 6

<170> PatentIn version 3.3

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P260

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P261

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INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/065681

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/5025 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/038314 A (SQUIBB BRISTOL MYERS CO [US]; VACCARO WAYNE [US]; CHEN ZHONG [US]; DOD) 5 April 2007 (2007-04-05) table 1	1-25
P,X	WO 2007/013673 A (ASTELLAS PHARMA INC [JP]; NAKAI KAZUO [JP]; TAKAHASHI FUMIE [JP]; FUJI) 1 February 2007 (2007-02-01) table 4	1-25
P,X	WO 2007/025540 A (SCHERING AG [DE]; PRIEN OLAF [DE]; BADER BENJAMIN [DE]; ZUEGEL ULRICH) 8 March 2007 (2007-03-08) the whole document	1-25

-/--

[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
8 February 2008	06/03/2008

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	Baston, Eckhard

Form PCT/ISA/210 (second sheet) (April 2005)

1263

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2007/065681

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [X] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/065681

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/025090 A (KALYPSYS INC [US]; PINKERTON ANTHONY B [US]; DAVIS ROBERT L [US]; GAHM) 1 March 2007 (2007-03-01) the whole document	1-25
A	BULLOCK A N ET AL: "Structural basis of inhibitor specificity of the human protooncogene proviral insertion site in Moloney Murine Leukemia Virus (PIM-1) Kinase" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 48, no. 24, 27 October 2005 (2005-10-27), pages 7604-7614, XP002405453 ISSN: 0022-2623 figure 2	1-25
A	MOURAD AE ET AL: "synthesis of imidazo[1,2-b]pyridazines: fenbendazole, oxifenbendazole analogs and related derivatives" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 30, October 1993 (1993-10), pages 1365-1372, XP002331979 ISSN: 0022-152X * Examples *	1
A	BARLIN G B ET AL: "Imidazo (1,2-b)pyridazines. II- 6-Alkylthio- and 6-Arylthio-3-methoxy-2-phenylimidazo(1,2-b)pyridazines" AUSTRALIAN JOURNAL OF CHEMISTRY, XX, XX, vol. 40, 1987, pages 1491-1497, XP009095679 ISSN: 0004-9425 pages 1496-97	1
A	BARLIN G B ET AL: "Imidazo(1,2-b)pyridazines. IV. Synthesis and Central Nervous System Activities of Some 3-Methoxy-6-phenoxy(substituted phenoxy and naphthyloxy)-2-phenylimidazo(1,2-b)pyridaz ines" AUSTRALIAN JOURNAL OF CHEMISTRY, XX, XX, vol. 41, 1988, pages 1735-1742, XP009095689 ISSN: 0004-9425 page 1739	1

-/--

1265

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/065681

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TREBSE, P. ET AL.: "A direct conversion of 5,6,7,8-Tetrahydro-2H-1-BenzoPyran-2,5-diones into substituted 1-Amino-5,6,7,8-Tetrahydroquinoline-2,5-diones" HETEROCYCLES, vol. 59, no. 1, 2003, pages 129-136, , XP001537844 * Scheme 1 *	1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2007/065681

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007038314 A	05-04-2007	AR 055177 A1 US 2007078136 A1	08-08-2007 05-04-2007
WO 2007013673 A	01-02-2007	NONE	
WO 2007025540 A	08-03-2007	DE 102005042742 A1	08-03-2007
WO 2007025090 A	01-03-2007	NONE	

1267

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *Prioridad*	(32) *Fecha*	(33) *País*
2006-213981	04/08/2006	JP
2006-331230	07/12/2006	JP
2007-144072	30/05/2007	JP

(51) Int Cl: **C07D 487/004**

(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

(72) Inventor(es) **NOZOMU SAKAI Y OTROS**

(74) Apoderado: **EMILIO FERRERO**

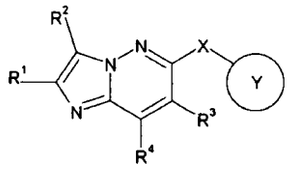
(85) Fecha limite inicio fase nacional: 04/03/2009
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 03/08/2007
No. de solicitud PCT/JP2007/065681

(87) Publicación internacional
Fecha: 07/02/2008
N° publicación: ***WO 2008/016192***

(54) Titulo: **DERIVADO HETEROCÍCLICO FUSIONADO Y SU USO**

Reivindicación(es):

1. Un compuesto representado por la fórmula (I):



(I)

en donde

el anillo Y es un grupo cíclico sustituido opcionalmente;

X es –O–, –S–, –S(O)–, –S(O)$_2$– o –NR– (en donde R es un átomo de hidrógeno o un sustituyente);

R^1 es un átomo de hidrógeno o un sustituyente;

R^2 es un átomo de hidrógeno o un sustituyente;

R^3 es un átomo de hidrógeno o un sustituyente;

R^4 es un átomo de hidrógeno o un sustituyente;

con la condición de que

cuando R^1 sea distinto de un amino sustituido opcionalmente, el anillo Y sea un grupo cíclico sustituido con un amino sustituido opcionalmente, en donde el grupo cíclico también está sustituido opcionalmente, y que se excluyan

[6–(feniltio)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

[6–(fenilsulfinil)imidazo[1,2–b]piridazin–2–il]carbamato de metilo,

6–(4–acetamidofenoxi)imidazo[1,2–b]piridazin–2–carboxilato de etilo,

6–[4–(4–acetilpiperazin–1–il)fenoxi]imidazo[1,2–b]piridazin–2–carboxilato de etilo,

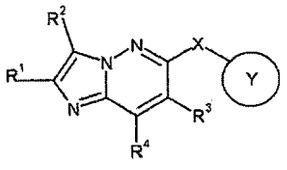
N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7,7–dimetil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

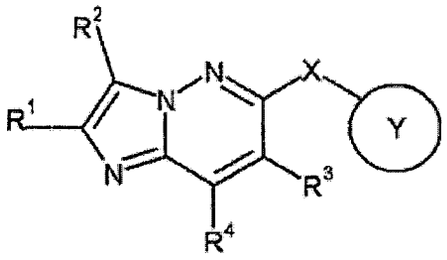
N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–2,5–dioxo–2,5,6,7–tetrahidro–1H–ciclopenta[b]piridin–3–il]benzamida,

N–[1–(imidazo[1,2–b]piridazin–6–ilamino)–7–metil–2,5–dioxo–1,2,5,6,7,8–hexahidroquinolin–3–il]benzamida,

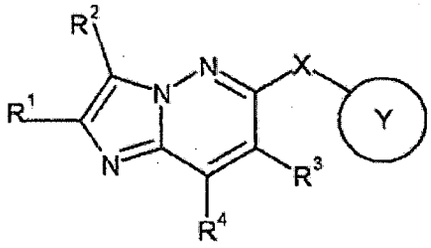
N–[(5E)–5–(imidazo[1,2–b]piridazin–6–ilhidrazono)–7–metil–2–oxo–4a,5,6,7,8,8a–hexahidro–2H–cromen–3–il]benzamida,



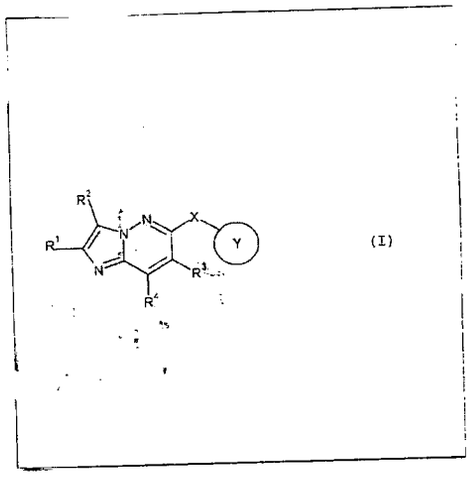
(I)



(I)



(I)



1269

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 16,799
FECHA : MARZO 2 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-022290- -00000-0000
Fecha: 2009-03-04 16:34:23 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1273

***** 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	19779045	02/03/2009	49,796,000.00

***** 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._____

Cdo 14656-841-043-6

7270

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2 .

RECIBO OFICIAL DE CAJA : 08 - 46,005
FECHA : JUNIO 9 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-022290- -00000-0000
Fecha: 2009-03-04 16:34:23 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1273

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2678328	09/06/2008	89,445,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	45	CAUCIONES	212,000.00
			TOTAL : $	212,000.00

SON: DOSCIENTOS DOCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14656-841043-6

1271

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 16,851
FECHA : MARZO 2 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-022290- -00000-0000
Fecha: 2009-03-04 16:34:23 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1273

***** C O N S I G N A C

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	19779045	02/03/2009	49,796,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	25,000.00
		TOTAL : $	25,000.00

SON: VEINTICINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14656-8410436

1272

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 16,705
FECHA : MARZO 2 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-022290- -00000-0000

Fecha: 2009-03-04 16:34:23 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1273

***** 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	19779045	02/03/2009	49,796,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	21 CERTIFICACIONES	12,000.00
		TOTAL : $	12,000.00

SON: DOCE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 14656-891-043-6

1273

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 12,691
[redacted]NA : FEBRERO 16 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-022290- -00000-0000
Fecha: 2009-03-04 16:34:23 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1273

***** 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	19779093	16/02/2009	16,385,000.00

***** C O N C E P T O *****

[redacted]T.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	1,000.00
			TOTAL : $	1,000.00

SON: MIL PESOS

RESPONSABLE : _____

Cdo 14656-841.043-6
Cdo 13203-841-015-6

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-022290- -00000-0000

Fecha: 2009-03-04 16:34:23 Dep: 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1273

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [1] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [1]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [1]
- Descripción de la invención [1]
- Dibujos de ser estos pertinentes [1]
- Comprobante de pago de las tasas establecidas [1]

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 [ ]

Sandra Rodriguez
Firma Responsable

Fecha Marzo 4-9

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	9 22290
	Solicitud internacional	PCT/JP2007/065681
	Fecha inicio fase nacional	04/03/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 4431

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.:9 22290

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 17 ABR. 2009
adpall